FDG PET/CT Early Dynamic Blood Flow and Late Standardized Uptake Value Determination in Hepatocellular Carcinoma¹

Hanna Bernstine, MD
Marius Braun, MD
Nikolay Yefremov, MD
Yechiel Lamash, MSc
Raz Carmi, PhD
Dorit Stern, MD
Adam Steinmetz, MD
Jacob Sosna, MD
David Groshar, MD

Purpose: To prospectively determine whether fluorine 18 fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) early dynamic blood flow estimates could be used to discriminate hepatocellular carcinoma (HCC) from background liver and to characterize HCC in patients with and those without angioinvasion; and to evaluate the association between blood flow measures at FDG PET/CT with metabolism in HCCs.

Materials and Methods: Institutional review board approval and written informed consent were obtained for this prospective study. Twenty-one consecutive patients (mean age, 65 years) with 30 established HCCs (mean size, 5.5 cm; seven lesions in five patients with angioinvasion) underwent a blood flow study with an FDG dynamic scan divided into 18 sequences of 5 seconds each and a standard PET/CT scan. On the dynamic study, three independent operators obtained volumes of interest (VOIs) for which three blood flow estimates were calculated (hepatic perfusion index [HPI], time to peak [TTP], and peak intensity [PI]). On the late study, a VOI was placed on the fused scan for each HCC, and maximum standardized uptake value (SUV max) was obtained. By using a mixed-effects model analysis, comparison of blood flow estimates between HCC with and that without angioinvasion and background liver was performed. The association between blood flow estimates and SUV max was also assessed.

Results: HPI and TTP showed better performance than did SUV max for discriminating HCC and background liver (areas under receiver operating characteristic curve: 0.96, 0.95, and 0.83, respectively; P < .05). HPI was higher in HCC in patients with angioinvasion (0.91 ± 0.15 [standard deviation]) than in those without angioinvasion (0.80 ± 0.18; P = .03). There was no difference in SUV max between HCC in patients with and those without angioinvasion (7.8 ± 2.9 vs 6.3 ± 3.4; P = .85). No clear association was found between HPI, PI, or TTP and SUV max (P = .49, .77, and .91, respectively).

Conclusion: Early dynamic blood flow FDG PET/CT may be used to help discriminate and characterize HCC tumors.

¹From the Department of Nuclear Medicine (H.B., N.Y., D.S., A.S., D.G.) and Liver Institute (M.B.), Rabin Medical Center, Petah Tikva, Israel; Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel (H.B., M.B., D.G.); CT/NM Unit, Philips Healthcare, Haifa, Israel (Y.L., R.C.); Department of Mechanical Engineering, Technion—Israel Institute of Technology, Haifa, Israel (Y.L.); Department of Nuclear Medicine, Assuta Medical Center, Tel Aviv, Israel 49100 (D.S., D.G.); Department of Radiology, Hadassah Hebrew University Medical Center, Jerusalem, Israel (J.S.); and Department of Radiology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Mass (J.S.). Received November 27, 2010; revision requested January 11, 2011; revision received February 28, accepted March 9; final version accepted March 15. Supported by grants from the Chief Scientist Office (Ministry of Health, Israel) and the Deucher Foundation (Rabin Medical Center). Address correspondence to D.G. (e-mail: davidgr2@clalit.org.il).

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Hepatocellular carcinoma (HCC) is the most common liver malignancy in adults and the third leading cause of cancer-related death worldwide (1). HCC is a highly vascular tumor and develops neovascularization through the process of angiogenesis. As a result of a marked increase in neovascularized arteries, the portal blood flow that normally provides 70% of the blood flow to liver parenchyma decreases, and the tumor is eventually fed mainly by arterial flow, reflected by increased tumor perfusion delivered from the hepatic artery (1).

Technical developments in diagnostic imaging have resulted in the detection of smaller tumors, improved ability to discriminate lesion pathologic types, and improved assessment of tumor and liver vascular features. However, a recent report of the National Cancer Institute Clinical Trials Planning Meeting (1) stated that “advanced HCC remains a significant unmet medical need” and recommended that research in HCC should be prioritized, including perfusion imaging modalities, to develop new prognostic indicators and effective therapies for the disease. Assessment of HCC perfusion and metabolic activity could substantially improve patient management and clinical trial eligibility and could potentially be used for personalized medicine decisions. Perfusion parameters may constitute physiologic markers related to tumor angiogenesis. Quantifying markers of tumor angiogenesis may be important for risk stratification, evaluation of disease progression, and monitoring treatment response for treatments such as angiogenic agents. Perfusion imaging methods, such as dynamic contrast material–enhanced magnetic resonance (MR) imaging and dynamic contrast-enhanced computed tomography (CT), show potential to be used to detect and follow HCC lesions and to assess biologic tumor changes (2–9).

