Original Contribution

18FDG-PET-CT
An Imaging Biomarker of High-Risk Carotid Plaques. Correlation to Symptoms and Microembolic Signals

Hubertus Fritz Georg Müller, MD; Aurélien Viaccoz, MD; Loraine Fisch, MD; Christophe Bonvin, MD; Karl-Olof Lovblad, MD; Osman Ratib, MD; Patrice Lalive, MD; Sabrina Pagano, PhD; Nicolas Vuilleumier, MD; Jean-Pierre Willi, MD; Roman Sztajzel, MD

Background and Purpose—We investigated whether uptake of \( ^{18} \text{Fluorodeoxyglucose} \) (18FDG) positron emission tomography–computed tomography (PET-CT) correlated to clinical symptoms and presence of microembolic signals (MES) detected by transcranial Doppler in patients with carotid stenosis.

Methods—18FDG-PET-CT and MES detection was performed in consecutive patients with 50% to 99% symptomatic or asymptomatic carotid stenoses. Uptake index was defined by a target to background ratio (TBR) between maximum standardized uptake value of the carotid plaque and the mean standardized uptake value of the jugular veins. End points for analysis were presence of symptoms and presence of MES.

Results—We included 123 stenosis derived from 110 patients, 60 symptomatic and 63 asymptomatic. MES positive (+) lesions were found in 16%. TBR values were higher in symptomatic compared with asymptomatic (median 2.07 versus 1.78; \( P<0.0018 \)) and in MES+ compared with MES− plaques (median 2.14 versus 1.86; \( P<0.008 \)). TBR values were also higher in asymptomatic MES+ compared with MES− plaques (median 1.97 versus 1.76; \( P<0.03 \)). The best TBR threshold value for symptomatic versus asymptomatic, for MES+ versus MES−, for symptomatic MES+ versus symptomatic or asymptomatic MES−, and for asymptomatic MES+ versus asymptomatic MES− plaques was 1.9. Sensitivity/specificity were, respectively, 56/77%, 73/63%, 79/64%, and 80/77%. We found a strong correlation between number of MES and TBR values (\( r=0.26; P=0.0043 \)).

Conclusions—18FDG-PET-CT accurately detected high-risk carotid plaques. Also given its strong correlation to MES, 18FDG-PET-CT may be a useful tool in clinical practice. (Stroke. 2014;45:00-00.)

Key Words: brain imaging ■ carotid plaque ■ carotid stenosis ■ imaging ■ stroke ■ vascular occlusion

Although the degree of lumen obstruction is a relevant marker of the risk of stroke, the recognition of the role of the vulnerable plaque has opened new insights in the field of atherosclerotic stroke.\(^1\) \(^2\) Vulnerability is dictated in part by plaque morphology, which, in turn, is influenced by pathophysiologic mechanisms at the cellular and molecular level. Thus, a certain number of features of plaque morphology may play an important role in the occurrence of cerebrovascular events.\(^3\) An unstable plaque, on the one hand, has a thin fibrous cap that contains large numbers of macrophages and T lymphocytes and a small number of smooth muscle cells. A stable plaque, on the other hand, has a thicker cap with larger numbers of smooth muscle cells and less inflammation.\(^4\)–\(^6\) Intensive research has been performed aimed at optimizing different imaging modalities to precisely analyze the arterial wall morphology, plaque composition, and degree of local inflammation. Among them, positron emission tomography (PET) using \( ^{18} \text{fluoro-2-deoxy-D-glucose} \) (18FDG) as a radiotracer has shown promise for detection of local inflammation in atherosclerotic plaques.\(^7\)–\(^8\) Indeed, high levels of glucose metabolism are typically seen in tissue with inflammatory activity.\(^9\) Moreover, significant positive correlations between histopathologic findings and degree of plaque inflammation depicted by 18FDG uptake have been documented.\(^10\)–\(^13\) Accordingly, a few clinical studies suggested a potential role of 18FDG-PET-computed tomography (CT) for the diagnosis of high-risk carotid plaques. Rudd et al\(^11\) showed that PET-CT might be used to image inflammatory cell activity within the carotid plaque. The study involved only 8 patients but was capable to demonstrate that 18FDG uptake was significantly higher within the symptomatic as compared with the contralateral plaque. Another study showed in a retrospective analysis...
that in recently symptomatic carotid stenosis, inflammation-related 18FDG uptake was associated with a higher count of following events independently of the degree of stenosis.17

