Underestimated Role of ^{18}F-FDG PET for HCC Evaluation and Promise of ^{18}F-FDG PET/MR Imaging in This Setting

TO THE EDITOR: We read with great interest the recent article by Cheung et al. on the utility of ^{11}C-acetate/^{18}F-FDG PET/CT for clinical staging and appropriate selection of patients with hepatocellular carcinoma (HCC) for liver transplantation based on the Milan criteria (*1*). The authors of this study were able to show the strength of PET/CT over dynamic contrast-enhanced CT to detect HCCs (particularly small ones measuring 1–2 cm) and to differentiate between benign and malignant hepatic lesions in the cirrhotic liver (*1*). However, Cheung et al. (*1*) were unable to show a complementary role for both tracers (i.e., ^{11}C-acetate and ^{18}F-FDG) in HCC. Apparently, the sensitivity of ^{11}C-acetate PET alone for TNM staging and selection of patients for liver transplantation based on the Milan criteria did not change after ^{18}F-FDG PET was added to the diagnostic algorithm (*1*). However, we believe the capabilities of ^{18}F-FDG PET were not fully exploited in this study. In this communication, we would like to emphasize the unrecognized value of ^{18}F-FDG PET for the evaluation of HCC and share our view on the promise of ^{18}F-FDG PET/MR imaging in this setting.

First, ^{18}F-FDG PET allows not only for tumor detection but also for characterization of cancer biology; that is, aggressive cancers tend to have higher levels of ^{18}F-FDG uptake whereas less aggressive cancers tend to have lower levels of ^{18}F-FDG uptake (*2*). This dimension of diagnostic information provided by ^{18}F-FDG PET is important because it can be used to improve determination of disease prognosis and treatment planning (*2*). A study published in *JNM* in 1995 already showed that ^{18}F-FDG uptake in HCC correlates with hexokinase/glucose-6-phosphatase activity and differentiation grade (*3*). These observations have been confirmed by a more recent study published in *JNM* in 2008 reporting that well-differentiated HCCs have a lower mean ^{18}F-FDG maximum standardized uptake value (SUV_{max}) than poorly differentiated HCCs (5.10 vs. 7.66), in contrast to nonsignificant differences in ^{11}C-acetate SUV_{max} (5.27 vs. 4.94). In addition, patients with ^{18}F-FDG–positive lesions were reported to have a significantly shorter survival than patients with ^{18}F-FDG–negative lesions ($P < 0.05$) (*4*). In the study by Cheung et al. (*1*), ^{18}F-FDG PET was used only for tumor detection rather than tumor detection and characterization. It would be of great interest to incorporate the ^{18}F-FDG PET information on HCC biology into a predictive model (to select patients for liver-directed interventions) that goes beyond the structural imaging–based Milan criteria (*5*).

Second, it is important to realize that the absolute accumulation of ^{18}F-FDG in a cell is a dynamic process, with ^{18}F-FDG release from the cell depending on the ratio of hexokinase to glucose-6-phosphatase. The dynamics of ^{18}F-FDG accumulation in HCCs, benign liver lesions, and background tissue go beyond 60 min after ^{18}F-FDG administration (the conventional time point at which ^{18}F-FDG PET is routinely performed, as was also done in the study by Cheung et al. (*1*)) (*6–8*). Additional PET imaging at a later time point (i.e., dual-time-point or delayed imaging) may be advantageous because ^{18}F-FDG accumulation in benign liver lesions and background tissue may decrease (*7,8*) whereas ^{18}F-FDG accumulation in HCCs may further increase (*6*). This, in turn, may improve the detection of both HCCs and metastases. Dual-time-point ^{18}F-FDG PET may also provide additional prognostic information, because more aggressive cancers tend to exhibit increasing ^{18}F-FDG levels over time, in contrast to less aggressive ones (*8,9*). For example, in a study published in *JNM* in 2010, it was reported that lung adenocarcinoma patients with an increase in ^{18}F-FDG SUV_{max} of at least 25% between 1 and 1.5 h after injection had a median survival of 15 mo, compared with 39 mo for those with less than a 25% ^{18}F-FDG SUV_{max} increase ($P < 0.001$) (*9*). Certainly, more work needs to be done to prove the value of dual-time-point ^{18}F-FDG PET in HCC, but given the potential of this technique (*7–9*), it would be inappropriate to disregard its value in HCC at this moment.