Fluorine 18 fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT is now commonly performed in the evaluation of patients presenting with cancer, and it provides important information about metabolism and anatomy. Standardized uptake value is an objective measurement of FDG uptake in tumors that represents the glucose metabolic activity. Varying uptake of FDG has been described in HCC lesions owing to the relatively high FDG uptake in normal liver tissue and the varying degrees of activity of the enzyme glucose-6-phosphatase (10–14). Mullani et al (15) compared blood flow by using oxygen 15 water and first-pass delivery of FDG to tumors and showed that an estimate of tumor blood flow can be obtained with FDG first-pass images. Evaluation of HCC with FDG PET/CT may be improved by measurements of first-pass delivery of FDG. The ability to obtain an estimate of both tumor blood flow and metabolism from a single FDG PET/CT study may enhance the ability to detect, characterize, and follow HCC lesions.

The purpose of our study was to prospectively determine whether FDG PET/CT early dynamic blood flow estimates could be used to discriminate HCC from background liver and to characterize HCC in patients with and those without angioinvasion. We also sought to evaluate the association between blood flow measures at FDG PET/CT with metabolism in HCC tumors.

**Materials and Methods**

**Patient Population**

Our study was approved by the institutional review board at Rabin Medical Center, and written informed consent was obtained. Authors who are not employees of Philips Healthcare had continuous control of all research data in this study (H.B. and D.G. acted as guarantors of integrity for the entire study). Twenty-one consecutive patients (mean age, 63 years; range, 48–80 years), including 17 men (mean age, 65 years; range, 48–80 years) and four women (mean age, 66 years; range, 55–78 years), with established HCC lesions were recruited between September 2009 and September 2010. HCC tumours were recruited between September 2009 and September 2010. HCC tumours were recruited between September 2009 and September 2010.

**Implication for Patient Care**

**Concurrent assessment of early dynamic blood flow and SUV<sub>max</sub> by using FDG PET/CT as one-stop shopping for estimating blood flow and metabolism may help discriminate and characterize HCCs.**

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**Advance in Knowledge**

- Blood flow estimates assessed by using early dynamic fluorine 18 fluorodeoxyglucose (FDG) PET/CT can be used to help characterize hepatocellular carcinoma (HCC).
- Hepatic perfusion index (HPI) and time to peak showed better performance than did maximum standardized uptake value (SUV<sub>max</sub>) for discriminating HCC and background liver (areas under receiver operating characteristic curves: 0.96, 0.95, and 0.83, respectively; *P* < .05).
- Whereas there was no difference in SUV<sub>max</sub> between HCC in patients with and those without angioinvasion (7.8 ± 2.9 [standard deviation] vs 6.3 ± 3.4; *P* = .85), HPI was higher in HCC in patients with angioinvasion (0.91 ± 0.15) than in those without angioinvasion (0.80 ± 0.18; *P* = .03).

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**Abbreviations:**

FDG = fluorine 18 fluorodeoxyglucose

HCC = hepatocellular carcinoma

HPI = hepatic perfusion index

PI = peak intensity

SUV<sub>max</sub> = maximum standardized uptake value

TTP = time to peak

VOI = volume of interest

**Author contributions:**

Guarantors of integrity of entire study, H.B., D.G.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; literature research, H.B., M.B., Y.L., R.C., J.S., D.G.; clinical studies, H.B., N.V., Y.L., R.C., D.S., A.S., D.G.; statistical analysis, N.Y., Y.L., R.C., D.S.; and manuscript editing, H.B., Y.L., R.C., D.S., J.S., D.G.

Potential conflicts of interest are listed at the end of this article.
lesions were confirmed with accepted diagnostic criteria, including either biopsy or positive results at two imaging modalities (including four-phase CT, MR imaging, or ultrasonography) with high levels of a-fetoprotein. Thirteen patients had a single lesion, seven patients had two lesions, and one patient had three lesions. Overall, there were 30 HCC lesions in 21 patients. The mean size of the HCC lesions was 5.5 cm ± 3.2 (standard deviation) (range, 1.8–13.6 cm). Five patients with a total of seven HCC lesions showed angioinvasion with portal tumor thrombus. Angioinvasion was recorded (D.S., with 30 years experience in body radiology and 7 years experience in PET/CT) when thrombosis and enlargement of the portal veins were present on CT images, and lack of thrombosis or presence of thrombosis without enlargement of a vein was considered absence of angioinvasion.

