Imaging of hepatic hypervascular tumors & clinical implications
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Chapter 7

Diagnostic accuracy of 18F-methyl-choline PET/CT for intra- & extrahepatic hepatocellular carcinoma
OBJECTIVE
Diagnosis of hepatocellular carcinoma (HCC) primarily involves imaging. The aim of this study was to assess the sensitivity and specificity of $^{18}$F-fluorocholine ($^{18}$F-FCH) PET for detection of HCC and evaluation of extent of disease.

SUBJECTS AND METHODS
Patients with HCC $>$1cm were included between 2009 and July 2011, follow-up closed February 2013. Diagnosis was based on AASLD criteria and all patients underwent $^{18}$F-FCH PET/CT-baseline prior to treatment, 6 underwent a second PET/CT post-treatment, and 1 patient a third during follow-up. Whole-body PET and low dose CT imaging were performed 15 minutes after $^{18}$F-FCH injection. Evaluation of imaging was done with standardized uptake value (SUV) ratios: SUVmax of the lesion divided by the SUVmean of surrounding tissue. Statistical analyses included descriptive analyses, ROC curve, McNemar test, and Kaplan Meier at 5% level of significance.

RESULTS
Twenty-nine patients revealed 53 intrahepatic lesions. In 48/53 lesions $^{18}$F-FCH PET was positive (SUV-ratio 1.95 ± 0.66; sensitivity 88%, specificity 100%). PET/CT showed uptake in 18 extrahepatic lesions and no uptake in 3 lesions affirmed non-HCC lesions, all lesions were confirmed with additional investigation (accuracy 100%). In 17/29 patients additional lesions were found on PET/CT imaging, with implications for treatment in 15 patients. Post-treatment PET/CT showed identical results compared to standard treatment evaluation.

CONCLUSION
This study shows additional value of $^{18}$F-FCH PET/CT for patients with HCC. The $^{18}$F-FCH PET/CT has implications for staging, management and treatment evaluation because of accurate assessment of extrahepatic disease.
sensitivity of 88% compared to FDG with 68% and was found to be useful for detection and follow-up of patients with HCC. In a recent study by Cheung et al. [18] the authors strongly suggest the use of dual-tracer PET/CT (FDG and tC-Acetate) in staging liver transplant patients as this modality has a higher sensitivity and specificity than contrast enhanced CT alone. Bone scintigraphy is and is only advised as pre-operative staging prior to liver transplantation [6] and no routine bone scan is necessary to detect asymptomatic bone metastases in patients with resectable HCC [19]. Some data is available on cases in previously published studies and uptake of choline tracer in HCC bone metastases [15; 20]. Early detection of (extrahepatic) HCC is of clinical importance [21; 22]. The \(^{18}\)F-FCH PET/CT is a promising additional diagnostic tool which might be useful in the diagnostic work-up of HCC, including assessment of metastatic disease and follow-up to assess treatment effectiveness, recurrence and disease progression.

‘The aims of this study are [1] to assess the sensitivity and specificity of the \(^{18}\)F-FCH PET/CT for detection of intrahepatic and metastatic HCC; [2] to determine the role of \(^{18}\)F-FCH PET/CT in patient management and to determine if \(^{18}\)F-FCH PET/CT accurately evaluates tumor response to treatment.’

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**Figure 1**

**Barcelona Clinic Liver Cancer (BCLC) staging classification [39]: Strategies are altered according to treatment effectiveness and side effects.**

