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Role of 18F-FDG PET-CT in initial staging of hepatocellular carcinoma and its impact on changing clinical decision

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Abstract

Background: Hepatocellular carcinoma (HCC) is one of the most common tumors worldwide. Extrahepatic metastasis from HCC occurs in one third of patients with most common sites being the lungs, lymph nodes, bone, and adrenal glands. Various conventional imaging modalities like ultrasonography, computed tomography, magnetic resonance imaging, and bone scan are used in the diagnosis and staging of HCC. Recently, PET performed with fluoro-2-deoxy-D-glucose (FDG) has proved valuable in providing important tumor-related qualitative and quantitative metabolic information that is critical to the diagnosis and staging of the disease. This article aims to show the role of 18F-FDG PET-CT in the initial staging of HCC and its impact on changing clinical decision.

Main text: We discussed the previous studies on the ability of 18F-FDG PET-CT to detect HCC, vascular invasion, regional and distant metastasis. We also studied the relation between the histopathologic grading of HCC and its detectability by 18F-FDG PET-CT.

Conclusions: 18F-FDG PET-CT has proved valuable in HCC staging and has a great impact on the clinical decision for HCC treatment.

Keywords: PET-CT, HCC, Staging

Background

Histolopathological diagnosis of hepatocellular carcinoma (HCC) is rarely needed nowadays as non-invasive imaging techniques are preferred. Dynamic magnetic resonance imaging and multiphasic contrast-enhanced computed tomography are the standard diagnostic methods for HCC. Many advances and recent imaging techniques are being explored to improve HCC detection, characterization, and staging of HCCs [1].

Nuclear imaging as positron emission tomography (PET) and single-photon emission computed tomography (SPECT) is currently used in the management of liver malignancy. Fluorine-18 fluorodeoxyglucose (18F-FDG) PET is the most commonly used nuclear imaging modality in liver cancer as in other cancers and has been proved to be effective in diagnosis, response evaluation, and recurrence detection as well as prognosis prediction [2].

Increased uptake of fluorine-18 fluorodeoxyglucose (18F-FDG) depending on increased glucose metabolism in cancer cells is a sensitive marker of detection of tumor viability [3]. Despite the fact of less sensitivity of FDG-PET scans for diagnosis of HCC, it still has an important role in the prognosis. This may be due to considering metabolic activity as a marker of differentiation; SUV values help to understand the histopathologic nature of tumor. PET fused with CT as a complementary methodology to CT is helpful in HCC staging by differentiating unsuspected regional as well as distant metastases [4].

In this review, we discussed the various studies that reported the role of 18F-FDG PET-CT in the diagnosis and staging of HCC.

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Main text

Role 18F-FDG PET-CT in HCC detection

Traditionally, primary HCC has been supposed to be insufficiently diagnosed by 18F-FDG PET alone. This is because the liver produces non-dietary glucose, at a rate of 2.0 mg/kg/min that maintains glucose homeostasis. The variety of glucose transporters and activity of glucose-6-phosphatase in HCC cause variable 18F-FDG uptakes. Sacks et al. [5] detected that FDG-PET scans likely have an extended capacity to detect higher HCC grades while have a diminished capacity to recognize HCC low-grades due to diminished FDG uptake.

18F-FDG PET specificity for HCC detection was seldom reported; one study by Wong et al. [6] reported it as 94% depending on a per-patient basis and 91% depending on a per-lesion basis. False-positive lesions or other FDG-avid lesions may include infective or inflammatory causes, focal nodular hyperplasia, adenoma, angiomyolipoma, and focal hepatic steatosis as well as many other primary and secondary tumors. They reported various studies that assessed the role of 18F-FDG PET alone in detection of HCC and data detected was as follows: For prediction of poorly differentiated HCC, a pre-operative 18F-FDG PET had shown 48–100% sensitivity, 35–86% specificity, 7–85% positive predictive value, and 50–100% negative predictive value. The overall accuracy was 57–81%.