**Imaging Protocol**

Patients fasted for a minimum of 4 hours before the intravenous injection of 500 MBq of FDG. All images were obtained by using an integrated eight-section PET/CT scanner (Discovery ST; GE Medical Systems, Milwaukee, Wis). The protocol included two PET/CT acquisitions: a dynamic blood flow PET acquisition (limited to a single bed position, centered on the liver, and started at the injection of the FDG with a low-dose CT scan) and a standard static PET/CT scan of the torso (skull base to midthigh, performed 60 minutes after FDG injection).

**Early dynamic blood flow PET/CT.**—A scout view of the upper abdomen was obtained, and the study centered on the liver, with PET coverage of 15.3 cm. A nondiagnostic low-dose CT (30 mAs) scan was acquired. FDG was injected as a rapid bolus that was flushed with 50 mL of 0.9% saline at a rate of 5.0 mL/sec by using an automatic power injector (GE-Nemoto Dual-Shot Injector; GE Healthcare, Waukesha, Wis). The blood flow study was acquired as a dynamic two-dimensional acquisition scan (matrix size, 128 × 128; section thickness, 3.27 mm) consisting of 18 sequential frames of 5 seconds each. After this session, the patients were transferred to the waiting room for 60 minutes, and 800–1000 mL of diluted iodinated contrast material was administered orally for bowel opacification.

**Standard PET/CT.**—Parameters for helical CT image acquisition were as follows: tube voltage, 120 kV; modulated tube current-time product, 80–280 mAs; section thickness, 2.5 mm; pitch, 0.875; with image reconstruction every 2.5 mm. First, an unenhanced CT scan of the liver was acquired. Then, 80–100 mL of iodinated contrast material (0.623-g/mL ipromide, Ultravist 300; Bayer Schering Pharma, Berlin, Germany) was intravenously administered at a rate of 4.0 mL/sec by using an automatic power injector (GE-Nemoto Dual-Shot Injector), with CT scanning of the upper abdomen initiated after a 20-second delay. A third CT scan of the full torso was acquired after a 70-second delay, which provided the attenuation map. The PET scan was acquired as a static two-dimensional acquisition at multiple (ie, 6–7) bed positions (150 seconds each). PET data after attenuation correction were reconstructed by using a two-dimensional ordered subset expectation maximization algorithm (two iterations, 20 subsets).

**Data Processing and Analysis**

**Early dynamic blood flow analysis.**—Three independent observers (N.Y., D.G., and H.B., with 10, 7, and 4 years experience in PET/CT) reviewed all available previous CT and MR images with the index examination at different times. On the blood flow PET/CT, a fused axial section at an anatomic level corresponding to the known hepatic lesions (ie, HCC) was chosen, and a three-dimensional volume of interest (VOI) (mean area, 59.8 cm²; range, 0.8–478 cm²) was created on the axial section of the fused PET/CT scan and manually adjusted to encompass the maximum available size of the lesions in all three planes. Three additional VOIs were outlined for sampling the abdominal aorta (mean area, 1.7 cm²; range, 1.3–2.7 cm²), the background liver parenchyma (mean area, 2.4 cm²; range, 1.6–14.1 cm²), and the spleen parenchyma (mean area, 2.6 cm²; range, 1.4–14.1 cm²).

Time-activity curves were generated from the mean activities for each VOI (Fig 1). Three blood flow parameters (ie, peak intensity [PI], time to peak [TTP], and hepatic perfusion index [HPI]) related to the first-pass delivery of FDG were derived for the HCC lesion and the background liver parenchyma, and TTP and PI were calculated for the spleen parenchyma.

**Blood flow estimation with PI.**—The concept of measuring tumor blood flow from the first-pass of FDG is based on the simple blood flow model of Mullanli and colleagues (16–19). The model postulates that, during the first pass of a tracer through tissue, the venous egress of the tracer is delayed by some time, which is a function of the distribution volume and vessel density of the tracer in the tissue of interest. During this delay time, for highly extracted tracers, most of the tracer is retained in the tissue so that venous egress is extremely small. On the basis of this assumption, the tissue blood flow, F, can be estimated by using the following equation:

\[
F = \frac{Q(T)}{E(T) \int_0^T C(t)dt},
\]

where \(Q(T)\) is the residual amount of the tracer in sampled tissue at any time, \(T\); \(C(t)\) is the arterial concentration of the tracer; and \(E(T)\) is the extraction fraction.

