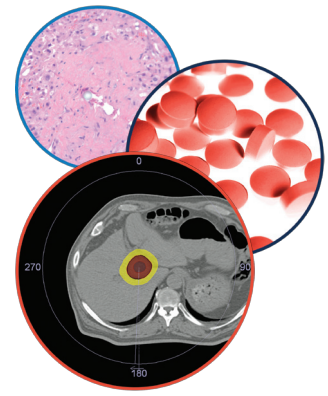
REVIEW

The emerging role of positron emission tomography in hepatocellular carcinoma



Hepatic Oncology

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SUMMARY Hepatocellular carcinoma (HCC) is a leading cause of cancer mortality worldwide. HCC a heterogeneous disease occurring on the background of cirrhosis. The presence of cirrhosis limits the sensitivity of conventional imaging modalities in differentiating HCC from surrounding cirrhotic parenchyma. Positron emission tomography (PET) using ^{18}F-fluorodeoxyglucose (^{18}F-FDG) is widely used for assessing a variety of malignancies, however, has poor sensitivity in the evaluation of HCC. This has led to the investigation of other radiotracers such as ^{11}C-acetate and ^{11}C-choline, with improved sensitivity in terms of detection and therapeutic response. In this review, we discuss the emerging field of PET imaging for the detection, staging and assessment of treatment response in HCC. In particular we discuss the role of ^{18}F-FDG-PET in imaging hepatocellular cancer, the limitations of this PET tracer and emerging novel PET tracers being investigated that exploit key metabolic processes including fatty acid and lipid synthesis, choline kinase activity and gene expression.

Practice points

- There is a clinical need for better imaging in hepatocellular carcinoma (HCC) as conventional imaging has low sensitivity in differentiating regenerative nodules from HCC.
- The utility of ^{18}F-FDG in detecting HCC is limited because of high background uptake of ^{18}F-FDG by normal hepatocytes.
- Clinically, ^{18}F-FDG is limited to detecting extra-hepatic disease and assessing response to poorly differentiated tumors.
- The addition of complementary radiotracers to ^{18}F-FDG can improve the overall diagnostic sensitivity of HCC and also predict survival and recurrence following liver resection or transplantation.
- Several novel PET tracers are currently under investigation and larger studies are needed to establish their role in HCC.

KEYWORDS: • choline kinase activity • fatty acid and lipid synthesis • hepatocellular carcinoma • positron emission tomography

Hepatocellular carcinoma (HCC) is the most common primary liver tumor worldwide and the third most common cause of cancer-related death [1,2]. It is the fifth most common cancer in men and seventh in women [3], with an increasing incidence rate of 3 per 100,000 in the western world, with up to 15 per 100,000 in areas with prevalent hepatitis B and C infections [4]. More than 80% of newly diagnosed HCCs arise in the context of liver cirrhosis, secondary to alcoholic liver disease,

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chronic infection by hepatotropic viruses or metabolic derangements like α-1 antitrypsin deficit and haemochromatosis. Cirrhosis is a progressive process that involves diffuse fibrosis of the liver characterized by the development of nodules that range from benign regenerative nodules to dysplastic nodules to HCC. Early diagnosis and staging of HCC is critical in determining long-term outcome in patients. In those patients where HCC is detected at an early stage, 5-year survival rates of at least 70% can be achieved through surgical interventions and transplantation. However, in patients with late-stage disease, 5-year survival rates are less then 10% despite advances in targeted therapies [5]. Therefore, accurate staging of HCC is critical in determining not only therapeutic options but for prognostication.

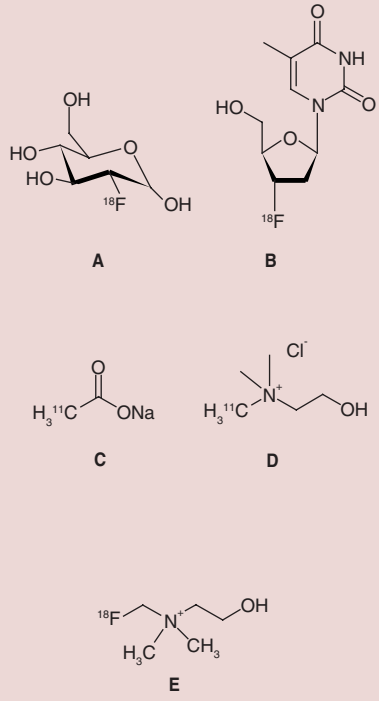
A wide range of imaging modalities such as ultrasound (USS), multiphase computed tomography (CT), dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) are used in diagnosis, staging and monitoring of treatment response, and although each imaging modality has its own individual merits, universal difficulties arise when characterizing small and hypovascular lesions due to their atypical enhancing patterns. The cirrhotic liver is not homogenous but contains regenerative or dysplastic nodules as well as HCC, which presents a challenge to conventional imaging techniques that have limited sensitivity in differentiating the varying pathological processes. Furthermore, there lie challenges in biopsy of lesions in the cirrhotic liver, with risk of needle track seeding, intraperitoneal bleeding and tumor heterogeneity [6]. Therefore, there is a real need for accurate imaging modalities to better image these tumors [7,8].

