https://doi.org/10.33472/AFJBS.6.2.2024.496-511

African Journal of Biological Sciences

Research Paper Open Access

Possible Role of 18F-FDG PET-CT in Detection of hepatocellular carcinoma and its Extrahepatic Metastasis

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Article History

Volume 6, Issue 2, April 2024

Received:19 April 2024

Accepted: 6 May 2024

Published: 16 May 2024

doi: 10.33472/AFJBS.6.2.2024.496-511

Abstract: Globally, hepatocellular carcinoma (HCC) ranks high among cancer-related deaths. In order to effectively manage HCC in the clinic, a variety of imaging modalities are necessary. Early detection, differentiation, precise staging, and evaluation of local, residual, and recurrent HCC have all been greatly enhanced by the introduction of positron-emission tomography (PET) or PET-computed tomography to the oncologic context. PET imaging provides a visual representation of treatment-related tissue metabolic data. Recent years have seen the rise of dual-tracer and dynamic PET imaging as supplementary tools for the diagnosis of HCC. Imaging techniques like immuno-PET and PET-magnetic resonance imaging, as well as novel radiotracers, have greatly enhanced lesion detection and therapy monitoring. Here we take a look back at what PET can provide for HCC diagnostics right now, as well as some supporting methods. Although 18F-FDG PET-CT has emerged as an important noninvasive diagnostic tool in HCC, especially in staging and detecting metastatic lesions, the low sensitivity of 18F-FDG PET-CT limits its clinical use, especially for routine surveillance. 18F-FDG PET-CT could be valuable in HCC staging and has a great impact on the clinical decision for HCC treatment.

Keywords: 18F-FDG, PET-CT, hepatocellular carcinoma, Extrahepatic Metastasis

Introduction: Hepatocellular carcinoma (HCC) is the second most common cause of death from cancer worldwide, with more than 740000 deaths each year[1]. Although modern management methodologies for HCC patients, such as surgical resection and comprehensive treatment (radiotherapy, chemotherapy, immunotherapy, in-terventional therapy, or combined) have been developed, the overall survival (OS) rate remains low. Liver transplantation (LT), partial liver resection, and ablation remain the main therapeutic tools for HCC and have a high rate of complete response. However, most patients are diagnosed at an advanced stage and are complicated with multiple lesions and liver cirrhosis; no more than 40% of HCC patients have the opportunity to undergo surgery[2].

Careful selection of candidates is vital for improving treatment outcomes. Evaluation of HCC should be referred to multidisciplinary teams that include surgeons, oncologists,

hepatologists, and radiologists. Serum alpha-fetoprotein (AFP) levels have been widely used to diagnose HCC in the early stage; however, this test is limited due to its low sensitivity of approximately 25%[3]. Contrast-enhanced ultrasound (CEUS) imaging is useful for HCC diagnosis only when the tumor sites are identified by B-mode US[4]. Contrast-enhanced computed tomography (CECT) or magnetic resonance imaging (MRI) are also available for HCC screening, and each has its own advantages, such as multiphase enhancement characteristics and easy acquisition, but their accuracy may be lower when lesions are smaller than 2 cm[5-7]. Digital angiography is another examination method that can diagnose HCC, but it is invasive and is usually only performed when transarterial treatment is necessary[4]. Although these examinations are well utilized by surgeons for preoperative staging, they often show only a part of the body and detect morphologic changes that can occur quite slowly in HCC. In addition, these traditional examination techniques cannot detect recurrent, residual, or metastatic lesions well.

Positron-emission tomography (PET) seems to be a more effective and noninvasive modality than traditional radiography techniques for scanning the whole body[8]. Although 2-deoxy-2-(^{18}F)fluoro-D-glucose (^{18}F-FDG) PET has a low sensitivity, between 36% and 70%, in detecting HCC[9-11], the application of PET-CT for diagnosing HCC has made great progress in recent years