Mullanli et al (15) compared the extraction fraction of FDG in tumor tissue with the extraction fraction for the more traditional tracer oxygen 15 water. They found that FDG is highly extracted in tumor tissue during the first pass of the tracer and that the ratio between the two extraction fractions was near 0.86. Then, assuming the FDG first-pass extraction fraction is close to 1, the expression for tumor blood flow estimates can be simplified to the following:

\[
F = \frac{Q(T)}{\int_0^T C(t)dt}.
\]

A typical selection of \(T\) is when the tissue reaches PI (milliliter of blood flow per minute per milliliter of tissue).
Gamma-variate fit was used to correct for arterial recirculation and to locate the tissue peak of activity for noisy samples. The gamma variate is a mathematical function shown to be successfully fitted to measure tracer dilution curves. The gamma variate can also be derived from a deterministic model of flow through a series of mixing chambers and, thus, provide a physiologic interpretation to the agreement with organ blood flow measurements (20). The basic gamma-variate function is defined as follows:

\[ y(t) = At^n \exp\left(-\frac{t}{\beta}\right), t > 0. \]

It can be shown (16, 17) that this expression is equivalent to the following:

\[ y(t) = y_{\text{max}} \left(\frac{t}{t_{\text{max}}}\right)^{\alpha} \exp\left(\alpha \left(1-\frac{t}{t_{\text{max}}}\right)\right), t > 0, \]

where \( A = y_{\text{max}} t_{\text{max}}^{-\alpha} \exp(\alpha) \) and \( \beta = t_{\text{max}}/\alpha \). Here, \( \beta \) and \( A \) are eliminated, and instead, \( y_{\text{max}} \) and \( t_{\text{max}} \) are introduced, where \( y_{\text{max}} \) is the maximum value and \( t_{\text{max}} \) is the time for the maximum. If the function begins at \( t = t_0 \), where \( 0 < t_0 < t_{\text{max}} \), we obtain the following:

\[ y(t) = y_{\text{max}} \left(\frac{t-t_0}{t_{\text{max}}-t_0}\right)^{\alpha} \exp\left(\alpha \left(1-\frac{t-t_0}{t_{\text{max}}-t_0}\right)\right), t > 0. \]

**Figure 1:** Graphs show typical time-activity curves (©) for aorta, liver, spleen, and HCC tumor derived from analyses of regions of interest, with gamma-variate function fit (line).

**Time to peak.**—HCCs are mainly nourished by arterial flow. At the first pass, the arterial flow reaches its peak a while before the portal flow. Therefore, the TTP is another discriminative quantity between background tissue and tumor in the liver. The following equation was used: \( \text{TTP} = t_{\text{max}} - t_0 \), where \( t_{\text{max}} \) is the time at which the region of interest reaches its peak and \( t_0 \) is the time of the aorta peak.

**Hepatic perfusion index.**—The HPI is the percentage of arterial supply of total liver blood flow (21, 22). The HPI can be measured by using the arterial first-pass slope, \( dC_{\text{art}}(t) \), and portal first-pass slope, \( dC_{\text{port}}(t) \), as follows:

\[ \text{HPI} = \frac{\frac{dC_{\text{art}}(t)}{dt}}{\frac{dC_{\text{art}}(t)}{dt} + \frac{dC_{\text{port}}(t)}{dt}}. \]

The PI of the spleen was used to distinguish between the arterial and portal flows.

**Late PET/CT.**—A radiologist (D.S., with 30 years experience in body radiology and 7 years experience in PET/CT) interpreted all available previous CT and MR studies and compared these to the index study. For each HCC lesion detected at CT and for background liver tissue, a three-dimensional VOI was created on the axial section of the fused PET/CT scan and was manually adjusted to encompass the lesion and background liver in all three planes. The maximum-intensity voxel within this VOI, calibrated...
to standardized uptake value normalized for body weight, was recorded as the maximum standardized uptake value (SUV$_{\text{max}}$).

