

**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  $^{18}\text{F}$ -FDG has never been underestimated.  $^{11}\text{C}$ -acetate and  $^{18}\text{F}$ -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 " $^{18}\text{F}$ -FDG is needed for a complete assessment of all of the Milan criteria (metastasis). Moreover,  $^{18}\text{F}$ -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."  $^{18}\text{F}$ -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  $^{18}\text{F}$ -FDG in the detection of poorly differentiated HCC and microvascular invasion for patients receiving a liver transplant. Patients with HCC tumors avid for  $^{18}\text{F}$ -FDG have significantly less favorable overall survival and an increased chance of HCC recurrence (4).

The quoted standardized uptake values of  $^{18}\text{F}$ -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  $^{18}\text{F}$ -FDG and the  $^{18}\text{F}$ -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  $^{11}\text{C}$ -acetate instead of  $^{18}\text{F}$ -FDG. Well-differentiated HCC cells are known to resemble normal hepatocytes morphologically and biochemically. It is not a matter of underestimating the value of  $^{18}\text{F}$ -FDG; the tumor's own biochemical preference in the early stage is to upregulate the use of fatty acid metabolism and use  $^{11}\text{C}$ -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  $^{18}\text{F}$ -FDG can predict poor prognosis is based on whether the HCC type is biochemically avid for this tracer implies that its complementary counterpart,  $^{11}\text{C}$ -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.  $^{11}\text{C}$ -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  $^{18}\text{F}$ -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 resolution for surgically pertinent information on the anatomic relationship between the tumor and adjacent vital organ structures—information that is crucial for the planning of complicated surgical procedures. If performed at individual centers with expertise, high-quality MR imaging may have the potential to replace or equate with traditional enhanced CT scanning.

Because of the low sensitivity of  $^{18}\text{F}$ -FDG PET for the detection of small and well-differentiated HCC, we have reservations on the use of integrated PET/MR imaging in the future for the selected population of our transplant study. MR imaging is more prone to respiratory averaging effects than CT for small lesions. Its uptake-clearance curve generated from dynamic hepatobiliary contrast agents is quite dependent on the region of interest drawn around the small HCC lesions and is easily obscured or affected by the surrounding cirrhotic background. Although PET/MR imaging is still at the investigational stage, we, as surgeons, are open-minded with regard to any objective data that are ultimately proven useful for patient selection and management.

In conclusion, different imaging modalities have their own limitations and advantages. At our tertiary referral center that manages more than 300 new cases of HCC per year, we believe that

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dual-tracer PET/CT technique plays a vital supplementary role in the clinical management of our patients with HCC and cirrhosis.

## REFERENCES

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