RADIOTRACERS

^{18}F-FDG is the most widely used radiotracer for PET-CT; ^{18}F has a long half-life (110 min), the best imaging spatial resolution, and favorable nuclear and chemical properties[12]. ^{18}F-FDG is a radiolabeled glucose analog in which the positron emitter radioactive isotope ^{18}F replaces the hydroxyl group at the C2 position in the glucose molecule. ^{18}F-FDG is transported across the cell membrane by glucose transporters (GLUTs); in HCC, GLUT1, GLUT3, and, more recently, GLUT12, have been associated with the transport of this radiopharmaceutical into cancer cells. Multidrug resistance (MDR) is the ability of tumor cells to become resistant to different drugs and represents a major barrier to successful treatments. The overexpression of MDR proteins is thought to be a major obstacle to successful chemotherapy in various cancer types, including HCC. Studies have shown that cells that present increased MDR protein expression exhibit lower ^{18}F-FDG accumulation[13]. In intracellular terms, ^{18}F-FDG is phosphorylated by hexokinase II to ^{18}F-FDG-6-phosphate, which cannot be metabolized in the glycolytic pathway and accumulates in metabolically active cells.

^{18}F-labeled amino acids and peptides have potential application value for PET imaging in HCC or other tumors[14-18]. Sun et al[19] synthesized *N*-(2-^{18}F-fluoro-propionyl)-L-glutamate (^{18}F-FPGLU), and the radiochemical purity was higher than 95%, with a specific activity of 30-40 GBq/μmol. Although the novel tracer showed good tumor-to-background contrast and good stability *in vitro*, ^{18}F-FPGLU was metabolically unstable in plasma, urine, and tumor tissues[20].

^{18}F-fluorocholine is another radiotracer used in PET imaging that radiolabels phosphocholine, the major metabolite in cancer cells that is responsible for choline uptake and has a steady distribution that is available within 10 min, demonstrating high sensitivities of 89% for hepatic HCC and 100% for extrahepatic HCC[21,22]. Although the ^{18}F-labeled metabolites are not able to be synthesized in every medical center, they still perform better than other radiolabels in diagnosing HCC.

Other promising radiopharmaceuticals currently used in PET-CT include ^{11}C-labeled acetate (^{11}C-ACT) and ^{11}C-labeled choline (^{11}C-CHOL)[23]. ^{11}C-ACT is a radiopharmaceutical that is widely used in the imaging of HCC, primary brain tumors, carcinoid tumors, prostate adenocarcinoma, and transitional cell carcinoma[24]. As a substrate, ^{11}C-ACT enters the Krebs cycle for β-oxidation in fatty acid synthase (FASN) and cholesterol synthesis. Fatty acid synthesis is thought to be the key factor for the uptake of ^{11}C-ACT by liver neoplasms. Increased ^{11}C-ACT uptake is often considered to reflect the increased *de novo* lipogenesis rate and to be associated with increased FASN expression[25,26]. Unlike ^{18}F-FDG, ^{11}C-ACT mainly reflects the growth activity of tumor cells and may provide a complementary role to conventional radiotracers[27].

^{11}C-CHOL is a precursor for phospholipid synthesis of the cell membrane. ^{11}C-CHOL has a high PET signal in liver tumor cells due to the increased activities of choline transporter and choline kinase. In addition, HCC foci gained a better tumor-to-background contrast with CHOL[28,29]. Nevertheless, ^{11}C has a short half-life of approximately 20 min, and the use of ^{11}C-labeled tracers is limited based on access to an on-site cyclotron, whereas ^{18}F has a longer half-life than ^{11}C[28].

Another alternative tracer is the ^{68}Ga-labeled 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) conjugate of serum albumin or peptides. With an appropriate physical half-life (68 min) and good blood clearance, ^{68}Ga-DOTA may be a potential radiotracer for use in imaging HCC[30,31]. Studies have shown that ^{68}Ga-DOTA has a higher sensitivity than ^{18}F-DOTA, as ^{68}Ga-DOTA had a greater PET uptake than ^{18}F-FDG in low-grade neuroendocrine tumors[29]. Gao et al[32] demonstrated that ^{68}Ga-asparagine-glycine-arginine uptake was higher than ^{18}F-FDG uptake for imaging well-differentiated HCC xenografts. However, limited data using ^{68}Ga for HCC are now emerging, and its potential clinical utility is unclear.