The presence of microembolic signals (MES) detected by means of transcranial Doppler in patients with carotid disease is considered a strong predictor of ipsilateral stroke in asymptomatic patients and of stroke recurrence in symptomatic ones.19–21 Furthermore, several studies established a link between surface abnormalities of the plaque, for example, thin fibrous cap, ulceration or thrombus, and presence of MES.22,23 A recent study showed a correlation between 18FDG-PET-MRI and presence of MES in 16 patients presenting with recent transient ischemic attack or minor stroke and 50% to 99% stenosis of the ipsilateral carotid bifurcation. There was a significant difference in the target to background ratio (TBR) values between MES positive (+) and MES negative (−) patients, reinforcing the notion that embolization occurring distal to carotid stenoses may be related to plaque inflammation.24

The aim of our study was to evaluate in a larger cohort of patients whether 18FDG-PET-CT of carotid artery could discriminate symptomatic from asymptomatic lesions and identify atherosclerotic stenoses generating MES detected by transcranial Doppler (TCD).

Methods

Patients with 50% to 99% symptomatic or asymptomatic carotid disease within degree of stenosis according to North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria were included. Carotid occlusion was not permitted. There were 2 groups of patients: patients with a history of a recent stroke or transient ischemic attack or minor stroke and in asymptomatic patients, within 7 days after diagnosis of the stenosis. Embolic signal interpretation was done manually by an experienced ultrasonographer based on the criteria of the International Consensus group on Microembolus Detection.26 Detection of ≥1 MES ipsilateral to the carotid stenosis resulted in a positive examination.

Ultrasound Analysis

Degree of stenosis was assessed, including longitudinal and transverse sections by color Duplex imaging combined with peak systolic velocities at the level of the stenosis as well as with the internal carotid artery/common carotid artery ratio (see online-only Data Supplement).

For MES detection, bilateral TCD recording with 2 different insonation depths was performed during 60 minutes. In symptomatic patients, the examination was performed within 72 hours after stroke onset, and in asymptomatic patients, within 7 days after diagnosis of the stenosis. Embolic signal interpretation was done manually by an experienced ultrasonographer based on the criteria of the International Consensus group on Microembolus Detection.26 Detection of ≥1 MES ipsilateral to the carotid stenosis resulted in a positive examination.

Brain and Vessel Imaging

All patients underwent a CT scan with contrast angiography of extra- and intracranial vessels. Degree of stenosis was established using NASCET criteria. Additionally, an MRI study was performed in all patients.
Statistical Methods

Receiver operating characteristics curve analysis was used to determine the prognostic accuracy of 18F FDG-PET-CT (TBR and SUVmax) and degree of stenosis for presence of symptoms, for MES, or for the combination of both. Best criterion for threshold values and area under the curve were also calculated and compared with a baseline area under the curve of 0.5. Correlation statistics were explored using the Spearman test for nonparametric data. For testing of significant difference between groups, the U Mann–Whitney test was applied (MedCalc, Ostend, Belgium).

Results

From 2007 to 2012, 114 patients with 130 stenoses underwent 18FDG-PET-CT. Of these, 123 stenoses (110 patients) were included for analysis because contrast angiography was missing in 4 patients. Thirteen patients had bilateral stenoses. Of the 123 stenoses investigated, 60 were symptomatic and 63 asymptomatic. All demographical data of the patients are summarized in Table 1. It is to mention that the cardiovascular risk profile was similar within the 2 groups of patients, except for degree of stenosis, which was slightly higher in symptomatic patients but failed statistical significance and for active smoking, which was significantly higher in the symptomatic group. The male sex predominated in both groups. A significantly more important proportion of symptomatic patients received a combined antiplatelet therapy of clopidogrel and aspirin and high doses of statins.

