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PET/CT as a Diagnostic and Prognostic Biomarker for Hepatocellular Carcinoma – Ready for Primetime?

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CONFLICTS OF INTEREST

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The diagnosis and staging of hepatocellular carcinoma (HCC) largely relies on multiphasic computed tomography (CT) scans or Magnetic Resonance Imaging (MRI). Unlike other malignancies, where the use of ^{18}F-FDG PET/CT is sensitive in staging and can correlate with tumor biology, it had not proven to be useful in HCC due to poor sensitivity in well differentiated disease and 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 – i.e. microvascular invasion or higher risk of post-transplant tumor recurrence, albeit in small retrospective cohort studies (2).

In this issue , John and colleagues conducted a retrospective cohort study in which they evaluate the incremental benefit of PET/CT after initial staging with CT/MRI in patients with HCC (3). The authors conclude that PET/CT detected additional extrahepatic metastasis in 11.9%-13.8% of patients and modification of Barcelona Clinic Liver Cancer (BCLC) staging compared to 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 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 due to 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 which 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 for HCC, those with pathologically confirmed vascular invasion on explant had significantly higher SUVmax, TSUVmax/LSVUmax ratio and higher TSUVmax/LSUV mean ratio on pre-transplant imaging; coincidentally these patients also were noted to have higher serum α-fetoprotein (AFP) levels and larger tumor size (6). Similarly, in a multi-center study in South Korea of BCLC stage 0 or A patients with HCC undergoing curative surgery, tumor 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 Liver Imaging Reporting and Data System (LIRADS)-5 HCC, 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 stage B to C) with subsequent change in clinical management in 10% of cases 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 post treatment 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 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 higher likelihood of metastases or worse survival in 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/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. While the existing data are promising, PET/CT requires more systematic evaluation prior to routine use in HCC diagnosis and management.

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