MINIREVIEWS

Positron-emission tomography for hepatocellular carcinoma: Current status and future prospects

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Abstract

Hepatocellular carcinoma (HCC) is one of the leading causes of cancer mortality worldwide. Various imaging modalities provide important information about HCC for its clinical management. Since positron-emission tomography (PET) or PET-computed tomography was introduced to the oncologic setting, it has played crucial roles in detecting, distinguishing, accurately staging, and evaluating local, residual, and recurrent HCC. PET imaging visualizes tissue metabolic information that is closely associated with treatment. Dynamic PET imaging and dual-tracer have emerged as complementary techniques that aid in various aspects of HCC diagnosis. The advent of new radiotracers and the development of immuno-PET and PET-magnetic resonance imaging have improved the ability to detect lesions and have made great progress in treatment surveillance. The current PET diagnostic capabilities for HCC and the supplementary techniques are reviewed herein.

Key words: Hepatocellular carcinoma; Positron-emission tomography; Radiotracer; Immuno-positron emission tomography

Core tip: Positron-emission tomography (PET) is an effective and noninvasive modality for visualizing hepatocellular carcinoma (HCC). This paper reviews the clinical utility of PET for HCC, including the detection of intrahepatic or extrahepatic lesions, differential diagnosis, prediction of differentiation and prognosis, and evaluation of therapeutic

response. Complementary technologies, such as dynamic blood flow and dual-phase and dual-tracer PET imaging, are also mentioned. Novel radiotracers and immuno-PET have shown great potential for PET imaging and have become the focus of current research, which may enhance the diagnostic capability of PET for HCC. An overview of the current PET diagnostic status of HCC is reviewed.

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, interventional 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. This review presents an overview of the current status and future prospects of PET for diagnosing HCC.

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. The important findings about these radiotracers are summarized in Tables 1 and 2.

^{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

Table 1 Positron emission tomography for intrahepatic or extrahepatic hepatocellular carcinoma

Isotopes	Half-life	Radiotracer	Year	First author	No. of patients	Study design	Intrahepatic		Extrahepatic		Related notable findings
							Sensitivity	Specificity	Sensitivity	Specificity	
[18]F	110 min	^{18}F-FDG	2019	Lee *et al*[11]	-	Review	0.36-0.70	NA	NA	NA	^{18}F-FDG PET has demonstrated a higher sensitivity for detecting extrahepatic metastasis compared to primary HCC
			2012	Hossein Jadvar[29]		Review	NA	0.91	NA	NA	
			2012	Lin *et al*[89]		Meta-analysis	NA	NA	0.77	0.98	
		^{18}F-FCH	2014	Bieze *et al*[21]	30	Prospective; single-center	0.88	1.0	1.0	1.0	^{18}F-FCH shows additional value in the assessment of intra- and extrahepatic diseases
[11]C	20 min	^{11}C-ACT	2009	Hwang *et al*[27]	13	Prospective	0.83	NA	0.77	NA	[11]C increases the sensitivity in the detection of HCC lesions of more than 10 mm
		^{11}C-CHOL	2016	Castilla-Lièvre *et al*[71]	28	Prospective; single-center	0.67	NA	NA	NA	Combining ^{18}F-FDG with ^{11}C-CHOL could be useful for clinicians in the management of HCC patients

HCC: Hepatocellular carcinoma; NA: Not available;
^{18}F-FDG: 2-deoxy-2-(^{18}F)fluoro-D-glucose; ^{18}F-FCH: ^{18}F-fluorocholine;
[11]C-ACT: 11C-acetate; ^{11}C-CHOL: ^{11}C-choline.