**Statistical Analysis**

A mixed-effects model that accounted for correlation of measurements within a patient was used to compare the blood flow estimates between HCC, background liver tissue, and spleen tissue; to compare SUV$_{\text{max}}$ between HCC and background liver tissue; and to compare blood flow parameters and SUV$_{\text{max}}$ in HCC and background liver between patients with and those without angioinvasion. The mixed-effects model was also used to assess the association between SUV$_{\text{max}}$ and blood flow estimates in HCCs. The statistical analyses of mixed-effects model were performed by using SPSS software (version 15.0; SPSS, Chicago, Ill). The Wilcoxon rank sum test for paired samples was used to compare blood flow estimates between liver and spleen, and the Mann-Whitney test was used to compare blood flow parameters and SUV$_{\text{max}}$ in background liver between patients with and those without angioinvasion. Receiver operating characteristic curve analysis for blood flow parameters and SUV$_{\text{max}}$ was used to determine the cutoff value that best discriminated HCCs from background liver parenchyma, in which the binary dependent variable was presence of HCC. The method of DeLong et al (23) for the calculation of the difference between two areas under the receiver operating characteristic curve was used to compare blood flow parameters with SUV$_{\text{max}}$. The single-measure intraclass correlation coefficient was used for estimating interobserver absolute agreement for blood flow measurements between three independent operators. Statistical analyses were performed by using MedCalc software (version 11.4.2.0; MedCalc Software, Mariakerke, Belgium). 

**Results**

Both HCC and spleen showed significantly different blood flow parameters than did background liver. HPI and PI were higher in HCC than in background liver (0.83 ± 0.17 vs 0.43 ± 0.14 and 0.60 ± 0.30 vs 0.29 ± 0.22, respectively; both P < .0001), and TTP was shorter in HCC than in background liver (17.0 seconds ± 11.6 vs 47.3 seconds ± 12.8, P < .0001) (Table 1). PI was higher in spleen than in HCC (0.99 ± 0.36 vs 0.60 ± 0.30, P < .0001), and TTP was shorter in spleen than in HCC (11.0 seconds ± 2.8 vs 17.0 seconds ± 11.6; P = .009) (Table 1). SUV$_{\text{max}}$, was significantly higher in HCCs than in background liver parenchyma (6.6 ± 3.3 vs 3.4 ± 0.8, P < .0001) (Table 1). Analysis of the area under the receiver operating characteristic curve revealed that the ability to discriminate HCC from background liver parenchyma was significantly higher with HPI or TTP than with SUV$_{\text{max}}$ (0.96, 0.95, and 0.83, respectively; both P < .05). There was no significant difference in the area under the receiver operating characteristic curve measured between SUV$_{\text{max}}$ and PI (0.83 and 0.86, respectively; P = .74) (Table 2).

HCC in patients with angioinvasion showed a significantly different HPI than did HCC in patients without angioinvasion (P = .03) (Table 3). There was no significant difference in SUV$_{\text{max}}$ of HCC between patients with and those without angioinvasion (Table 3). There was no significant difference in blood flow estimates in background liver between patients with and those without angioinvasion (Table 3).

Mixed-effects model analysis showed no clear association between SUV$_{\text{max}}$ and the blood flow parameters HPI, PI, and TTP (P = .49, .77, and .91, respectively) (Figs 2, 3).

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**Table 1**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Background Liver (n = 21)$^*$</th>
<th>Spleen (n = 21)$^*$</th>
<th>HCC (n = 30)$^*$</th>
<th>P Value$^\dagger$</th>
<th>Liver vs Spleen</th>
<th>Liver vs HCC</th>
<th>Spleen vs HCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPI</td>
<td>0.43 ± 0.14 (0.23–0.84)</td>
<td>...</td>
<td>0.83 ± 0.17 (0.45–1.0)</td>
<td>...</td>
<td>&lt; .0001</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>TTP</td>
<td>47.3 ± 12.8 (20.0–72.0)</td>
<td>11.0 ± 2.8 (6.5–19.0)</td>
<td>17.0 ± 11.6 (1.2–55.8)</td>
<td>&lt; .0001</td>
<td>&lt; .0001</td>
<td>.009</td>
<td></td>
</tr>
<tr>
<td>PI</td>
<td>0.29 ± 0.22 (0.12–1.0)</td>
<td>0.99 ± 0.36 (0.45–1.7)</td>
<td>0.60 ± 0.30 (0.25–1.34)</td>
<td>&lt; .0001</td>
<td>&lt; .0001</td>
<td>&lt; .0001</td>
<td></td>
</tr>
<tr>
<td>SUV$_{\text{max}}$</td>
<td>3.4 ± 0.8 (2.3–5.5)</td>
<td>...</td>
<td>6.6 ± 3.3 (2.1–14.2)</td>
<td>...</td>
<td>...</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Data are means ± standard deviations, with ranges in parentheses.