A calcified component was present in 101 plaques, whereas 22 showed exclusively a soft component on CT angiography. Overall, we found 19 stenoses (16%) with MES ipsilaterally during TCD recording. The proportion of

| Table 1. Main Baseline Characteristics of the Symptomatic and Asymptomatic Groups |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
|                                | Symptomatic (N=60)              | Asymptomatic (N=63)            | Symptomatic (N=55)              | Asymptomatic (N=55)            |
|                                | Mean | Range | Mean | Range | %   | N | %   | N | P Value                                    |
| Degree of stenosis, %          | 76.1 | 55–95 | 72.9 | 50–80 | 0.06 |
| Age, y                         | 71.7 | 47–89 | 72.3 | 48–91 | 0.9  |
| High blood pressure            | 76   | 42    | 69   | 38    | NS  |
| Diabetes mellitus              | 27   | 15    | 27   | 15    | NS  |
| Hypercholesterolemia           | 44   | 24    | 58   | 32    | NS  |
| Smoking                        | 49   | 27    | 56   | 31    | <0.001 |
| Coronary disease               | 20   | 11    | 18   | 10    | NS  |
| Peripheral arterial disease    | 15   | 8     | 16   | 9     | NS  |
| Sex (male)                     | 80   | 44    | 71   | 39    | NS  |
| Stroke                         | 78   | 43    | ...  |       | ... |
| TIA/amaurosis fugax            | 22   | 12    | ...  |       | ... |
| Antplatelets at admission      |      |       |      |       | 0.001 |
| Monotherapy                    | 31   | 17    | 69   | 38    | 0.001 |
| Combination*                   | 69   | 38    | 31   | 17    | 0.001 |
| Statins at admission           |      |       |      |       | 0.001 |
| Low or moderate dose           | 16   | 9     | 49   | 27    | 0.03 |
| High dose                      | 84   | 46    | 51   | 28    | 0.03 |
| Anticoagulants                 | 7    | 4     | 11   | 6     | NS  |

TIA indicates transient ischemic attack.

*Aspirin–clopidogrel.

Table 2. Predictive Values of 18FDG-PET-CT Compared With Degree of Stenosis for the Identification of Symptomatic vs Asymptomatic Plaques

<table>
<thead>
<tr>
<th>Best Criterion (n=123)</th>
<th>AUC</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>P Value (Area 0.5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBR &gt;1.9</td>
<td>0.66</td>
<td>55%</td>
<td>76%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SUV max &gt;2.4</td>
<td>0.6</td>
<td>46%</td>
<td>71%</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>Degree of stenosis &gt;75%</td>
<td>0.6</td>
<td>45%</td>
<td>66%</td>
<td>0.06</td>
</tr>
</tbody>
</table>

AUC indicates area under the curve; SUV, standardized uptake value; and TBR, target to background ratio.
MES+ stenoses was higher in the symptomatic group (25%; n=14/57) when compared with the asymptomatic one (9%; n=5/59; P=0.01). The mean number of MES detected was 10 (range 1–50). In all cases, MES were present on 1 side only. There was no statistically significant difference in MES count between patients with and without dual antiplatelet therapy, a fact that persisted when analyzing only symptomatic patients. Further, dual therapy was initiated the same day of TCD recording in 62% of the patients; in 8.6% of the patients, dual therapy was already taken before admission. The rest of the patients received dual therapy >24 hours after TCD recording. There was no difference regarding MES count between the 3 groups.

We found higher TBR values in symptomatic compared with asymptomatic (median 2.07 versus 1.78; P=0.0018; Figure [A]) and in MES+ compared with MES− plaques (median 2.14 versus 1.86; P<0.008; Figure [B]). TBR values were also higher in asymptomatic MES+ compared with MES− plaques (median 1.97 versus 1.76; P<0.03; Figure [C]). The best TBR threshold value for symptomatic versus asymptomatic (Table 2), for MES+ versus MES− (Table 3), for symptomatic MES+ versus symptomatic or asymptomatic MES− (Table 4), and for asymptomatic MES+ versus asymptomatic MES− (Table 5) plaques was 1.9. Sensitivity/specificity were, respectively, 56/77%, 73/63%, 79/64%, and 80/77%. Within the MES+ subset of subjects, there was a strong correlation between the number of MES and TBR values (ρ 0.26, 95% CI, 0.0848–0.425; P=0.0043; Figure [D]).