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)

Table 2 Positron emission tomography in animal experiments of hepatocellular carcinoma

Isotopes	Half-life	Radiotracer	Year	First author	Animal models	Related notable findings	Limitations
^{18}F	110 min	^{18}F-FPGLU	2017	Sun *et al*[19]	Tumor-bearing mice (HCC SMCC-7721)	Radiochemical purity is higher than 95% with a specific activity of 30-40 GBq/μmol Stable *in vitro* High uptake and retention in tumor	Unstable in plasma, tumor, and urine
^{64}Cu	12.7 h	^{64}CuCl$_2$	2011	Lièvre *et al*[71]	Athymic mice bearing extrahepatic HCC xenografts	Increased ^{64}Cu radioactivity is well visualized Useful for detection of intracranial HCC metastasis	Abundant physiological distribution in liver
^{68}Ga	68 min	^{68}Ga-NGR	2017	Gao *et al*[32]	Tumor-bearing mice (HCC SMCC-7721)	^{68}Ga-NGR could visualize CD13-positive tumors ^{68}Ga-NGR uptake is significantly higher than that of 18F-FDG in well-differentiated HCC xenografts	The uptake performance of ^{68}Ga-NGR for poorly differentiated HCC needs further investigation
^{89}Zr	78.4 h	^{89}Zr-αGPC3	2014	Sham *et al*[79]	HepG2 tumor-bearing mice	Excellent specificity Even smaller tumors (<1 mm) are able to be identified	Long half-life in the blood, leading to suboptimal imaging pharmacokinetics, poorer tumor penetration, and increased immunogenicity due to relatively large size and intact Fc regions
		^{89}Zr-αGPC3-F(ab')2	2014	Sham *et al*[80]	HepG2 tumor-bearing mice	Significantly reduces blood circulation time Lower background liver uptake allows for early imaging	Potential risk of fragment concentration in the kidneys, leading to organ dysfunction
		^{89}Zr-DFO-1G12	2014	Yang *et al*[81]	HepG2 tumor-bearing mice	Specifically taken up by GPC3-positive HCC xenografts regardless of GPC3 expression levels High tumor-to-liver ratio	This probe should be further validated using a humanized anti-GPC3 antibody
		^{89}Zr-Df-YY146-ZW800	2016	Hernandez *et al*[82]	HepG2 tumor-bearing mice	Excellent CD146-affinity, specificity, and stability Both PET and NIRF imaging are achieved	Bone-displaying PET signal is not matched by NIRF

HCC: Hepatocellular carcinoma; PET: Positron emission tomography;
^{18}F-FPGLU: *N*-(2-^{18}F-fluoropropionyl)-L-glutamate;
^{68}Ga-NGR: ^{68}Ga-labeled asparagine-glycine-arginine;
^{89}Zr-αGPC3: ^{89}Zr-anti glypican-3; ^{89}Zr-αGPC3-F(ab')2: ^{89}Zr-anti glypican-3-F(ab')2; ^{89}Zr-DFO-1G12: ^{89}Zr-desferrioxamine-1G12; ^{89}Zr-Df-YY146-ZW800:
^{89}Zr- deferoxamine-YY146-ZW800; NIRF: Near-infrared fluorescence.

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]. 18F-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 18F-FDG PET-CT[43,46,47] and easily missed by conventional CT and MRI. Overall, 18F-FDG PET-CT has additional value for HCC staging.

Differential diagnosis

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.

18F-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]. 18F-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. 18F-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 18F-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

18F-FDG PET is expected to describe tumor aggressiveness of HCC, and high accumulation of FDG is associated with biological malignancy[55]. Moderately and well-differentiated HCC may show low glucose metabolism, whereas 18F-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 18F-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.

18F-FDG PET-CT can also predict the prognosis of patients with HCC after treatment. 18F-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]. 18F-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 1).

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].

DUAL-TRACER PET-CT

Dual-tracer PET-CT with ^{11}C-ACT and ^{18}F-FDG are biochemical probes of HCC and are complementary to each other. ^{11}C-ACT uptake is related to well-differentiated HCC and a less aggressive cancer or a fair prognosis[69]. The regenerative nodules are avid for either of the two tracers, and they can be distinguished from HCC[70]. Combining ^{11}C-CHOL and ^{18}F-FDG PET-CT may also be a valuable option to detect HCC in the background of chronic liver disease. ^{11}C-CHOL improves the detection rate for HCC in cases that are negative on conventional ^{18}F-FDG PET-CT (Figure 2), and the combination of two tracers can increase the sensitivity of PET-CT to approximately 93%[71]. Dual-tracer PET-CT enhances its capacity to identify lesions and benefits the management of HCC patients.