PET imaging has emerged as an important decision-making tool in oncology particular with the advent of targeted therapies, which tend to produce cytostatic responses on standard imaging, with changes in tumor size taking months to develop, such that patients can be exposed to potential adverse side effects of drugs without any therapeutic benefit [9]. PET allows imaging of molecular pathways and biological processes, and several radiotracers have been investigated within oncology exploiting the key hallmarks of tumorigenesis (e.g., cell proliferation, angiogenesis, apoptosis) [10]. PET imaging involves the intravenous administration of trace amounts of radiolabeled isotopes, which are either substrates of normal physiological processes or specifically bind to biological targets, allowing the evaluation of these processes or substrate–target interaction [11]. It is a noninvasive functional imaging technique that can be combined with CT or MRI to improve spatial resolution. In this way, molecular biological processes such as glucose metabolism, choline kinase activity, gene expression as well as lipid synthesis can be imaged. **Figure 1** highlights different radiotracers that have shown potential use in HCC.

^{18}F-fluorodeoxyglucose

^{18}F-fluorodeoxyglucose (^{18}F-FDG) has emerged as an important noninvasive diagnostic and prognostic tool in several malignancies (e.g., lung, breast and lymphoma) [12]. ^{18}F-FDG is taken up by the cell and phosphorylated by the enzyme hexokinase, it then becomes trapped within the cell. In hepatocytes, however, ^{18}F-FDG is released from the cell due to the high rate of glucose-6-phosphatase, thereby, resulting in reduced accumulation of ^{18}F-FDG in low and intermediate grade HCC. In the primary diagnostic setting, several studies have shown ^{18}F-FDG to have poor sensitivity rates (50–55%) compared with contrast-enhanced CT, USS and MRI[13–16]. It is worth noting, however, that these earlier studies only utilized PET while later scans employ the use of PET/CT that improve resolution. These earlier studies were also limited in the small numbers of patients enrolled. In the largest series of patients with HCC (n = 91), Wudel and colleagues, reported sensitivity rates of 64% with ^{18}F-FDG [17]. Routine use of ^{18}F-FDG, therefore is limited in the primary setting as the rate of gluconeogenesis in well-differentiated HCC and the surrounding liver is similar resulting in almost equivalent uptake of ^{18}F-FDG and therefore poor differentiation of tumors.

^{18}F-FDG has, however, shown promise in the detection of extrahepatic disease, where it can be used in complement with CT. Extrahepatic disease is not uncommon in patients with HCC, reported in up to 37% of patients with the main sites of disease being lung, lymph nodes and bone [18]. Additionally, poorly differentiated HCCs tend to metastasize, and are more likely to be ^{18}F-FDG avid [19]. Sugiyama *et al.*, reported on the use of ^{18}F-FDG in detection of extrahepatic disease in a prospective study involving 19 patients. ^{18}F-FDG had a sensitivity rate of 83% for detecting extrahepatic disease measuring greater than 1 cm, and 13% for lesions less



A **^{18}F-Fluorodeoxyglucose:** A glucose analog with a positron-emitting radioactive isotope Fluorine-18. Half-life 109.8 minutes

B **3′-Deoxy-3′-[^{18}F]-Fluorothymidine:** A substrate for Thymidine Kinase (TK-1, cell cycle regulated enzyme), that phosphorylates ^{18}F-FLT to ^{18}F-FLT monophosphate in tumour cells which leads to trapping within cells and acts as a marker of proliferation. Half-life 109.8 mins

C **^{11}C-Acetate:** A metabolic PET tracer that is rapidly picked up by tumour cells and metabolised to acetyl-CoA, required for membrane fatty acid construction. Half-life 20.3 mins

D **^{11}C-Choline:** Choline is natural substrate within cells and required for the synthesis of phosphatidylcholine (cell membrane integrity). Malignant transformation is associated with changes in pathways of choline transport and utilisation. Half life 20.3 mins

E **^{18}F-Fluorocholine:** ^{18}F labelled choline tracer that is used in imaging of overexpression of choline kinase in malignant transformation. Half-life 109.8 mins

Figure 1. Chemical structures of common tracers involved in imaging of hepatocellular carcinoma.

than or equal to 1 cm [20]. On the basis of their results, resection of isolated extrahepatic metastases was carried out in five patients, with two out of five patients being alive and disease free for greater than 12 months at latest followup.