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**Figure 2**

Choline enters the cell by means of facilitated diffusion or via transporters. In the mitochondria of the hepatocyte the CDP-pathway takes place (top). Another pathway of choline metabolism is its oxidation into betaine which can clear homocysteine from the cell, or can act as an osmolyte to maintain cellular homeostasis [4]. Furthermore, not only the CDP-pathway can produce phosphatidyl choline, also the methylation-pathway in which S-Adenosylmethionine and phosphatidyl ethanolamine is used, can produce this compound of the cell membrane. The enzymes catalyzing the processes are in italic.
This study is a prospective, single center, investigator driven study for diagnostic accuracy. The study was approved by the local medical ethics committee and written informed consent was obtained from all patients. Patients with suspicion of HCC were presented at multidisciplinary meetings and screened for potential inclusion for the study. Patients were eligible if primary or recurrent intrahepatic HCC larger than 2 cm was present and the patients were 18 years of age or older. Patient inclusion depended on availability of the \(^{18}\text{F}-\text{FCH}\) tracer in regard with the fast-track treatment plan, on the mobility of the patient and his or her proximity to the hospital (over 30 minutes of travelling time were considered unethical for the severely ill patient). Only if PET imaging could be combined with other necessary investigations were these patients asked to participate in the study. After patient inclusion laboratory tests were assessed for alfa-fetoprotein and liver function tests (AST normal <40U/L; ALT normal <45U/L; AP normal <120U/L; yGT normal <60U/L). History of hepatitis, Gau- ther’s disease, haemochromatosis and other pre-existing hepatic conditions were noted.

Thirty non-consecutive patients, median age 65 (range 18 – 84 years) were included between 2008 and July 2011, follow-up closed February 2014. Table 1 summarizes patient characteristics. In 3 patients the lesion(s) were incidentally found on imaging performed for general check-up or other unrelated indications. In 12 patients the lesion(s) were found during follow-up of high-risk underlying parenchymal disease, and in 15 patients the presenting symptoms were consistent with HCC on imaging.

\(^{18}\text{F}-\text{FCH}\) PET/CT

\(^{18}\text{F}-\text{FCH}\) has a half-life of 110 minutes, the kidney is the dose-critical organ, and \(^{18}\text{F}-\text{FCH}\) reaches a steady distribution in the liver within 10 minutes [23]. Via the choline transporter(s) [24] or facilitated diffusion choline is transported into the cell. Three major metabolic pathways of choline are known: choline deamination, homochromatosis and other pre-existing hepatic conditions were noted.

Thirteen non-consecutive patients, median age 65 (range 18 – 84 years) were included between 2008 and July 2011, follow-up closed February 2014. Table 1 summarizes patient characteristics. In 3 patients the lesion(s) were incidentally found on imaging performed for general check-up or other unrelated indications. In 12 patients the lesion(s) were found during follow-up of high-risk underlying parenchymal disease, and in 15 patients the presenting symptoms were consistent with HCC on imaging.

Diagnosis, staging and treatment selection was made according to the AASLD criteria [5; 6; 29]. The primary diagnosis was based on one or two imaging modalities consistent with HCC: imaging with Gadolinium contrast or with additional hepatobiliary contrast EOB-DTPA (Primovist®, Bayer, Germany) were used to confirm diagnosis. The MR was performed with a 1.5 Tesla MRI scanner (Avanto, Siemens Medical System, Erlangen). MR series consisted of conventional in- and opposed-phase imaging, coronal T2 fatsat, diffusion weighted echo planar imaging, T2 HASTE, pre- and post- contrast T1 fatsat. Hepatobiliary phase images, if used, were made at 20 minutes post-injection. The images were evaluated on characteristic morphology of the lesion. Hyperintensity on the arterial T1w series with subsequent loss of signal intensity (wash-out) on the portal T1w series was diagnostic for HCC. As secondary imaging modality multiphase CT imaging was used. CT images consisted of pre-contrast, arterial, portal/venous, and late series. Characteristics of HCC included hyperintensity on the arterial phase and subsequent wash-out during portal or late phase of imaging. Whenever histopathology was obtained this was used as final standard of reference. The histological specimen was obtained by biopsy or resection. In 1 patient (18 years old) the 4 hepatic lesions were primarily diagnosed as HCC and after resection diagnosed as hepatic blastomas [31]. The \(^{18}\text{F}-\text{FCH}\) PET/CT imaging data from this patient were excluded from analyses.