† Mixed-effects model.

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**Table 2**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cutoff Value</th>
<th>Area under Receiver Operating Characteristic Curve*</th>
<th>P Value$^\dagger$</th>
</tr>
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<tbody>
<tr>
<td>HPI</td>
<td>&gt; 0.62</td>
<td>0.96 (0.86, 0.99)</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>TTP</td>
<td>&lt; 36.0</td>
<td>0.95 (0.85, 0.99)</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>PI</td>
<td>&gt; 0.27</td>
<td>0.86 (0.74, 0.94)</td>
<td>.74</td>
</tr>
<tr>
<td>SUV$_{\text{max}}$</td>
<td>&gt; 4.5</td>
<td>0.83 (0.70, 0.92)</td>
<td>...</td>
</tr>
</tbody>
</table>

* Data in parentheses are 95% confidence intervals.

† Method of DeLong et al (23) used to compare findings with those of SUV$_{\text{max}}$. 

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### Table 3

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HCC (n = 7)</th>
<th>No Angioinvasion (n = 23)</th>
<th>P Value*</th>
<th>HCC (n = 5)</th>
<th>No Angioinvasion (n = 16)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPI</td>
<td>0.91 ± 0.15 (0.62–1.0)</td>
<td>0.80 ± 0.18 (0.45–1.0)</td>
<td>.03</td>
<td>0.37 ± 0.08 (0.23–0.45)</td>
<td>0.44 ± 0.15 (0.24–0.84)</td>
<td>.82</td>
</tr>
<tr>
<td>PI</td>
<td>0.57 ± 0.12 (0.45–0.61)</td>
<td>0.64 ± 0.34 (0.25–1.3)</td>
<td>.37</td>
<td>0.27 ± 0.13 (0.19–0.50)</td>
<td>0.30 ± 0.24 (0.12–1.0)</td>
<td>.56</td>
</tr>
<tr>
<td>TTP</td>
<td>9.2 ± 5.7 (1.2–16.1)</td>
<td>19.3 ± 11.9 (3.3–55.8)</td>
<td>.06</td>
<td>48.0 ± 7.6 (37.4–56.4)</td>
<td>47.1 ± 14.3 (19.9–72.0)</td>
<td>.70</td>
</tr>
<tr>
<td>SUV&lt;sub&gt;max&lt;/sub&gt;</td>
<td>7.8 ± 2.9 (3.6–12.8)</td>
<td>6.3 ± 3.4 (2.1–14.2)</td>
<td>.85</td>
<td>3.2 ± 0.9 (2.3–4.5)</td>
<td>3.5 ± 0.8 (2.3–5.5)</td>
<td>.40</td>
</tr>
</tbody>
</table>

Note.—Unless otherwise specified, data are means ± standard deviations, with ranges in parentheses.

* Mixed-effects model.
† Mann–Whitney test.

### Figure 2

**Figure 2:** Early dynamic blood flow and late FDG PET/CT images in a 66-year-old man. (a–c) Axial fused PET/CT sequential blood flow images show preferential arterial supply to HCC (arrow) versus background liver. For HCC and background liver, TTPs were 13.8 and 58.1 seconds, respectively; HPIs were 1.0 and 0.38, respectively; and PIs were 0.42 and 0.24, respectively. Arrowhead = aorta. Late PET/CT: axial (d) contrast-enhanced CT, (e) fused PET/CT, and (f) PET images at the anatomic level of the 7.9-cm HCC show increased FDG uptake in HCC versus that in liver (SUV<sub>max</sub>: 6.5 vs 4.1).

There was very good absolute agreement between the three independent observers for TTP (intraclass correlation coefficient, 0.93; 95% confidence interval: 0.90, 0.96) and good absolute agreement for HPI (intraclass correlation coefficient, 0.72; 95% confidence interval: 0.57, 0.83) and PI (intraclass correlation coefficient, 0.75; 95% confidence interval: 0.66, 0.83).