We also found a correlation between degree of stenosis and TBR values when considering the whole cohort (ρ 0.19, 95% CI, 0.02–0.3; P=0.02). The correlation was significant but in fact weak if we consider the ρ value. Also the mean TBR values were slightly more elevated within the group with severe compared with the 1 with moderate degree of stenosis; the difference, however, was not significant (mean 2.02 versus 1.8; P=0.06). No correlation was further found between degree of stenosis and presence of symptoms or MES (respectively, ρ 0.17, 95% CI, 0.0129–0.342; P=0.06 and ρ 0.14, 95% CI, 0.0369–0.320; P=0.1), which was expected given the fact that in our sample all stenoses were >50%.

Discussion

The results of our study contribute to the validation of 18FDG-PET-CT as imaging biomarker to detect high-risk carotid plaques. Indeed, our findings indicated that inflammatory activity expressed as a high uptake of 18FDG within the atherosclerotic carotid plaque was able to discriminate between symptomatic and asymptomatic plaques. Moreover, higher 18FDG uptake values also accurately identified MES+ plaques not only within the symptomatic (11/14, 79%) but also within the asymptomatic group (4/5, 80%).

In fact, we found a strong correlation between the presence and the number of MES and TBR values. Several studies demonstrated that symptomatic plaques generating MES represented a subgroup of high-risk lesions more likely to embolize.19–21 Also cessation of MES after more aggressive antithrombotic therapy was related to a reduced risk of recurrent arterioembolic transient ischemic attack or stroke.22–24 In these conditions, presence of MES seemed to be useful for risk stratification. However, in clinical practice, MES recording presents a certain number of limitations. In fact, an absent temporal bone window may be found in ≈10% of the patients rendering MES recording not possible.25 Moreover, it is known from prior studies that occurrence of MES is time-related; in fact, microembolism is a frequent phenomenon during the days that follow symptoms of cerebral ischemia, but its prevalence drops significantly afterward.30 Also, although MES recording was performed quickly after patient’s admission, still the time interval between recording and onset of symptoms remained variable.

The prevalence of MES in our symptomatic group was relatively lower than reports from the literature.19 This could be because of early and aggressive treatment with combination therapy of clopidogrel and aspirin. Indeed double antiplatelet therapy has been shown to reduce presence of MES.27,28 Therefore, even though presence of MES was highly correlated to symptomatic disease in our study, we cannot rule out that a certain number of MES− lesions presenting otherwise elevated TBR values (>1.9) could also be potentially at higher risk for recurrence.

| Table 3. Predictive Values of 18Fluorodeoxyglucose Positron Emission Tomography–Computed Tomography Compared With Degree of Stenosis for the Identification of Microembolic Signals (MES)+ Plaques vs MES− Plaques |
|---------------------------------|-----------|---------|----------|--------|
| **Best Criterion (n=116)**      | **AUC**  | **Sensitivity** | **Specificity** | **P Value (Area 0.5)** |
| TBR                             | >1.9     | 0.69    | 79%      | 59%    | <0.002 |
| SUV max                         | >2.6     | 0.6     | 47%      | 80%    | 0.2    |
| Degree of stenosis              | >70%     | 0.61    | 73%      | 44%    | <0.012 |

AUC indicates area under the curve; SUV, standardized uptake value; and TBR, target to background ratio.

| Table 4. Predictive Values of 18Fluorodeoxyglucose Positron Emission Tomography–Computed Tomography Compared With Degree of Stenosis for the Identification of Symptomatic Microembolic Signals (MES)+ vs Symptomatic or Asymptomatic MES− Plaques |
|---------------------------------|-----------|---------|----------|--------|
| **Best Criterion (n=116)**      | **AUC**  | **Sensitivity** | **Specificity** | **P Value (Area 0.5)** |
| TBR                             | >1.9     | 0.69    | 79%      | 64%    | <0.01  |
| SUV max                         | >2.4     | 0.56    | 50%      | 60%    | 0.5    |
| Degree of stenosis              | >75%     | 0.57    | 50%      | 63%    | 0.4    |