Staging and extent of the disease were assessed with standard of care using CT thorax and abdomen [5]. Size, location, and additional hepatic lesions were noted. Abdominal lymph nodes and lung nodules larger than 1 cm in short axis were considered enlarged in patients without underlying inflammatory hepatic disease, and larger than 2 cm in patients with inflammatory hepatic disease. No radiological screening for bone lesions was performed as part of standard of care [5]. Results of \(^{18}\text{F}-\text{FCH}\) PET/CT imaging were always checked on primary imaging, additional investigation, or close follow-up, especially when treatment might be altered based on the results. See flowchart of the study (figure 3).

Methods

PET and PET/CT imaging were used for diagnostic accuracy. The study was approved by the local medical ethics committee and written informed consent was obtained from all patients. Patients with suspicion of HCC were presented at multidisciplinary meetings and screened for potential inclusion for the study. Patients were eligible if primary or recurrent intrahepatic HCC larger than 2 cm was present and the patients were 18 years of age or older. Patient inclusion depended on availability of the \(^{18}\text{F}-\text{FCH}\) tracer in regard with the fast-track treatment plan, on the mobility of the patient and his or her proximity to the hospital (over 30 minutes of travelling time were considered unethical for the severely ill patient). Only if PET imaging could be combined with other necessary investigations were these patients asked to participate in the study. After patient inclusion laboratory tests were assessed for alfa-fetoprotein and liver function tests (AST normal <40U/L; ALT normal <45U/L; AP normal <120U/L; yGT normal <60U/L). History of hepatitis, Gau- ther’s disease, haemochromatosis and other pre-existing hepatic conditions were noted.

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Results

Statistical analysis was performed using SPSS 20 (IBM Corporation, Chicago, IL). Descriptive statistics were used to assess study population. A Kaplan Meier estimator plot of cumulative survival was made. An ROC curve was performed to assess the cut-off for the SUV-ratio. Mann Whitney test was used to assess continuous factors. Pearson’s Chi square and Fisher’s exact correlation tests were used for categorical data analyses. Sensitivity and specificity were based on the McNemar test. The positive and negative predictive value of the test was calculated and the confidence interval of the proportions was based on the Wilson procedure without correction for continuity [30]. All statistical tests were evaluated at the 5% level of significance.

Diagnosis in the 29 patients with HCC was confirmed with histopathology in 17 patients (14 resection specimen, 3 biopsy specimens). In 12 patients diagnosis was based on imaging. Curative treatment was performed in 13 patients with resection and 1 patient with RFA. Palliative care was performed in 15 patients: 6 with TACE and 9 with Sorafenib (with or without local treatment with RFA and/or TACE). One patient died of other causes and was excluded from survival analyses. Eleven patients died due to spread of the disease. Seventeen patients were alive in February 2013 when follow-up closed. The cumulative survival is shown in figure 4.

In all, 29 patients with 81 lesions on baseline 18F-FCH PET/CT were evaluated: 53 intrahepatic HCC and 28 extrahepatic lesions. Results are shown in the flowchart and online supplement Table I. The ROC of SUV-ratio on baseline PET/CT imaging was performed, with Figure 5, resulting in a SUV-ratio cut-off of 1.12 (sensitivity 0.912; specificity 1.0).

35/53 (66%) intrahepatic lesions were typical HCC on standard imaging and 18/53 (34%) lesions were missed, atypical, or non-HCC on standard imaging (online supplement Table I). The additional findings were found correct on imaging, additional investigation, or by means of follow-up (online supplement Table I). Extrahepatic lesions were found on standard imaging in 4/28 (14%) lesions. 18/28 (64%) lesions were missed, atypical, or non-HCC on standard imaging and found correct on standard imaging, additional investigation, or by means of follow-up (online supplement Table I). The remaining 6 lesions (4 patients) did not have reference on standard imaging or additional investigation; however, if lesions were found positive this would not have changed treatment in 3/4 patients, therefore no additional investigation needed to be performed. In 1/4 patient there was no thorax imaging to corroborate additional lung and lymph node lesions detected on 18F-FCH PET/CT. This might have changed treatment strategy from local therapy (TACE) to Sorafenib. Future follow-up will have
to determine the extent of disease. These 6 lesions were excluded from 18F-FCH PET/CT SUV ratio evaluation for extrahepatic disease. AFP was not significant for increased SUV ratio of SUVmax of the lesion (0.941 and P = 0.825). AFP was significant for overall survival: patients with AFP>30 had worse survival compared to patients with normal AFP levels (P =0.003).