Yoon *et al.*, compared the sensitivity of ^{18}F-FDG PET with MRI and CT prior to treatment for the detection of extrahepatic disease [21]. Out of 87 patients, 24 were found to have extrahepatic disease, all of which were detected with ^{18}F-FDG. In addition, MRI and CT performed poorly, unable to detect lymph node metastases in four patients and bone metastases in six patients. As a result, a change in TNM staging was seen in 5% of patients which led to a change in clinical management. Furthermore, the authors note that those with primary tumors ≥5 cm were more likely to develop extrahepatic metastases. A recent systematic review and meta-analysis by Chun Yi Lin *et al.* [22], summarized the findings of eight studies (seven retrospective, one prospective), using ^{18}F-FDG in the detection of extrahepatic metastases or recurrent HCC. Pooled estimates of sensitivity and specificity for the detection of extrahepatic disease was reported as 77 and 98%, respectively. The detection of recurrent intrahepatic HCC with ^{18}F-FDG was reported as having a sensitivity of 82% and specificity of 89%. This meta-analysis is important in that it confirms the poor sensitivity of ^{18}F-FDG in the assessment of the primary disease, but suggests a role in the early detection of extrahepatic metastases, which may potentially offer the chance for surgical resection and long-term survival [23,24].

^{18}F-FDG has also shown a promising role in the setting of detecting HCC recurrence. Early detection of recurrent disease is critical, with early surgical resection correlating with better post-recurrent survival rates [7]. Due to high recurrence rates post liver resection (50–60% at 5 years) and liver transplantation (LT; 15–20%) [25,26], ^{18}F-FDG has been investigated as a potential marker of disease recurrence. Yang *et al.* [27] investigated the role of ^{18}F-FDG in determining tumor recurrence following LT in a retrospective study of 38 patients with HCC meeting Milan criteria [5,25]. They reported a significant association between tumor recurrence and PET positivity ($p = 0.016$) with patients with PET-positive tumors having an overall higher risk of recurrence than PET-negative patients (OR = 7.6; 95% CI: 1.9–28.9). In addition, the study reported a statistically significant

association between PET-positive scans and pre-operative serum alpha feto-protein (AFP), whereby positivity of PET imaging correlated with serum AFP greater than 200 ng/ml and vascular invasion ($p < 0.05$). The authors concluded that PET positivity may reflect the aggressiveness of HCC supported by several studies that have reported pre-operative AFP levels as well as vascular invasion to be key factors for tumor recurrence post LT [26,28–31].

The utility of ^{18}F-FDG in the assessment of residual, viable tumor following transarterial chemoembolization (TACE) therapy and radiofrequency ablation (RFA) has also been reported [32,33]. TACE is an effective palliative treatment option for patients with intermediate stage disease but follow up with imaging has proven difficult, as CT is unable to distinguish viable tumor, due to the hyperattenuating lipoidal deposition, which is seen post TACE [32]. The predictive value of ^{18}F-FDG post TACE was reported in a recent study by Song *et al.* [34]. Based on a retrospective review of 83 patients treated with TACE, they evaluated the utility of ^{18}F-FDG in predicting treatment response. All patients underwent ^{18}F-FDG PET within 3 days prior to TACE. They reported that the standardized uptake value ratio (T_{SUV} max, SUV max of tumor/L_{SUV} max, Liver mean SUV; cut-off value 1.90) was significantly associated with overall survival. Those patients whose tumors had a high SUV ratio (≥1.90) had an overall survival of 38 months compared with 10 months in those with a low SUV ratio (<1.90). The results from Song *et al.*, are provocative in suggesting that FDG uptake is a measure of the biological behavior of HCC, and in turn, a marker of treatment response, results that need further exploration in large, prospective, multicenter studies with biological correlates from tumor biopsies.