Third, Cheung et al. (*1*) compared ^{11}C-acetate/^{18}F-FDG PET with dynamic contrast-enhanced CT. However, dynamic contrast-enhanced CT has been shown to be inferior to dynamic contrast-enhanced MR imaging with hepatobiliary contrast agents in the cirrhotic liver, especially for the detection of lesions measuring 1–2 cm (*10*). The sensitivity of MR imaging in this setting was 85%, versus 65% for CT ($P < 0.01$), whereas specificity (94% and 89%, respectively) was comparable. We envision an important role for combined ^{18}F-FDG PET/MR imaging for the evaluation of patients with HCC, given the utility of dynamic contrast-enhanced MR imaging with hepatobiliary contrast agents for HCC detection (this technique is already used on a routine clinical basis), the aforementioned unexploited new dimensions of ^{18}F-FDG PET, and the rise of integrated PET/MR imaging systems. Although the number of clinical PET/MR imaging systems is currently still limited, this technique is rapidly spreading. Thus, it can be expected that the availability of PET/MR imaging to HCC patients will soon increase. At that time, ^{18}F-FDG PET/MR imaging may well prove to be a more clinically feasible method than a diagnostic approach that uses ^{11}C-acetate PET, requiring an on-site cyclotron.

In conclusion, we believe that ^{18}F-FDG PET has an important role in the evaluation of HCC, if the information provided in an ^{18}F-FDG PET scan is correctly interpreted (^{18}F-FDG uptake reflects HCC biology and should not be used merely for cancer detection) and the technique is optimized (dual-time-point imaging has the potential to improve detection of both primary and metastatic HCC and can provide additional prognostic information). Finally, given the fact that advanced but clinically mature MR imaging techniques are superior to CT for HCC detection, we foresee an important role for ^{18}F-FDG PET/MR imaging for the evaluation of HCC patients.

COPYRIGHT © 2013 by the Society of Nuclear Medicine and Molecular Imaging, Inc.

REFERENCES

1. Cheung TT, Ho CL, Lo CM, et al. ^{11}C-acetate and ^{18}F-FDG PET/CT for clinical staging and selection of patients with hepatocellular carcinoma for liver transplantation on the basis of Milan criteria: surgeon's perspective. *J Nucl Med.* 2013;54:192–200.
2. Kwee TC, Basu S, Saboury B, et al. A new dimension of FDG-PET interpretation: assessment of tumor biology. *Eur J Nucl Med Mol Imaging.* 2011;38:1158–1170.

3. Torizuka T, Tamaki N, Inokuma T, et al. In vivo assessment of glucose metabolism in hepatocellular carcinoma with FDG-PET. *J Nucl Med.* 1995;36:1811–1817.
4. Park JW, Kim JH, Kim SK, et al. A prospective evaluation of ^{18}F-FDG and ^{11}C-acetate PET/CT for detection of primary and metastatic hepatocellular carcinoma. *J Nucl Med.* 2008;49:1912–1921.
5. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med.* 1996;334:693–699.
6. Lin WY, Tsai SC, Hung GU. Value of delayed ^{18}F-FDG-PET imaging in the detection of hepatocellular carcinoma. *Nucl Med Commun.* 2005;26:315–321.
7. Cheng G, Alavi A, Lim E, et al. Dynamic changes of FDG uptake and clearance in normal tissues. *Mol Imaging Biol.* October 23, 2012 [Epub ahead of print].
8. Cheng G, Torigian DA, Zhuang H, et al. When should we recommend use of dual time-point and delayed time-point imaging techniques in FDG PET? *Eur J Nucl Med Mol Imaging.* 2013;40:779–787.
9. Houseni M, Chamroonrat W, Zhuang J, et al. Prognostic implication of dual-phase PET in adenocarcinoma of the lung. *J Nucl Med.* 2010;51:535–542.
10. Di Martino M, De Filippis G, De Santis A, et al. Hepatocellular carcinoma in cirrhotic patients: prospective comparison of US, CT and MR imaging. *Eur Radiol.* 2013;23:887–896.

Marnix G.E.H. Lam*
Thomas C. Kwee
Sandip Basu
Abass Alavi
**University Medical Center Utrecht*
3584 CX Utrecht, The Netherlands
E-mail: m.lam@umcutrecht.nl

Published online Jun. 18, 2013.
DOI: 10.2967/jnumed.113.123273

REPLY: We thank Lam and his colleagues for their interest in and comments concerning our study (*1*) and would like to reply with the following remarks.