With intra- and extrahepatic lesions combined, a total of 36 additional lesions on 18F-FCH PET/CT imaging were found in 17/29 (59%) patients. This led to change in 15/29 (52%) patients (flowchart). In 1/30 patient the intrahepatic lesion was photopenic on 18F-FCH PET/CT, but typical HCC on standard imaging. Final histopathology of the resection specimen showed moderately differentiated HCC.

Baseline 18F-FCH PET/CT imaging for intrahepatic HCC showed a sensitivity of 88% (CI 76-94%; Table 2), with median SUV ratio of 1.95 ± 0.66 (range 1.14 - 4.24) for positive lesions. Baseline 18F-FCH PET/CT imaging for extrahepatic lesions showed a sensitivity of 100% (CI 82-100%); with median SUV ratio of 4.41 ± 3.62 (2.48-13.80) for positive lesions (Table 2).

**TREATMENT EVALUATION & FOLLOW-UP**

In 6 patients treatment evaluation 18F-FCH PET/CT was performed. Results are shown in the Flowchart and online supplement Table II. In 4/6 patients evaluation of treatment was possible with 18F-FCH PET/CT and showed identical results as standard imaging: No recurrence in one patient and progressive disease in 3 patients. Progressive disease presented as increase of SUV ratio (Supplement Table II, indicated under PET/CT with †) and/or presence of new (extrahepatic) lesions on 18F-FCH PET/CT (figure 3C). Additional findings were made with the 18F-FCH PET/CT: In 1/6 treatment evaluation 18F-FCH PET/CT showed extrahepatic disease (lung and adrenal gland), while standard imaging of the patient showed no new disease or recurrence as the findings were outside the imaging field. Finally, one patient showed progressive disease on 18F-FCH PET/CT imaging and standard imaging; by increased size and number of lesions. However, treatment evaluation and additional follow-up 18F-FCH PET/CT showed decrease in SUV ratio.

**TABLE 2 — Sensitivity and specificity of baseline FCH PET/CT**

<table>
<thead>
<tr>
<th></th>
<th>FCH PET/CT intrahepatic lesions *</th>
<th>FCH PET/CT extrahepatic lesions **</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HCC</td>
<td>No HCC</td>
</tr>
<tr>
<td>FCH positive</td>
<td>44</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>PPV 1.00</td>
<td>NPV 0.14%</td>
</tr>
<tr>
<td>FCH negative</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Sensitivity 0.88</td>
<td>Specificity 1.0</td>
</tr>
<tr>
<td></td>
<td>Accuracy 0.88</td>
<td></td>
</tr>
</tbody>
</table>

* 1 intrahepatic lesions were excluded from analyses because no reference for diagnosis was available.
** 7 extrahepatic lesions were excluded from analyses because no reference for diagnosis was available.

PPV = positive predictive value
NPV = negative predictive value (NPV is calculated for HCC lesions, with only one non-HCC lesion. This NPV can therefore not be used to conclude on non-HCC lesions which are assumed negative using 18F-FCH PET/CT.)
Cumulative survival curve of patients in this study treated with curative and palliative care. Median 2-year survival for patients treated with curative intent was 75% compared to 40% for patients treated with palliative care.

ROC curve. The cut-off with highest sensitivity and specificity was an SUV ratio of 1.12.

A: Shows a hyperintense hepatic HCC lesion in segment 2/3 on coronal, sagittal and transverse $^{18}$F-FCH PET/CT images (center of the orange cross).

B: Shows a hyperintense peritoneal lesion compared to surrounding mesenterium, suspect for HCC metastasis. Standard imaging missed this lesion, and additional biopsy proved HCC. (From left to right: coronal, sagital and transverse $^{18}$F-FCH PET/CT images).