^{64}Cu radionuclide has a half-life of 12.7 h and is a novel biomarker for molecular imaging of HCC. $^{64}CuCl_2$ PET-CT was able to detect early intracranial and other extrahepatic metastases located in areas with low physiological uptake, such as musculoskeletal tissues, which is important for determining the stage and prognosis of patients with HCC. This radionucleotide also plays an important role in treatment method selection. However, ^{64}Cu has an abundant physiological distribution in the liver, which will decrease the tumor-to-background contrast and make the lesions unrecognizable, which will limit its value of evaluation for HCC. Furthermore, altered copper metabolism is expected to be a target for

radionuclide therapy of HCC using therapeutic copper radionuclides[33]. Another promising radiotracer, ^{89}Zr, will be reviewed in relation to immuno-PET in detail later in the article.

^{18}F-FDG PET

Detection of intrahepatic or extrahepatic lesions

Although HCC is the only solid tumor that can be diagnosed by the characteristics of "arterial phase hyperenhancement" and "washout" on CT or MRI after contrast medium injection[5], there are still limitations in the biology of HCC that CT or MRI cannot show but that can be presented by the metabolic information from PET-CT[34]; however, none of these examinations can present the local tumor extent or detect distant metastases in the same examination. ^{18}F-FDG PET-CT can also enhance the detection capacity for synchronous neoplasms in patients with HCC, which may be misdiagnosed as primary lesions or metastasis[35].

^{18}F-FDG PET gives hepatologists complementary imaging details about primary HCC lesions and extrahepatic metastases, and this additional information is associated with treatment selection[36]. ^{18}F-FDG PET-CT is usually a complementary method for routine examinations because the accumulation of FDG in HCC varies. According to the current European Association for the Study of the Liver Clinical Practice Guidelines for the management of HCC, ^{18}F-FDG uptake was observed in less than 40% of HCC patients[37]. Studies have demonstrated that low ^{18}F-FDG uptake is correlated with high FDG-6-phosphatase activity, high expression of P-glycoprotein, and low expression of GLUT1 or GLUT2 in moderately and well-differentiated HCC[38]. ^{18}F-FDG is transported into cells and phosphorylated to FDG-6-phosphate, which is trapped within cells. However, high levels of FDG-6-phosphatase hydrolyzes FDG-6-phosphate to FDG, which is then transported outside the cells, and high expression of P-glycoprotein acts as an efflux pump to also transport FDG out of the cell, and low expression of GLUT1 or GLUT2 reduces the uptake of FDG. These reasons contribute to lower FDG accumulation in tumors[11,39,40].

PET scanning has a high sensitivity for detecting extrahepatic metastases but a low sensitivity for primary HCC[41]. The reason is that normal liver tissue has a relatively high FDG uptake, which reduces the tumor-to-liver standardized uptake value (SUV) ratio (TLR) and makes it difficult to visualize tumor lesions[42]. However, extrahepatic metastases usually have a low FDG uptake background to visualize. Based on the Barcelona Clinic Liver Cancer staging classification, patients with HCC have lymph node metastasis that usually indicates an advanced stage. Metastasis is a fairly common sequela in HCC, occurring in more than 50% of patients; most of these metastases frequently affect the lungs (18%-53.8%), lymph nodes (26.7%-53%), and diaphragm and skeleton (5.8%-38.5%)[43,44]. Among them, lymph node metastasis most frequently occurs, with an incidence of more than 50%. Retroperitoneal lymph node metastasis is more frequent than porta hepatis lymph node metastasis[45]. ^{18}F-FDG PET-CT has a higher sensitivity to detect lymph node metastasis, which is a poor prognostic factor for HCC[29].

In view of the potential value of PET-CT for extrahepatic lesions, PET-CT should be considered for initial HCC staging work-ups to formulate a plan for patients who are candidates for hepatic resection (HR) or LT[44]. Although CT, MRI, and bone scintigraphy are recommended for preoperative HCC staging, HCC metastasis to uncommon sites, such as the oral cavity, jaw, thyroid, and adrenal glands, may be detected only by ^{18}F-FDG PET-CT[43,46,47] and easily missed by conventional CT and MRI. Overall, ^{18}F-FDG PET-CT has additional value for HCC staging.

