Positron Emission Tomography With Computed Tomography as a Diagnostic and Prognostic Biomarker for Hepatocellular Carcinoma: Ready for Prime Time?

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The diagnosis and staging of hepatocellular carcinoma (HCC) largely rely on multiphasic computed tomography (CT) scans or magnetic resonance imaging (MRI). Unlike other malignancies, for which the use of [^{18}F]fluorodeoxyglucose ([^{18}F]FDG) positron emission tomography (PET) with CT is sensitive in staging and can correlate with tumor biology, it was not proven to be useful in HCC due to poor sensitivity in well-differentiated disease and had limited evidence of incremental benefit in staging.[1] However, in the last decade, there has been some evidence to support the use of PET-CT to identify patients with unfavorable risk factors, ie, microvascular invasion or a higher risk of posttransplant tumor recurrence, albeit in small retrospective cohort studies.[2]

In this issue, John et al. conducted a retrospective cohort study in which they evaluated the incremental benefit of PET-CT after initial staging with CT or MRI in patients with HCC.[3] The authors concluded that PET-CT detected additional extrahepatic metastasis in 11.9%-13.8% of patients and modification of Barcelona Clinic Liver Cancer (BCLC) staging compared with CT/MRI alone in 5.9%-18.8% of patients, therefore providing additional prognostic information and subsequent changes to clinical management in up to a fifth of patients. The degree of [^{18}F]FDG avidity was independently associated with increased risk of metastases and worse overall survival in multivariate analysis.

This study adds to the growing literature on the utility of PET-CT to improve staging and as a proxy of tumor biology in patients with HCC. Increased glucose uptake in malignant tumors is hypothesized to be a result of increased levels of glucose transporters and intracellular enzymes that promote glycolysis. Increased cellular concentration of [^{18}F]FDG in tumors represents the glycolytic activity of viable tumor cells that has been variably shown in patients with HCC.[4] In surgical specimens of patients with HCC, increased [^{18}F]FDG activity was related to aggressive tumor biology and poor overall survival, whereas well-differentiated tumors had low PET avidity.[5] In a study of patients who underwent liver transplantation

Abbreviations: [^{18}F]FDG, [^{18}F]fluorodeoxyglucose; BCLC, Barcelona Clinic Liver Cancer; CT, computed tomography; HCC, hepatocellular carcinoma; LSUVmax, liver maximum standardized uptake value; MRI, magnetic resonance imaging; PET, positron emission tomography; SUVmax, maximum standardized uptake value; TSUVmax, tumor maximum standardized uptake value.

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for HCC, those with pathologically confirmed vascular invasion on explant had significantly higher maximum standardized uptake value, (SUVmax), tumor maximum standardized uptake value (TSUVmax)/liver maximum standardized uptake value (LSUVmax) ratio, and higher TSUVmax/LSUV mean ratio on pretransplant imaging. Coincidentally, these patients also were noted to have higher serum alpha-fetoprotein levels and larger tumor size.[6] Similarly, in a South Korean multicenter study of BCLC stage 0 or A patients with HCC undergoing curative surgery, tumor [^{18}F]FDG avidity on PET-CT was highly correlated with microvascular invasion.[7] These studies highlight the potential utility of [^{18}F]FDG PET-CT as a prognostic imaging marker, in addition to its potential utility in providing more accurate staging.

In the present study, among the 148 patients with HCC of a Liver Imaging Reporting and Data System score of 5, PET-CT detected additional extrahepatic metastases in 12% of treatment-naïve patients, including 11 cases of lymph node involvement that were initially read as reactive on initial CT or MRI. Additionally, BCLC staging was modified in 6% of patients (most often migration from BCLC stages B to C) with subsequent change in clinical management in 10% of patients including changing to systemic therapy or best supportive care. Similarly, in treatment-experienced patients, the addition of PET-CT detected extrahepatic metastasis in 14% of patients and, importantly, detected posttreatment recurrence in approximately 20% of patients not detected on initial CT or MRI. Again, modification in BCLC staging was seen in 20% of patients, largely with migration from BCLC stage 0 to A. This concept of stage migration of BCLC classification and real-time change in treatment management as a result of PET-CT is an important and novel aspect of this study.

The limitations of this study include its single-center, retrospective nature, a homogenous patient population of Caucasian male veterans, and a lack of a comparator arm. There was also a selection bias where higher risk patients were recommended to undergo PET-CT. Future studies using systematic evaluation of patients with HCC with PET-CT would be required to accurately evaluate the routine utility of PET-CT in this population. In addition, 8% of patients underwent physical harm, including 5% with severe physical harm (including intraoperative biopsy and appendectomy) due to false-positive findings from the PET-CT.

Although the findings of a higher likelihood of metastases or worse survival in [^{18}F]FDG-avid tumors is not novel, this study highlights the use of PET-CT to improve the accuracy of staging and as a prognostic biomarker for disease management in patients with HCC. The authors show that PET-CT can provide incremental information over standard diagnostic CT or MRI. Future studies evaluating PET-CT should include evaluation in the context of a comparator arm, correlation with explant pathology, and novel serum and radiographic HCC biomarkers. Although the existing data are promising, PET-CT requires more systematic evaluation prior to routine use in HCC diagnosis and management.

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