AUC indicates area under the curve; SUV, standardized uptake value; and TBR, target to background ratio.
Usefulness of 18FDG-PET-CT in asymptomatic plaques and its strong link to the presence of MES has to our knowledge never been studied to date. Recent analyses have shown that with more intensive medical therapy, the annual risk of stroke in patients with asymptomatic carotid stenosis has become lower than that reported in the endarterectomy trials. Nevertheless, still a small group of patients remains at significant risk for stroke, and it is therefore important to have methods to better identify those patients. As demonstrated in several studies, presence of MES may be a powerful predictor of subsequent cerebrovascular events and its recording seems therefore as helpful. However, as already mentioned, this technique has a certain number of constraints. In addition, as shown in our study and in others, prevalence of MES was much lower in asymptomatic than in symptomatic plaques. It must also be mentioned that MES detection by TCD is time consuming, cumbersome, and necessitates skillful equipment and operators.

Accordingly a complementary method, such as PET imaging, able to establish a similar risk estimate than MES recording may be valuable.

As already suggested by Graebe, molecular identification of the vulnerable plaque by means of 18FDG-PET-CT may become a standard examination to select plaques at high-risk and potential candidates either for intervention or for more aggressive medical treatment. In our study, uptake is supposed to be detectable for around 1 month after symptoms, which is much longer than presence of MES. PET–CT for clinical application should, however, be mentioned, including its cost, higher radiation to the patient, and potential side effects of iodine contrast (allergy, renal impairment). The cost-benefit of PET–CT should, therefore, be studied more in detail. Moreover, the analysis might be affected by partial volume effect, complicated ROI definition, and possible contamination by neighboring high-uptake structures, and as a consequence, visual assessment of hot plaques is supposed to be unreliable.

Finally, we did not perform in our study high resolution MRI considered as another imaging biomarker of plaque vulnerability. Further studies comparing these 2 techniques are therefore necessary.

**Conclusions**

The results of our study contribute to the validation of 18FDG-PET-CT as imaging biomarker to detect high-risk carotid plaques. Also given its strong correlation to the presence and number of MES and considering the high number of factors, which may negatively influence MES detection, 18FDG-PET-CT may be a useful tool in clinical practice and should become a part of the standard examination to select potential candidates either for intervention or for more aggressive medical treatment.

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**Disclosures**

None.
References


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SUPPLEMENTAL MATERIAL

Supplemental Methods

Patients were considered as symptomatic whenever they presented cerebrovascular or retinal events (TIA or stroke) within the previous month in the territory of the stenosis of the internal carotid artery. TIA was defined by any transitory event <1h with no lesion detected on DWI MRI sequence. Patients were considered as asymptomatic in the absence of any history of recent neurological or retinal deficit, of ipsilateral MRI lesions or of stroke attributed to another origin than carotid disease. All symptomatic patients had a complementary work up including cardiac ultrasound examination and long duration electrocardiogram for seven days to exclude stroke origin from cardioembolism.

Image acquisition

The protocol included at least 6 hours of fasting before injection of 18FDG at a dose of 370 MBq. Spiral PET-CT (SIEMENS, Biograph 64) was realized 90 minutes after 18FDG injection and consisted in an initial low radiation CT for attenuation correction, followed by PET acquisition scan and co-registering of a contrast (iodine) angiography (CTA) scan from the aortic arch rostral. This study being carried out on a hybrid PET-CT the CTA study was acquired on the same scanner during the same session ensuring perfect alignment of the two modalities (PET and CTA). Furthermore, the patients were positioned in a head holder with a « heat adjustable » facemask that prevents the patient from moving their head.
The physical resolution of the PET-CT was 4.2 mm for the transaxial resolution and 4.7 mm for the axial resolution (in FWHM).

The image reconstructions were made with a slice thickness of 5 mm and a matrix of 336x336 pixels and a pixel size of 2.03 mm.

CTA images were acquired with a slice thickness of 2 mm and a matrix size of 512x512 pixels of 0.58 mm pixel size.

Differences in spatial resolution were taken into account by the image fusion software.

**Image analysis**

The advanced DICOM viewer Osirix (Osirix, Geneva, Switzerland) was used to delineate regions of interest (ROI) on the contrast enhanced scan.