There are few studies on the differential diagnosis of HCC, and the utility of PET-CT for differential diagnosis is limited. Several case reports[48-50] have shown that PET-CT is a useful tool to differentiate primary or secondary neoplasms, but these studies did not systematically summarize the signs of differential diagnosis from HCC. Malignant lesions may increase radiotracer uptake, and PET-CT is of value for the following reasons.

^{18}F-FDG PET-CT is very helpful to assess the malignant potential of hepatic lesions of unknown origin through simultaneous visualization of the liver and extrahepatic tissue and for further confirmation of a clinically suspected extrahepatic metastasis of known HCC[51]. ^{18}F-FDG PET-CT has the potential value to distinguish malignant thrombus from a bland thrombus of the portal vein in patients with HCC, which is of great clinical significance for determining the therapeutic approach, predicting survival, and assessing candidates for LT[52]. However, no studies have shown that PET-CT has higher value to diagnose bland thrombus than CT, MRI, or even fine needle biopsy. ^{18}F-FDG PET-CT may play an important role in differentiating malignant lymph metastasis from lymphoproliferative diseases[53]. However, there is no denying that these conclusions are drawn from case reports, and more evidence is needed to support these topics in further studies.

Additionally, there is a lack of literature to differentiate between HCC and intrahepatic cholangiocellular carcinoma using ^{18}F-FDG PET alone. Conventional CT and MRI, especially with contrast enhancement, are useful[54], and developing new specific radiotracers can be a desirable alternative for enhancing the ability of differential diagnosis.

Prediction of differentiation and prognosis

^{18}F-FDG PET is expected to describe tumor aggressiveness of HCC, and high accu-mulation of FDG is associated with biological malignancy[55]. Moderately and well-differentiated HCC may show low glucose metabolism, whereas ^{18}F-FDG uptake by poorly differentiated HCC may be visualized as a hot spot on a PET scan[56]. The main reason is the high FDG-6-phosphatase activity in well-differentiated HCC, which resembles normal liver tissue, thus reducing FDG accumulation in the lesions[34,39].

Pretreatment ^{18}F-FDG PET has incremental prognostic value for OS in both intrahepatic and extrahepatic diseases. In addition, for patients with intermediate-to-advanced stage HCC confined to the liver, TLR is an independent prognostic factor for progression-free survival (PFS) and OS[57,58]. A TLR of 1.2 or more has a statistically significant association with microvascular invasion (MVI)[59,60]. Patients with MVI and those with poorly differentiated grade show significantly higher recurrence rates[55]. Kobayashi et al[61] suggested that the

combination of an SUV_{max} of 3.2 or greater and an AFP-L3 level of 19% or greater are useful for selecting small numbers of HCC patients for HR or LT.

^{18}F-FDG PET-CT can also predict the prognosis of patients with HCC after treatment. ^{18}F-FDG PET-CT is sensitive to detecting recurrent extrahepatic lesions of HCC after hepatectomy or radiofrequency ablation, which has a diagnostic sensitivity of 90–100% for recurrent or metastatic hepatic tumors[62]. ^{18}F-FDG PET-CT is a valid prognostic tool in patients with HCC who are candidates for orthotopic liver transplantation (OLT); positivity on PET is the only factor related to early recurrence of HCC after OLT, and the combination of findings on PET and the AFP levels provides even more decisive results[63].

Evaluation of therapeutic response

^{18}F-FDG uptake is closely related to therapeutic response in HCC and can offer additional information on the risk of HCC recurrence after surgery. PET status may be a significant and independent risk factor for posttreatment recurrence of HCC after LT[55]. ^{18}F-FDG PET-CT scans reflect tissue metabolism, while the size changes do not serve as a predictor of tumor control.