DYNAMIC BLOOD FLOW AND DUAL-PHASE PET IMAGING

To obtain a better diagnostic result, additional emerging technologies can be performed, including early dynamic PET imaging and dual-phase PET-CT. Dynamic blood flow PET-CT is centered on the liver, beginning with the injection of ^{18}F-FDG, to reveal information about both the spatial distribution and temporal kinetics of the tumor, and enables quantitative interpretation of PET data[72].

Time-activity curves are generated from the mean activities for each volume of interest; three blood flow parameters related to the first-pass delivery of FDG are acquired, including peak intensity, time to peak (TTP), and hepatic perfusion index (HPI), which are derived for the HCC lesion and the background liver parenchyma[42]. Studies show that TTP and HPI demonstrate significantly better performances than SUV$_{max}$ for the discrimination between HCC and background liver tissue, and HPI represents the percentage of arterial supply of the total blood flow in the liver. Early dynamic ^{18}F-FDG PET-CT generates significantly greater contrast during the arterial phase of imaging and similar contrast during the venous phase compared to CECT[73].

Of course, a conventional (standard static) PET-CT scan of the torso is routinely performed 60 min after FDG injection. Early dynamic ^{18}F-FDG PET-CT allows for the improvement of the detection rate for HCC in cases that are negative for HCC on conventional ^{18}F-FDG PET-CT (Figure 3), and the combination of early dynamic ^{18}F-FDG PET-CT and conventional PET-CT improves the detection ability for HCC[74]. These results indicate that dynamic PET-CT may serve as an alternative where CECT
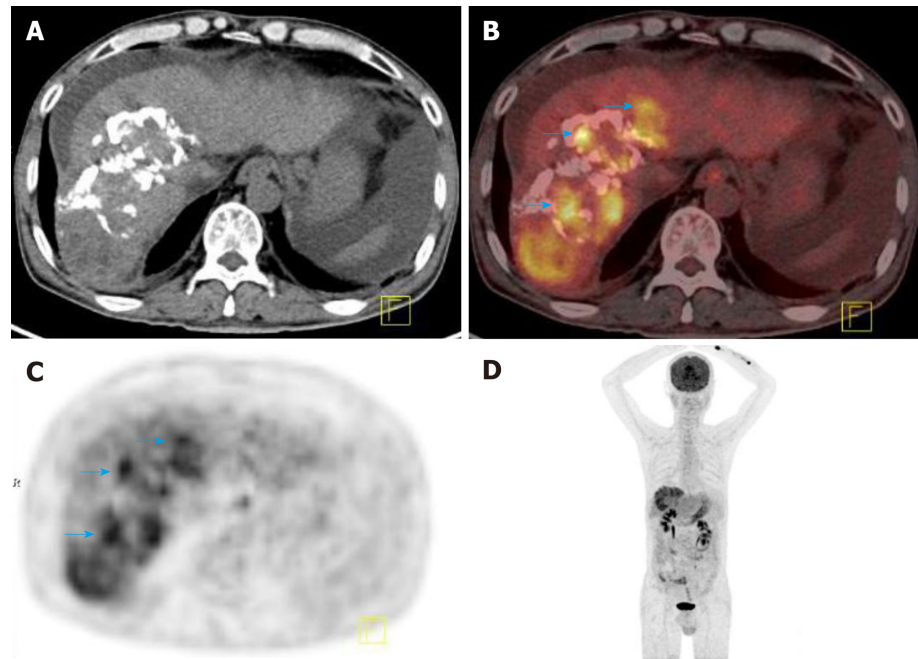
Figure 1 2-Deoxy-2-(^{18}F)fluoro-D-glucose positron-emission tomography-computed tomography detected tumor recurrence after intervention therapy in a 58-year-old male patient with hepatocellular carcinoma. A: Cross-sectional computed tomography (CT) image showing a large sheet of lipiodol deposition in the right lobe of live after HCC intervention therapy; B: Cross-sectional positron-emission tomography (PET-CT) fusion image showing increased ^{18}F-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 ^{18}F-FDG uptake in the right lobe of the liver; D: Maximum intensity projection image showing increased ^{18}F-FDG uptake in the right lobe of the liver. ^{18}F-FDG: 2-deoxy-2-(^{18}F)fluoro-D-glucose; CT: Computed tomography; PET: Positron-emission tomography.