For the carotid plaque on each axial slice a circular or elliptical ROI ≥ 1 mm² was fitted manually in the center part of the plaque. This was done separately for the soft, calcified and combined parts (Fig I). For each ROI the maximum standardized uptake value of pixel activity (SUVmax) was assessed from the fused PET-CT scan. For data analysis only the highest values were selected, no averaging or partial volume correction was performed. We also measured CT attenuation in Hounsfield units (HU) of the different parts of the carotid plaque (soft, calcified and combined).

We further assessed mean and maximum SUV of the ipsilateral carotid artery, at slices 10 mm superior and inferior of the respective limits of the carotid plaque.
and for both carotid arteries at 10 mm inferior of the bifurcation. For blood-pool readings the jugular vein was analyzed bilaterally with measurements done intraluminally (SUVmean of the ROI).

An uptake index was assessed and defined by a target to background ratio (TBR) between SUVmax and the mean SUV of both jugular veins.

Areas showing a highly capturing structure in the direct neighborhood of the carotid artery / jugular vein with risk of contamination were avoided and the measurement was shifted to the next uncontaminated slice.

Based on the tissue density on the CT images, calcifications were identified in tissue segments that have a density above 130 Hounsfield units (HU). We measured HU of the different parts of the carotid plaque (soft, calcified and combined).

**Ultrasound Analysis**

All investigations were performed using a diagnostic ultrasound device (Antarares SIEMENS, 7.5-MHz probe). Degree of stenosis was assessed including longitudinal and transverse sections by color Duplex imaging. The morphological lumen reduction calculation in diameter was combined with peak systolic velocities at the level of the stenosis as well as with the internal carotid artery/common carotid artery ratio. The following values were used to distinguish 2 different groups of degree of stenosis: 50% to 69% with peak systolic velocities >120 and <220 cm/s and internal carotid artery/common carotid artery >1.5 and <3.7; and 70% to 99% with peak systolic velocities >220 cm/s and internal carotid artery/common carotid artery >3.7. Stenoses of >80% were considered whenever end-diastolic velocity was >135 cm/s (25). For microembolic signal detection (MES) bilateral transcranial doppler (TCD) recording
with two different insonation depths was performed during 60 minutes. In symptomatic patients, the examination was performed within 72 hours after stroke onset and in asymptomatic ones within 7 days after diagnosis of the stenosis. The two 2 MHz probes (Multidop, DWL) were attached to the patients temporal bone windows by means of a helmet. Embolic signal interpretation was done manually by an experienced ultrasonographer based on the criteria of the International Consensus group on Microembolus Detection, with analysis of the doppler and the power mode spectra and by listening to the acoustic signal (26). Detection of at least one MES ipsilateral to the carotid stenosis resulted in a positive examination. These patients were defined as MES positive (+).

**Brain and vessel imaging**

All symptomatic and asymptomatic patients underwent a CT scan with contrast angiography of the extra- and intracranial vessels. Degree of stenosis was established by means of the angiographic data, using NASCET criteria. Additionally, a magnetic resonance imaging (MRI) study was performed in all patients with T1, T2 and T2* (hemo), diffusion weighted (DWI) and fluid attenuated inversion recovery (FLAIR) sequences.
Supplemental Figure

Figure I. Standardized uptake values (SUV) measurement in the region of interest (ROI) of the different plaque components.
18FDG-PET-CT
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(Stroke. 2014;45:3561-3566.)

Table 3. Predictive Values of 18Fluoro-2-Deoxy-ß-Glucose Positron Emission Tomography–Computed Tomography Compared With Degree of Stenosis for the Identification of Microembolic Signals (MES)+ Plaques vs MES− Plaques

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<th>Sensitivity</th>
<th>Specificity</th>
<th>P Value (Area 0.5)</th>
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<tbody>
<tr>
<td>TBR</td>
<td>&gt;1.9</td>
<td>0.69</td>
<td>79%</td>
<td>59%</td>
</tr>
<tr>
<td>SUV max</td>
<td>&gt;2.6</td>
<td>0.60</td>
<td>47%</td>
<td>80%</td>
</tr>
<tr>
<td>Degree of stenosis</td>
<td>&gt;70%</td>
<td>0.61</td>
<td>73%</td>
<td>44%</td>
</tr>
</tbody>
</table>

AUC indicates area under the curve; SUV, standardized uptake value; and TBR, target to background ratio.