C: Shows a hyperintense area in the left femur head of a patient with HCC (center of the orange cross). The patient developed local pain in that area, which was successfully treated with radiotherapy.
### TABLE I — Additional value of FCH PET/CT imaging per patient

<table>
<thead>
<tr>
<th>Additional findings on FCH PET/CT to primary imaging (42/29)</th>
<th>Treatment</th>
<th>Standard PET/CT</th>
<th>PET/CT baseline</th>
<th>Treatment Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>NA</td>
<td>Additional investigation not applicable;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RP</td>
<td>+ Addtional investigation: biopsy HCC;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RP</td>
<td>- Additional investigation: biopsy no HCC;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RI</td>
<td>+ Additional investigation: imaging HCC;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RI</td>
<td>- Additional investigation: imaging no HCC;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RH</td>
<td>+ Additional investigation: histology HCC;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RH</td>
<td>- Additional investigation: follow-up no HCC (no typical HCC, no increase in size or number);</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>RF</td>
<td>+ Additional investigation: follow-up HCC (typical HCC, or increase in size and number);</td>
<td></td>
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<tr>
<td>RF</td>
<td>- Additional investigation: follow-up no HCC (no typical HCC, no increase in size or number);</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>* RF FALSE negative HCC lesion on FCH PET/CT</td>
<td></td>
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</tbody>
</table>

| TABLE II — Post-treatment and follow-up FCH PET/CT imaging per patient (6 patients) |
|-------------------------------------|-----------------|-----------------|-----------------|
| Treatment & Lesions | Standard PET/CT baseline | Standard PET/CT post-treatment | Conclusion |
| ID_05 TACE | Hepatic lesion | No | Yes | Yes | Yes | Yes | Progressive disease |
| ID_06 Sorafenib | Hepatic lesions | No | Yes | Yes | Yes | Yes | Progressive disease |
| ID_07 Resection | Hepatic lesion | No | Yes | No | No | Yes | Progressive disease |
| ID_12 Resection | Hepatic lesion | No | Yes | Yes | No | Yes | Progressive disease |
| ID_28 TACE & Sorafenib | Hepatic lesions | No | Yes | Yes | Yes | Yes | Progressive disease |

**FCH PET**

**TACE**

**Sorafenib**

**Resection**

**Screening**

**FNA**

**Histology**

**PET/CT**

**Histopathology, Imaging**

**Clinical progressive disease with elevated AFP.**

**Additional investigation proved HCC.**

**HistoPathology, Imaging**

**Suppl Table I**

**Suppl Table II**

**Increase in size, number, or SUV ratio.**

**Stable disease; stable SUV ratio.**

**Decrease in size, number, or SUV ratio.**

**R** Standard imaging in retrospect HCC

* Clinical progressive disease with elevated AFP.

+ Additional investigation proved HCC.

(histoPathology, Imaging)
DISCUSSION

This study showed that the 18F-FCH PET/CT can depict intrahepatic HCC with 88% accuracy. Second is the detection of extrhepatic disease on 18F-FCH PET/CT which is not visible on standard imaging. Finally, the results suggest the option for a potential novel way to evaluate the biological response to treatment.

In case HCC shows no extrahepatic spread of the disease, ablative local regional treatment is possible. However, extrhepatic metastases are not uncommon and treatment of these patients is restricted to palliative systemic treatment with poor prognosis. Therefore, accurate pre-treatment staging of HCC is crucial. Our study shows that in over half of the included patients additional lesions were found on 18F-FCH PET/CT imaging, with treatment implications in 50% of patients. The additional value of the 18F-FCH PET/CT lies in accurate whole body assessment in regards to extent of disease which has direct implications for staging and treatment decisions. Sensitivity for the 18F-FCH PET/CT for hepatic HCC was 89% and for extrhepatic HCC sensitivity was 100%.

