Improving Detection of Hepatocellular Carcinoma – A Path Forward

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Mini Review

With over 800,000 incident cases reported in 2018, primary cancer of the liver, of which greater than 75% being hepatocellular carcinoma (HCC), is the 4th most common cause of cancer related deaths worldwide [1,2]. The incidence of HCC continues to rise while other cancers are stable or declining, and with marginal improvements in overall prognosis, HCC is truly a global health crisis. HCC is unique in that diagnosis can be established without tissue biopsy, based on noninvasive imaging modalities, specifically dynamic, contrast-enhanced, multidetector computerized tomography (MDCT) and magnetic resonance imaging (MRI), for patients who are at high risk [3]. To aid in radiologic interpretation, the American College of Radiology developed the Liver Imaging Reporting and Data System (LI-RADS) which assigns a category to liver lesions based on radiologic observations that are associated with malignancy [4]. This system is fully integrated with the AASLD clinical practice guidelines and is consistent with NCCN guidelines, providing a valuable framework for practitioners managing HCC.

Several limitations exist for radiologic diagnosis of HCC, however. Contrast enhancement based MDCT and MRI are inherently non-specific, and especially challenging in defining lesions within heterogeneous tissue associated with chronic liver disease requiring trans jugular intrahepatic portosystemic shunt (TIPS) or after liver directed therapies, such as trans-arterial chemoembolization (TACE) [5], as the enhancement characteristics will differ in these patients. These modalities also lack high level of spatial resolution, have limited specificity for well-differentiated HCC and are not well suited to characterize small lesions. In fact, in the current guidelines only lesions ≥1cm can be categorized as LI-RADS 5, or confirmatory for HCC. Failure to diagnose small lesions contributes to the high rates of early intrahepatic recurrence of HCC, defined as within 2 years after surgical resection, which ranges from 40-50% [6,7]. Although technological advancements such as diffusion-weight imaging (DWI), and hepatocyte-specific gadolinium contrast agents for MRI, and spectral CT imaging have improved diagnosis for small HCC and evaluation of therapeutic effect following TACE [8], respectively, there are still significant shortcomings with these modalities. Up to 20% of HCCs are not identifiable by hepatocyte-specific gadolinium contrast agents due to hepatocyte abnormalities and poor tracer uptake [9-11]. Comparison of contrast enhanced MDCT and MRI to liver transplant explant pathology demonstrates a sensitivity for HCC of approximately 50% for both modalities [12]. Newer and more specific technologies are needed for the accurate diagnosis of small HCCs.

Fluorodeoxyglucose (18FDG) PET is broadly utilized in oncology to detect small metastasis, but unfortunately its avidity is highly variable, and the lack of biological information provided by this modality limits its usefulness in specifically identifying HCC [13]. To improve detection with this technology, novel radiotracers with increased hepatocyte specificity have been investigated. Radiolabeled choline with 18Fluorine or 11Carbon has demonstrated significant increase in sensitivity in detecting HCC compared to traditional FDG PET [14,15]. Dynamic PET imaging, dual-phase PET-CT, and dynamic blood flow PET-CT with FDG PET are also being evaluated as a way to improve sensitivity for HCC [16]. Another compelling new technology being developed to specifically identify tumors based on molecular targets is immuno-PET [17]. Advances in cellular and molecular biologic techniques has identified novel...
tumor associated antigens that are targeted by specific moieties, such as peptides and monoclonal antibodies (mAb). Through labeling of these targeting moieties with positron emitting tracers, tumors are identified based on the specific expression of a cell surface marker. This technology combines the high specificity of antibody technology with the spatial resolution and sensitivity of PET imaging.

Over the last decade, several tumor antigens associated with HCC have shown promise as targets for immuno-PET imaging. Glypican-3 (GPC3) is a cell surface protein that is highly expressed on HCC and other tumors and is being utilized as a target for clinical immunohistochemistry and numerous therapies in HCC [18-21]. Our group has developed a specific immuno-PET imaging agent using 89Zirconium labeled GPC3 targeting mAb or F(ab’)2 to identify GPC3 positive tumors in an orthotopic mouse model [22,23]. Prostate specific membrane antigen (PSMA) has also been demonstrated to be expressed by HCC, and 68Galium-PSMA correctly identified 36 of 37 HCC lesions in 7 patients in a pilot study [24]. 89Zirconium labeled CD146, or MCAM, has demonstrated promise in detecting multiple tumors, including HCC, using PET and near-infrared fluorescence (NIRF) technologies [25]. Antibody targeting of CD38, a cell surface protein associated with hematologic malignancies and found to be expressed in some HCC, with daratumumab radiolabeled with 64Copper successfully identified HepG2 heterotopic tumors in a subcutaneous flank model [25]. Although not antibody targeted, 68Galium-citrate targeting of transferrin receptor has recently been trialed in a single patient for the evaluation of HCC metastasis [26]. Many of these cell surface antigens not only are useful in identification of malignant cells but they can reflect tumor biology. CD146 for instance, has been associated with aggressive tumor biology and decreased patient survival, particularly in HCC [27]. Therefore, in addition to tumor identification, evaluating expression of these markers with immuno-PET enables prognostication and risk stratification of patients with HCC. Newer and more specific technologies for tumor identification show promise to reshape the landscape of diagnosis for HCC. Through ongoing research and development of these modalities, we can see a path forward to early and more specific detection of HCC, which will have a paradigm shifting effect on therapy, leading to improved care and outcomes for our patients.

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Conflict of Interest

No conflict of interest.

References