or other conventional contrast-enhanced modalities are contraindicated or unavailable. However, early dynamic ^{18}F-FDG PET-CT shows perfusion parameters, and ^{18}F-FDG can be absorbed into cells and become involved in intracellular metabolism at the same time[74]; therefore, more precise algorithms are needed to separate these parameters from those necessary for image analyses. In addition, formal and prospective clinical studies with a larger number of subjects are needed to explore the value of early dynamic ^{18}F-FDG PET-CT in HCC diagnosis.

Dual-phase PET begins with whole-body scanning 60 min after the injection of ^{18}F-FDG, and delayed scanning begins approximately 2 h after ^{18}F-FDG injection. The tumor may be more clearly visualized by delayed PET-CT imaging of ^{18}F-FDG, and the uptake may be higher, thus supporting the diagnosis of HCC[75]. Dual-phase imaging of ^{11}C-ACT PET acquires early scan immediately after tracer administration and conventional scan in 11-18 min, and it seems to be an available method for the differential diagnosis of focal nodular hyperplasia (FNH) and small hemangioma from malignant lesions[76,77]. Both FNH and small hemangioma are hypervascularized lesions and exhibit positive tracer uptake ratios in early-phase imaging, followed by an immediate decline in the late phase[76]. However, well-differentiated HCC demonstrates an increasing tracer uptake over time. Furthermore, compared to CT, MRI, or ultrasound, ^{11}C-ACT PET images are not easy to acquire because ^{11}C has a short half-life (20 min), which limits its utility in clinical work.

IMMUNO-PET

To date, immuno-PET has emerged as a targeted molecular imaging method that represents a promising approach for diagnosing HCC. Glypican-3 (GPC3) is a cell surface protein that is highly expressed in HCC, melanoma, and clear cell carcinoma of the ovary. GPC3 has been proposed as an immunohistochemistry marker to differentiate HCC from benign hepatocyte nodules[78].

[89]Zr possesses a better half-life (78.4 h) than other radiotracers and performs well, especially when conjugated with monoclonal antibodies (mAbs). The [89]Zr-conjugated mAb against GPC3 ([89]Zr-αGPC3) demonstrates antibody-dependent and antigen-specific tumor binding; the αGPC3 protein was created using the human GPC3
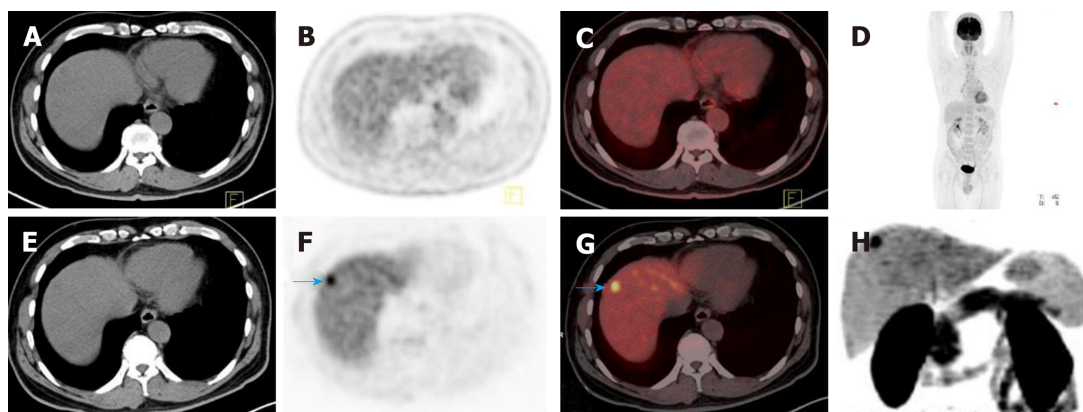
Figure 2 **11C-choline positron-emission tomography-computed tomography detected a tumor that was missed on conventional 2-deoxy-2-(18F)fluoro-D-glucose positron-emission tomography-computed tomography in a 58-year-old patient with hepatocellular carcinoma.** A-D: 2-deoxy-2-(18F)fluoro-D-glucose positron-emission tomography-computed tomography (18F-FDG PET-CT) showed that there was no increased 18F-FDG uptake in the liver; E-H: 11C-choline (11C-CHOL) PET-CT showed focal increased 11C-CHOL uptake in the upper segment of the anterior lobe of the liver, and the size of the lesion was 1.2 × 1.3 cm (blue arrow in F and G). Pathological examination confirmed well-differentiated hepatocellular carcinoma. 18F-FDG: 2-deoxy-2-(18F)fluoro-D-glucose; CT: Computed tomography; PET: Positron-emission tomography; 11C-CHOL: 11C-choline.