### Discussion

FDG PET/CT can be used to assess tumor glucose metabolism by means of standardized uptake value and is widely used in clinical oncology. To the best of our knowledge, an estimate of tumor blood flow with PET/CT by using first-pass delivery of FDG has been largely unexplored. Mullani et al (15) compared tumor blood flow by using oxygen 15 water with first-pass delivery of FDG in tumors and showed that an estimate of tumor blood flow can be obtained with PET FDG first-pass images. They pointed out that the early first-pass images of FDG could potentially include both free and trapped FDG, which may lead to an overestimation of perfusion. However, understanding this limitation,
first-pass delivery of FDG may have potential use as a blood flow index in HCC. Relative to dynamic contrast-enhanced CT, there are some potential advantages in measuring blood flow estimates with first-pass delivery of FDG in HCC. FDG PET/CT has a larger z-axis than dynamic contrast-enhanced CT and, with no additional radiation dose, it offers the possibility to concurrently measure metabolic activity.

Our results show a significant difference in blood flow parameters between HCC and background liver. Several studies (2,3,5,7–9) have demonstrated similar observations with dynamic contrast-enhanced CT perfusion. The values for TTP and HPI that we obtained are similar to those reported by Ippolito et al (2) for dynamic contrast-enhanced CT in 35 patients. HPI represents the percentage of arterial supply of total blood liver flow and was significantly higher in HCC compared with background liver. These observations confirm that the hepatic artery preferentially supplies HCC tumors and suggest that FDG blood flow parameters might be a possible estimate of vascularity in HCCs.

Our findings demonstrate a significant difference in HPI between HCC lesions with and those without angioinvasion. We have also noted similar blood flow estimates in uninvolved liver in patients with and those without angioinvasion. These findings are in contrast to those reported by Sahani et al (9), who reported no significant difference in CT perfusion parameters in HCC between patients with and those without angioinvasion. They also noted higher perfusion values in uninvolved liver in patients with angioinvasion. This discrepancy could be related to differences in the study population, since they studied large tumors (mean size, 9.1 cm ± 3.8) with a limited CT scan thickness of 2 cm. Furthermore, our findings are consistent with the common belief that HCC lesions in patients with angioinvasion overexpress stimulators of angiogenesis, such as vascular endothelial growth factor C, thus leading to increased tumor vascularity (24).

TTP and HPI demonstrated significantly better performance than did SUV_{max} for being used to discriminate between HCC and background liver tissue. SUV_{max} measurements were similar in HCC patients with and those without angioinvasion. Therefore, FDG blood flow measurements, as opposed to SUV_{max}, might be useful in characterizing tumor angioinvasion in HCC.

Studies on the relationship between metabolism of tumors and their blood flow have shown variable results. Miles et al (25) studied tumor blood flow with dynamic contrast-enhanced CT and
glucose metabolism with FDG PET in 18 patients with non–small cell lung cancer. They found that blood flow–metabolic relationships are not consistent and are dependent on the tumor size and stage. Veit-Haibach et al (7) used an integrated CT–liver perfusion in a routine FDG PET/CT study to evaluate the relationship of blood flow with dynamic contrast-enhanced CT and metabolism with FDG in 46 patients with a number of different liver tumors (only four primary liver cancers). They found moderate but significant correlation (r = −0.40, P < .006) between mean transit time and SUV\textsubscript{max}.

In our study, there was no clear association between FDG blood flow parameters and SUV\textsubscript{max} within HCCs (HPI, P = .50; PI, P = .76; TTP, P = .91). These findings suggest that in HCC, an extremely heterogeneous malignancy, there are singular sources of cellular energy with an inconsistent association between perfusion and metabolism in HCC tumors.

Our study had a number of limitations. The patient population was small. We used a simple one-compartment flow model, with the intrinsic limitations described by Mullan et al (15), to obtain an estimate of the blood flow, recognizing that it might be an overestimate. Also, we cannot exclude partial volume effects leading to an underestimation of the activity in VOI sampling. However, most of the tumors imaged in this study were larger than 2 cm in diameter, and hence, no partial volume corrections were applied to the tumor data (15). Furthermore, a good absolute agreement was found between three independent operators, and the VOIs were meticulously adjusted to encompass the maximum available size of the lesion.

In conclusion, concurrent assessment of early dynamic blood flow and SUV\textsubscript{max} by using FDG PET/CT as one-stop shopping for estimating blood flow and metabolism may help discriminate and characterize HCC tumors.

**Disclosures of Potential Conflicts of Interest:**
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