The use of ^{18}F-FDG has also been reported as a potential tool in detecting earlier recurrence post RFA in HCC [33]. This small retrospective study (n = 24) showed that disease recurrence was detected in more patients using ^{18}F-FDG post RFA in the first 4–9 months compared with CT (8 vs 4 months), and an overall detection rate of 92 versus 75% was observed. Although this was a small study, a significant correlation was noted between SUV values pre-RFA to the time to recurrence detected by ^{18}F-FDG, with patients with high SUV tending to recur earlier than those with lower SUV values. While, several studies have investigated the role of ^{18}F-FDG and its predictive value, it is clear that larger scale studies are needed for further validation of the utility of this tracer, in particular given its limitations in imaging intrahepatic lesions [35].

^{11}C-acetate

The advent of new radiopharmaceuticals has sparked interest in the imaging of HCC, especially given the limitations of ^{18}F-FDG in the primary diagnostic setting. ^{11}C-acetate is used to evaluate fatty acid synthesis which is associated with tumor cell growth and invasiveness [36]. Through an anabolic pathway, acetate is converted into fatty acids by acetyl coenzyme A of the Krebs cycle and then incorporated into the intracellular phosphatidylcholine membrane microdomains. The uptake of acetate is thought to be related to the expression of fatty acid synthetase – a multienzyme that catalyzes the formation of palmitate from acetyl coA and is elevated in well-differentiated HCC [37]. Hence, there is a rationale for using ^{11}C-acetate to better differentiate between neoplastic lesions and inflammation within the liver compared with ^{18}F-FDG. The use of ^{11}C–acetate in the primary diagnosis of HCC, has been reported in a study by Ho *et al.* where differentiation between liver masses was evaluated [38]. The sensitivity rate ^{11}C-acetate in detecting HCC was 87% with no uptake observed in other liver masses (i.e., metastatic lesions secondary to colon, breast and lung, cholangiocarcinoma and carcinoid tumors).

The differential uptake pattern seen with different tracers due to heterogeneity within tumors can be exploited, and in a further study, Ho *et al.* reported the use of ^{11}C-acetate in conjunction with ^{18}F-FDG in patients with HCC [19]. They reported that while sensitivity using ^{11}C-acetate alone was good in well-differentiated tumors, ^{18}F-FDG was better in the detection of poorly differentiated tumors. By using both tracers, there was a 100% sensitivity rate in the detection of HCC. Park *et al.* also evaluated the use of dual tracers (^{11}C-acetate and ^{18}F-FDG) in a prospective study involving 90 patients diagnosed with HCC [39]. They reported a sensitivity rate of 83% using the combination of tracers compared with 60% with ^{18}F-FDG alone, and 75% with ^{11}C-acetate. The study also highlighted that higher sensitivity rates were related to larger tumor size (≥5 cm), and again confirming the results from previously discussed studies that ^{18}F-FDG had higher detection rate for extrahepatic metastases.

In a similar study, Cheung *et al.*, utilized a dual tracer approach with ^{11}C-acetate and ^{18}F-FDG to predict microvascular invasion before LT or surgical resection in 58 patients with HCC [40]. The sensitivity in detecting HCC using a dual tracer approach was 93% compared with 43% using ^{18}F-FDG alone. The addition of ^{11}C-acetate improved the overall sensitivity of ^{18}F-FDG, providing more information on the number of lesions, histological grade of the tumor as well as the probability of microvascular invasion in patients being considered for LT [40]. Overall, ^{11}C-acetate may be of use in primary setting but used in combination with ^{18}F-FDG seems to be of benefit in metastatic HCC. However, routine clinical use of a dual tracer approach is limited given the duration of time to perform, the high overall radiation dose delivered to the patient as well as the short half-life of ^{11}C-acetate (20.4 min) necessitating an onsite cyclotron.

^{11}C-choline

Choline is a substrate for the synthesis of phosphatidylcholine, a major phospholipid in the cell membrane [41]. During malignant transformation, overexpression of key enzymes involved in choline metabolism are seen (e.g., choline kinase-α [CHKα]), leading to increased phosphocholine and total choline containing compounds [41]. Deranged choline metabolism, and in particular, overexpression of CHK-α, has been reported in several cancers such as prostate, colon, ovarian and breast [42,43]. As such PET imaging with choline tracers is used clinically for staging prostate cancer, and is being investigated in several other tumor types. Despite its promising role in imaging malignancy, ^{11}C-choline has not been established in HCC. A recent retrospective study by Yamamoto *et al.*, failed to show statistical significance in evaluation of ^{11}C-choline, with sensitivity rate of 63 vs 50% compared with ^{18}F-FDG in the detection of HCC [44]. A further, small prospective study (n = 12) by Talbot *et al.* using ^{18}F-fluorocholine (^{18}F-FCH) reported a 100% detection rate on a per-patient analysis in newly diagnosed and recurrent HCC [45]. The authors observed a trend between high SUV and well-differentiated HCC. ^{18}F-FCH may therefore be potentially useful in visualizing HCC, however, this was a small study and patients selected had large lesions, mean size (8.15 ± 3.9 cm).