Referring to the prior studies reported by Ho et al. (*2,3*), our affiliated research group for this study, the value of ^{18}F-FDG has never been underestimated. ^{11}C-acetate and ^{18}F-FDG are complementary tracers in the role of a functional and biochemical probe for detecting both primary and secondary hepatocellular carcinoma (HCC) through the degree of tumor cell differentiation (*2,3*). In the "Discussion" section of our paper, we explicitly mentioned that "^{18}F-FDG is needed for a complete assessment of all of the Milan criteria (metastasis). Moreover, ^{18}F-FDG, as a marker of dedifferentiated HCC tumor pathology, has been shown by other researchers to be a predictor of tumor recurrence and a less favorable outcome after transplantation." ^{18}F-FDG has been documented by numerous data in the literature to serve as an indicator of aggressiveness for a variety of cancer types. In fact, we have also published on the role of ^{18}F-FDG in the detection of poorly differentiated HCC and microvascular invasion for patients receiving a liver transplant. Patients with HCC tumors avid for ^{18}F-FDG have significantly less favorable overall survival and an increased chance of HCC recurrence (*4*).

The quoted standardized uptake values of ^{18}F-FDG in well-differentiated (5.10) and poorly differentiated (7.66) HCC in Lam's reference were based on a heterogeneous population of mixed-HCC cases and across PET scanners of different designs. According to our experience over the past 13 y in performing dual-tracer PET studies on HCC, well-differentiated HCC is mostly nonavid or only minimally avid for ^{18}F-FDG and the ^{18}F-FDG standardized uptake value approaches that of liver (2.0–3.0). For HCC patients to be qualified as liver transplant candidates, the first condition is to meet the size and number specifications under the Milan criteria. Candidates therefore have early HCC tumors that are usually small and well differentiated and thus are mostly avid for ^{11}C-acetate instead of ^{18}F-FDG. Well-differentiated HCC cells are known to resemble normal hepatocytes morphologically and biochemically. It is not a matter of underestimating the value of ^{18}F-FDG; the tumor's own biochemical preference in the early stage is to upregulate the use of fatty acid metabolism and use ^{11}C-acetate as the source of energy instead of glycolysis. "Detection" and "characterization" are not 2 separate entities in functional imaging; the tumor's biochemistry needs to be characterized before it can be detected by the correct substrate. The fact that whether ^{18}F-FDG can predict poor prognosis is based on whether the HCC type is biochemically avid for this tracer implies that its complementary counterpart, ^{11}C-acetate, should have the potential to predict a more favorable prognostication. This biochemistry has been characterized and reported by our study on a group of HCC patients with isolated metastatic bone disease (*5*).

In addition, diagnosing HCC without performing a biopsy is not difficult for larger tumors in many of the experienced centers. The real challenge for the diagnosis of HCC is mainly the low sensitivity for the detection of tumors smaller than 2 cm. The guideline of the American Association for the Study of Liver Diseases suggests that a biopsy is needed if fewer than 2 imaging modalities show typical features of HCC (*6*). The imaging modalities suggested for small-HCC detection are contrast-enhanced ultrasound and contrast-enhanced MR imaging (*7*). However, if one or both tests are not conclusive, then the false-negative detection rate of HCC is greater than 50%. A new, more sensitive, detection method is thus required to diagnose small HCC without a biopsy. In our analysis, we found that the overall sensitivity (91.3%) of dual-tracer PET/CT for HCC patients with small HCC was significantly higher than that of contrast CT (43.5%) (*1*). These results, as we pointed out, are attributed to 2 main reasons: first, the Milan criteria preselect patients with early HCC disease, and second, these patients have background hepatic cirrhosis as the intrinsic structural disadvantage. Our study was to focus on potential liver transplant candidates, not on the general HCC population. ^{11}C-acetate is thus the biochemical probe of greater importance in this clinical setting.

Dual–time-point evaluation of HCC using both tracers was studied in detail at the institution of Ho et al. more than 10 y ago during the initial implementation of dual-tracer research on HCC. Our experience and unpublished data show that delayed imaging of a small HCC lesion initially nonavid for HCC would not have any additional value for improving its primary diagnosis in the liver. In contrast, for small extrahepatic metastatic lesions that might have shown some clonal change into greater dedifferentiated pathology, a delayed scan can sometimes increase the confidence of detection but may also lead to erroneous conclusions. The liver possesses an enzyme system with relative constituents different from other organs such as lung or bone, and different tumors often have different degrees of ^{18}F-FDG utilization whereas benign entities such as tuberculosis, some fungal infections, or loculated abscesses also have increased uptake on delayed scans and thus cannot reliably be used as absolute evidence to differentiate from metastases.

MR imaging with new contrast agents has been shown to increase the sensitivity of HCC detection (*8*) and may be an alternate imaging modality in future practice. However, from a surgeon's point of view, enhanced CT scanning can provide a higher reso-