Role of 18F-FDG PET-CT in detection of extrahepatic metastasis

In a meta-analysis of three 18F-FDG PET studies on 239 patients by Lin et al. [7], Ho et al. [8] and Seo et al. [9], the detected sensitivity and specificity for diagnosis of extrahepatic metastases were 77% and 98%, respectively. The cause of relatively higher sensitivity of 18F-FDG PET for extrahepatic metastases of HCC compared to the primary lesions could be due to increased occurrence of metastases in poorly differentiated HCC which tends to have more FDG uptake. They reported that 18F-FDG PET was more sensitive than bone scintigraphy for detecting of bone metastases.

Kawaoka et al.'s [10] study compared PET-CT, MDCT, and bone scintigraphy efficacy in detection of extrahepatic metastases of HCC in 34 patients. The results were as follows: for diagnosis of lung metastasis, mean sensitivity and specificity were 85.2 and 88.9% for MDCT and 59.2 and 92.6% for PET-CT, respectively. These values in detection of lymph node metastasis were 62.5 and 79.2% for MDCT, and 66.7 and 91.7% for PET–CT, respectively. For detection of bone metastasis, they were 41.6 and 94.5% for MDCT, 83.3 and 86.1% for PET-CT, and 52.7 and 83.3% for bone scintigraphy, respectively. MDCT sensitivity for detection of lung metastasis was significantly higher than PET-CT. This probably was mainly due to higher sensitivity for detecting lesions with maximum diameter of equal to or less than 10 mm by MDCT than PET-CT.

Xia et al. [11] reported that survival analysis showed lymph node metastasis to be the only risk factor of overall survival indicating that HCC patients with lymph node metastasis had a very poor prognosis. Several recently published reports which compared PET/CT with conventional medical imaging in the detection of extrahepatic metastasis of HCC concluded that 18F-FDG PET-CT was a better and non-invasive diagnostic tool for the detection of extrahepatic metastases.

Divisi et al. [12] reported that solitary pulmonary nodules (SPNs) are incidentally found from 0.09 to 7% on chest imaging studies. The etiology of SPNs is broad and includes both benign (such as caused by infection, inflammation, or hemorrhage) and malignant disease (such as lung cancer and pulmonary metastases). At high MSCT, there is considerable overlap in the assessment of benign and malignant SPN characteristics. FDG-PET is a well-established indication for the evaluation of SPNs. In this study, a semi-quantitative determination of FDG uptake calculated by standardized uptake value in a region of interest (ROI) is the most common method for assessment of pulmonary nodules. FDG uptake on PET scan can be qualitatively and semi-quantitatively evaluated. Visual assessment is based upon comparison between FDG lesion uptake and mediastinum, but nodules with similar FDG uptake to the mediastinal pool are challenging; for these reasons, a 2.5 cut-off of the SUVmax has been used for the establishment of malignancy. The combination of computed tomography and PET showed an excellent performance in the SPN classification.

For bone metastases, several studies (e.g., Kawaoka et al. [10] and Seo et al. [9]) reported a higher sensitivity of PET-CT relative to MDCT and bone scintigraphy. PET-CT was more sensitive than bone scintigraphy in bone metastasis from HCC by both patient-based and region-based analyses and offered additional information on survival. PET-CT has a role in early diagnosis and appropriate treatment of bone metastasis from HCC.

Yang et al. [13] reported that some uncommon metastatic sites of HCC, such as skin or soft tissues, have not been detected by PET or have not been reported yet. On the other hand, lesions in these tissues can be missed by using CT or MRI technologies. The FDG-PET scan, by measuring elevated glucose metabolism in tumors, has shown promise in distinguishing extrahepatic metastatic tumors from normal surrounding tissue.

Role of 18F-FDG PET-CT in detection of vascular invasion

For prediction of vascular invasion, Wong et al. [6] 2017 reported pre-operative 18F-FDG PET has 30–90%

sensitivity, 37–92% specificity, and 35–88% positive predictive value, while negative predictive value has less variation (60–95%). So the predictive values of 18F-FDG PET was more reliable to rule out than to rule in vascular invasion with prevalence of 15 to 52%; and the overall accuracy was 62 to 88%.