The complementary role of radiolabeled choline analogs has also been investigated in HCC, as it can preferentially detect well-differentiated lesions that are not ^{18}F-FDG-avid [46]. A prospective study by Wu *et al.*, evaluated 76 patients with HCC who underwent ^{18}F-FDG PET/CT. They reported that 48 out of 76 (61%) patients had positive ^{18}F-FDG PET/CT scans. Those with no uptake seen on ^{18}F-FDG scans (n = 28) were subsequently scanned with ^{11}C-choline PET/CT. The study showed that imaging with ^{11}C-choline increased the sensitivity of ^{18}F-FDG alone from 63 to 90% ($p < 0.001$), and that ^{18}F-FDG showed a lower sensitivity for well-differentiated HCC (36 vs 67%) compared with ^{11}C-choline [46]. Larger studies are needed to confirm use of these tracers and evaluate their specificity.

Other potential PET tracers in imaging HCC

• ^{18}F-fluorothymidine

Thymidine is a nucleoside utilized in DNA replication by proliferating cells, and both thymidine and its analogs have been extensively studied as markers of cellular proliferation. After injection, ^{18}F-fluorothymidine (^{18}F-FLT) enters the cell by both active transport, via sodium-dependent nucleoside transporters, and by passive diffusion. ^{18}F-FLT follows the salvage pathway of DNA synthesis and like thymidine undergoes phosphorylation by thymidine kinase–1 (TK1) to ^{18}F-FLT-monophosphate [47]. ^{18}F-FLT is a selective substrate for TK1 whereas thymidine is also phosphorylated by TK2. TK1 is virtually absent in quiescent cells but is increased in proliferating cells [48,49]. Phosphorylated ^{18}F-FLT is not incorporated into DNA and is trapped within the cytosol. The rate-limiting step for ^{18}F-FLT accumulation is the initial phosphorylation by TK1; it is also the rate-limiting step in the salvage pathway of DNA synthesis, therefore the handling of ^{18}F-FLT reflects cellular proliferation [50].

The 'accuracy' of ^{18}FFLT PET in demonstrating proliferation has been illustrated in a number of studies where ^{18}F-FLT PET parameters have been shown to correlate with the histological marker of proliferation, Ki67 labeling index, in colorectal, breast and lung cancer [51–53]. In a small pilot study, Eckel et al. utilized ^{18}F-FLT PET to visualize HCC [54]. Eighteen untreated patients with clinical suspicion of HCC underwent USS, MRI or CT followed by ^{18}F-FLT PET. The results showed a mixed pattern of uptake on PET and poor sensitivity rates: (69%) in the

detection of HCC. However, the sensitivity of ^{18}F-FLT PET in detecting HCC was hampered by high background activity within the normal liver, the result of rapid delivery and metabolism of ^{18}F-FLT to ^{18}F-FLT-glucuronide. This limits the utility of ^{18}F-FLT in assessing proliferation in liver tumors and further studies in HCC have not been pursued.

• 9–(4–^{18}F-Fluoro-3-hydroxymethylbutyl) guanine (^{18}F-FHBG)

^{18}F-FHBG is used to image gene expression of herpes simplex virus type-1 thymidine kinase (HSV1-tk) and is a safe and stable radiotracer with a rapid blood clearance and acceptable radiation doses [55]. Gene therapy offers a new area of treatment for patients with HCC, whereby the introduction of genetic material into tumor tissue produces therapeutic benefit either through the restoration of tumor suppressor genes, the activation of a prodrug, the stimulation of antitumor immune activity or via oncolytic virotherapy [56]. PET offers a safe, sensitive and reproducible imaging modality of monitoring of transgene expression with the aid of a reporter gene and probe that accumulates only in the organ of interest. In a Phase I study performed by Penuelas *et al.* [57], ^{18}F-penciclovir analog (^{18}F-FHBG) was used to analyze transgene expression of herpes simplex virus thymidine kinase (HSV1-tk) in seven patients with HCC after intratumoral introduction of a recombinant adenoviral vector encoding thymidine kinase (AdCMVtk). This study identified that all patients who displayed accumulation of ^{18}F-FHBG in tumor lesions within the first hours of injecting the viral vector containing HSV1-tk showed stable disease a month later compared with patients without detectable ^{18}F-FHBG tumor lesions who progressed at 1 month. This study suggests that PET imaging can be used to assess transduction efficiency of a viral vector as well as predict the efficacy of gene-therapy strategies, making it a potential tool in early phase clinical trials.