In this study 6 patients underwent post-treatment 18F-FCH PET/CT imaging and based on 18F-FCH PET/CT treatment evaluation was accurate compared to standard imaging. Local effects after TACE, RFA, or Sorafenib including necrosis in the lesion were shown as decrease in SUVratio as an indication of altered tumor metabolism. Also, recurrence of HCC after RFA and TACE or detection of new (extrahepatic) lesions shows on 18F-FCH PET/CT and could be used for follow-up of HCC patients. Song M et al. used SUVratio (SUVmax / S UmVmean liver) as method to evaluate HCC lesions with 18F-FDG PET/CT [34]. The authors concluded that with this method tumor progression can be predicted. The use of SUVratio is especially useful with underlying parenchymal disease like a cirrhotic liver, which affects the tracers’ uptake. The patient is his or her own control as the surrounding liver is used as reference and in this way the SUVratio better represents tumor metabolism in light of underlying disease. Hypothesis generating 18F-FCH PET/CT imaging could be used in the future for modified RECIST for HCC [35].

One patient, who underwent a total of three 18F-FCH PET/CT studies, showed results that differed from the expected result: The first two 18F-FCH PET/CT studies showed positive hepatic disease with extrahepatic spread with progression both in size and in SUVratio. The final 18F-FCH PET/CT study, after several months of Sorafenib use, showed decrease in SUVratio of the hepatic lesion (extrahepatic disease positive). The size of hepatic involvement did increase, as well as serum AFP, and the number of extrhepatic lesions. This decrease in SUVratio could be explained by dedifferentiation of the hepatic lesion during the course of the disease, resulting in no uptake of 18F-FCH. Studies show that 18F-FCH is most sensitive in well- and moderately differentiated HCC, and less in poorly differentiated hepatic HCC lesions [36].

When patients present with typical HCC and a history of another malignancy, lung lesions for example are difficult to characterize on imaging as one or the other. 18F-FCH PET/CT imaging in this study was sensitive in differentiating extrahepatic HCC lesions from renal cell carcinoma and urothelial carcinoma. A Study by Talbot et al. suggests that 18F-FCH PET/CT imaging does not show uptake in colorectal liver metastases [36]. However, further study will have to determine whether colorectal lung metastases do show up on 18F-FCH PET/CT imaging and could differentiate between both entities.

The SUVratio might also have prognostic value as was shown by Morris et al for breast cancer [37] and by Lee et al for HCC [38].

MR imaging is the most sensitive imaging modality for (small) HCC lesions as it has the potential to combine dynamic evaluation of the lesion, and in and out phase, and diffusion images. The latter is useful for detection of very small lesions (<2cm) and this method increases detection of possible HCC lesions [9]. The additional value of the 18F-FCH-PET/CT is therefore not intrahepatic, but extrhepatic: to evaluate metastatic disease.

This study has some limitations. The inclusion of patients was not consecutive due to logistics and evaluation of 18F-FCH PET/CT imaging was performed by one experienced nuclear medicine physician. Logistics of 18F-FCH PET/CT imaging might impair its use as synthesis of the 18F-FCH tracer and the possibility of PET/CT imaging are not available in every medical center. Finally, PET/CT imaging is costly when implemented in pre-treatment work-up for patients with HCC. However, accurate pre-treatment staging will prevent unnecessary interventions including expensive surgery, TACE and experimental local treatment. This study has a limited number of patients and therefore further investigation in a larger cohort is warranted to confirm our findings and to determine in more detail at what timepoint the 18F-FCH PET/CT is most valuable for the individual patient. A study with prospective design, including consecutive patients with HCC confirmed on imaging is preferable. Nuclear medicine physician(s) should be blinded for outcomes of standard imaging and abdominal radiologist(s) evaluating standard imaging should be blinded for outcome of PET/CT imaging. If possible results should be discussed in MDT to discuss outcomes of both imaging modalities to maximize treatment options and evaluation.

CONCLUSIONS

This study shows additional value of 18F-FCH PET/CT to conventional imaging in assessment of extent of intra- and extrhepatic disease in patients with HCC. 18F-FCH PET/CT has additional value in accurate assessment of extent of hepatic involvement. The SUVratio might also have prognostic value as was shown by Morris et al for breast cancer [37] and by Lee et al for HCC [38].

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