The SUV ratio is an important factor affecting treatment response, and a decreased SUV ratio after external beam radiotherapy is associated with the degree of tumor necrosis on the histological examination[64]. Kim et al[65] indicated that the maximum tumor-to-background ratio calculated by the inferior vena cava (TBR_{IVCmax}) and the uptake-volume product measured by margin thresholds of the TBR_{IVC} exhibit higher predictive power for patients after transplantation than other indices. PET-CT was also performed 1 month after interventional treatment to evaluate the therapeutic response. Song et al[66] revealed that ^{18}F-FDG PET-CT was efficient in assessing the viability of HCC after transcatheter arterial chemoembolization (TACE) and was superior to CECT in grades I and II and similar in grade III; moreover, nonattenuation-corrected PET data may be helpful for avoiding false-positive results of tracer uptake induced by lipiodol deposition (Figure (Figure11).

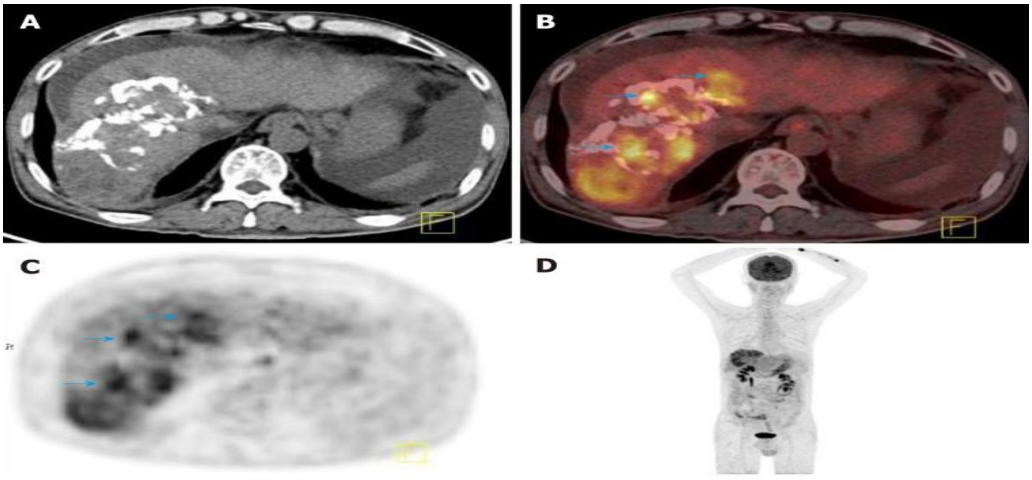

Figure 1:2-Deoxy-2-(18F)fluoro-D-glucose positron-emission tomography-computed tomography detected tumor recurrence after intervention therapy in a 58-year-old male

patient with hepatocellular carcinoma. A: Cross-sectional computed tomography (CT) image showing a large sheet of lipiodol deposition in the right lobe of live after HCC intervention therapy; B: Cross-sectional positron-emission tomography (PET-CT) fusion image showing increased 18F-FDG uptake in and around the area of lipiodol deposition (blue arrow); the size of the lesion was 5.8 × 13.3 cm; C: Cross-sectional PET image showing increased 18F-FDG uptake in the right lobe of the liver; D: Maximum intensity projection image showing increased 18F-FDG uptake in the right lobe of the liver. 18F-FDG: 2-deoxy-2-(18F)fluoro-D-glucose; CT: Computed tomography; PET: Positron-emission tomography.

TLR only represents the point of the highest metabolic activity of the tumor and does not account for the tumor extent, while metabolic tumor volume (MTV) is a better parameter that represents the extent of abnormally increased FDG uptake by tumor tissue beyond the intensity of FDG uptake in normal tissue. MTV may be an independent prognostic factor for PFS and OS in patients with HCC after TACE[67].

Apart from HCC, ^{18}F-FDG PET-CT is also a good predictive tool to assess treatment outcomes of HCC metastasis and for the early identification of treatment failure, especially when additional treatments remain a possibility. One study showed that preradiotherapy SUV ratios and a decline in postradiotherapy SUV ratios were identified as independent predictive factors for bone metastasis, and when combined, these factors predicted outcomes much more effectively than other methods[68].

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%.

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.

Main text

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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. [71], Ho et al. [72] and Seo et al. [73], 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 [74] 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. [75] 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. [76] 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. [74] 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. [77] 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. [70] 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. [78] 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 [78].

Cho et al. [79] 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. [74] 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.

Conclusion

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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