protein and demonstrated high-affinity binding. 89Zr-αGPC3 PET has shown a great capacity for identifying primary liver malignancies, even smaller lesions (< 1 mm), and has demonstrated the capacity to overcome background liver activity[79].

However, mAbs have long half-lives in the blood, leading to suboptimal imaging pharmacokinetics, poor tumor penetration, and increased immunogenicity due to their relatively large size and intact Fc regions. Smaller targeting moieties, such as F(ab')2 fragments, have emerged as an alternative to mAbs. The half-life of 89Zr-αGPC3-F(ab')2 in the blood is approximately 11 h and enables clear tumor visualization on PET 4 h after administration and has an excellent signal-to-noise ratio at an early time point[80].

Yang *et al*[81] synthesized a new PET probe, 89Zr-DFO-1G12, by bioconjugating and radiolabeling anti-GPC3 mAbs (clone 1G12) with 89Zr; this probe can be specifically taken up only by GPC3-expressing cells and achieved a high TLR. 89Zr-DFO-1G12 detected all GPC3-positive orthotopic HCC xenografts regardless of the level of GPC3 expression, highlighting its clinical value in the diagnosis of all GPC3-expressing HCC.

Another attractive molecular target is CD146, which is overexpressed in multiple cancers and associates with a high histological grade in HCC, but not in normal liver tissue. YY146 is an anti-CD146 mAb; when conjugated, the zwitterionic near-infrared fluorescence (NIRF) dye ZW800-1 and the chelator deferoxamine (Df) enable the labeling of Df-YY146-ZW800 with 89Zr and its subsequent detection with PET and NIRF imaging[82]. 89Zr-Df-YY146-ZW800 showed excellent properties as a dual-modality imaging agent and exhibited good stability.

The dual-modality imaging capacity not only provides diagnostic information but also may guide surgical resection. All radiotracers for immuno-PET benefit from the long half-life of 89Zr; hence, these radiotracers showed better properties for PET imaging. In addition, GPC3 is proposed to be an immunohistochemistry marker that can differentiate HCC from benign hepatocyte nodules[79]. However, most studies regarding immuno-PET were performed in animals, and further studies are needed to transfer this technique to clinical use.

PET-MRI

Combined PET and MRI utilize the advantages of MRI, including increased soft tissue contrast, multiple sequences, lack of ionizing radiation exposure, and use of MRI-specific contrast agents[83]. Diffusion-weighted imaging is widely used in tumor evaluation, and the apparent diffusion coefficient can quantify the Brownian motion of water molecules in tissue, which changes during a pathophysiological state. Kong *et al*[84] indicated that there may exist a negative correlation between increased FDG accumulation and water diffusion in hepatic tumors. PET-MRI is available in HCC staging and follow-up after treatment[85].