Nguyen et al. [14] reported that contrast-enhanced FDG PET-CT scan, a combination of dynamic contrast-enhanced CT and PET scan in a single examination, was feasible and convenient for the identification of FDG-avid portal vein tumor thrombus (PVTT). The intraluminal filling defect, consistent with the thrombus within the portal vein; expansion of the involved portal vein; contrast enhancement; and linear increased FDG uptake of the thrombus are considered findings of FDG-avid PVTT from HCC.

Role of 18F-FDG PET-CT in HCC staging

Clinical studies and autopsy findings indicate that extrahepatic metastases are not unusual in patients with HCC. Sites frequently involved are the lung (18–53.8%), bone (5.8–38.5%), and lymph nodes (26.7–53%). Other potential sites of involvement are the adrenal gland, peritoneum, skin, brain, and muscle. Loco-regional therapies, such as liver transplantation (LT), are not indicated in patients with extrahepatic metastases, the latter constituting systemic disease. Precision in staging of HCC is therefore critical for appropriate therapeutic choices, especially if LT is contemplated. 18F-FDG PET-CT has value in initial staging of early (BCLC A) or intermediate HCC (BCLC B), especially if hepatic resection or LT is planned [15].

Cho et al. [15] published a retrospective study on 457 patients with HCC and they reported the impact of 18F-FDG PET-CT on initial staging of HCC using BCLC staging system. This was the first large-scale retrospective cohort analysis to evaluate the contribution of 18F-FDG PET-CT in initial work-up of HCC by tumor staging conventions and its results were as follows: Prior to 18F-FDG PET-CT, BCLC staging was as follows: stage 0, 139 patients (29.9%); stage A, 119 patients (25.6%); stage B, 71 patients (15.3%); stage C, 73 patients (15.7%); and stage D, 55 patients (11.8%). After 18F-FDG PET-CT, revisions were as follows: stage 0, 139 patients (29.9%); stage A, 113 patients (24.7%); stage B, 70 patients (15.3%); stage C, 80 patients (17.5%); and stage D, 55 patients (11.8%). Seven patients (1.5%) of 457 patients had a shift in BCLC from stage A to C (6/119, 5.0%) and from stage B to C (1/71, 1.4%), while none of the patients classified as BCLC stage 0, C, or D by dynamic CT had shown a shift in BCLC after 18F-FDG PET-CT (P value 0.001). Prior to 18F-FDG PET-CT, 163 patients (35.7%) did not meet Milan criteria but increased to 168 patients (36.8%) after 18F FDG PET/CT evaluations,

with 5 additional patients (1.1%) deemed ineligible by Milan criteria.

Wong et al. [6] mentioned that in a study of 64 HCC patients, treatment in 16 patients (25%) was changed (mostly from a curative treatment to Sorafenib therapy) when FDG-PET upstaged the HCC according to the Barcelona Clinic Liver Cancer (BCLC) classification. In another study of 457 HCC patients, FDG-PET led to an upstaging in seven out of 190 (3.7%) patients who were classified as BCLC early (A) or intermediate (B) stages, but none of the 267 patients in the other stages; hence, the use of FDG-PET might be appropriate for A to B stages especially before resection or transplantation. The reported data on FDG-PET for HCC staging have yet to reach a wider consensus on when to perform FDG-PET to detect extrahepatic metastases.

Conclusions

18F-FDG PET when used as separate imaging modality is insufficient for diagnosis of primary HCC lesions, but when adding diagnostic CECT using 18F-FDG PET-CT combination, the detection rate increases. 18F-FDG PET scans have an expanded capacity to identify higher grade HCCs. Using 18F-FDG PET-CT combination has a role in detecting vascular invasion, regional metastatic lymph nodes and extrahepatic metastatic lesions when compared to separate 18F-FDG PET or CECT scans. Detection of metastasis using the available imaging modalities can help to correct decision-making using time-saving metastasis workup.

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