Although PET-MRI is promising in many aspects, PET-MRI systems are still relatively rare, and there are several hurdles that prevent its clinical application.
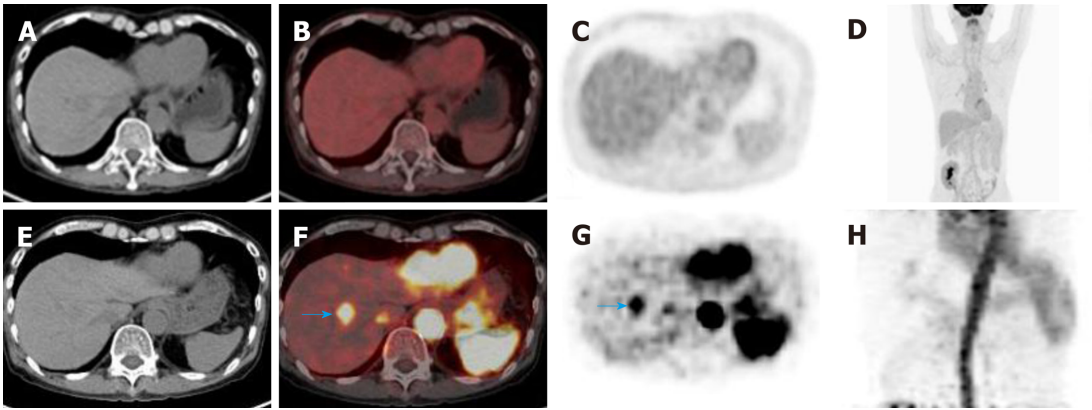
Figure 3 Early dynamic 2-deoxy-2-(18F)fluoro-D-glucose positron-emission tomography-computed tomography detected a tumor that was missed on conventional 2-deoxy-2-(18F)fluoro-D-glucose positron-emission tomography-computed tomography in a 64-year-old patient with hepatocellular carcinoma. A-D: 2-deoxy-2-(18F)fluoro-D-glucose positron-emission tomography-computed tomography (18F-FDG PET-CT) showed that there was no increased 18F-FDG uptake in the lesion on conventional 18F-FDG PET-CT; E-H: Early dynamic 18F-FDG PET-CT showed focal 18F-FDG hyperperfusion in the upper segment of the anterior lobe of the liver, and the size of the lesion was 1.7 × 1.9 cm (blue arrow in F and G). 18F-FDG: 2-deoxy-2-(18F)fluoro-D-glucose; CT: Computed tomography; PET: Positron-emission tomography.

Interpretation of PET-MRI requires technician knowledge on both nuclear medicine and MRI, and the examination may take more time. On the other hand, PET-MRI has limited evaluation of pulmonary parenchyma, and patients with metal implants in their bodies cannot undergo MRI. Further studies of PET-MRI utility in clinical applications are needed[83].

CONCLUSION

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[86]. To improve the sensitivity of PET-CT for HCC diagnosis, many new techniques have been carried out, and several methods have been applied. The advent of novel radiotracers and dual-tracer PET-CT increases the sensitivity and enables the visualization of other metabolic processes apart from glucose metabolism. The new modalities require technical expertise and on-site cyclotron facilities; in addition, these radiotracers are expensive and inconvenient for patients[87]. Dynamic or dual-phase PET imaging is an alternative modality when other CE modalities cannot be utilized; dual-phase PET imaging provides multiple parameters for quantitative analysis and reflects the blood perfusion in detail. Although false-positive findings might sometimes occur in dynamic PET imaging, it has certain value in diagnosis and differential diagnosis[73].

Radiotracer synthesis and targeted molecular imaging modalities, such as immuno-PET, have already become the focus of current research, and their diagnostic capacity for smaller HCC lesions is encouraging. However, most research about radiotracers and immuno-PET is performed on experimental animals, and immuno-PET also shows the overexpression of molecular targets in many non-liver malignancies[79,88]. Further evaluation of their immune reactivity is needed, and clinical translation requires more evidence. Additionally, a useful surrogate marker of MVI in small HCC has not yet been established[61]. It is imperative to develop new molecular targets and new probes that can specifically bind to each other. The development of new probes will not only improve diagnostic sensitivity and specificity but also be adapted for the targeted delivery of therapeutic agents[81].

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