There is still no ideal PET tracer for the assessment of HCC, and the search for potential tracers continues to be in development (Table 1). Recent attempts, with ^{11}C-metomidate (methyl derivative of etomidate), previously used as an imaging tool in detection of adrenocortical tumors, have been disappointing with low sensitivity for detection of HCC compared with ^{11}C-acetate [58]. The tracer binds to GABA (gamma-aminobutyric acid) receptors, which are upregulated in HCC [59]. Further preliminary work has also been carried out investigating the use of (4*S*)-4-(3–18F-fluoropropyl)-L-glutamate (^{18}F-FSPG), for imaging of x_C^- transporter activity in HCC [60]. x_C^-, is a sodium independent transporter system that is responsible for the defense machinery in cells against oxidative stress and mediates uptake of cysteine in exchange for intracellular glutamate [61,62]. Thiol containing molecules such as glutathione are essential for the deactivation of reactive oxygen species, and this defense mechanism, offers a particular advantage for tumor cell growth [63].

Conclusion & future perspective

The low sensitivity of ^{18}F-FDG in the assessment of intrahepatic HCC patient, limits routine clinical use, and is limited to the evaluation of extrahepatic disease in some centers. The advent of new radiotracers enables the visualization of other metabolic processes apart from glucose metabolism and have improved diagnostic sensitivity both in conjunction with ^{18}F-FDG PET or as when used as single agent for imaging of HCC. While the role of dual tracers in imaging will continue to evolve this strategy is limited because of need for on-site cyclotron facilities, cost and inconvenience for patients. It is also important to consider other limitations of PET, in particular the inability to detect small lesions (<2 cm) due to poor spatial resolution, and partial volume effects as well as additional radiation exposure. PET imaging also involves quite complex scanning protocols and set up and analysis is resource intensive. These limitations mean that we will continue to combine imaging procedures using CT, MRI and PET. This multiparametric imaging approach uses both morphological and molecular information, enabling us to understand the biologic processes and guides us in management decisions for patients [64].

The advent of PET/MRI hybrid imaging systems has the potential for improved accuracy of staging, with MRI providing information on tumor extent and identification of small lesions that are pivotal for treatment decisions and in assessing whether patients are suitable for radical or palliative approach. Treatment response is often difficult to assess using RECIST criteria, especially with the advent of targeted drugs, which often produce cytostatic changes or necrosis. The role of PET, therefore, allowing

Table 1. Summary of translational studies that have investigated use of positron emission tomography in hepatocellular carcinoma.

Radiotracer	Study	Number of patients	Sensitivity (%)	Specificity (%)	Accuracy (%)	Ref.
^{18}F-FDG	Cheung	58	43% detection of primary HCC55% predicting MI	69 predicting MI		[67]
	Wu	76	63% detection of primary HCC83% detection of EM	95 in EM	91 in EM	[68]
	Ho	121	79% detection of EM	91		[19]
	Chen	31	73% detecting HCC recurrence	100		[7]
	Wang	11	100% detecting HCC recurrence	67		[69]
	Ho	257	62% detection of EM			[70]
	Yamamoto	12	50% detection of primary HCC			[44]
	Khan	20	55% detection of primary HCC			[13]
	Park	99	64% detection of primary HCC; 86% detection of EM	100		[39]
	Paudyal	24	92% detection of recurrence	100		[33]
^{18}F-FLT	Eckel	16	69% detection of primary HCC			[54]
^{11}C-Acetate(in combination with ^{18}F-FDG)	Ho	39	87% primary HCC			[38]
	Ho	257	93% alone97% combined with ^{18}F-FDG detection of EM			[70]
	Park	99	84% alone; detection of primary HCC 77% alone; detection of EM86% combined with 18F-FDG detection of EM			[39]
	Cheung	58	93% predicting MI	0		[67]
^{11}C- Choline	Wu	76	86% detection of primary HCC 90% (dual tracer with ^{18}F-FDG)			[68]
	Yamamoto	12	63% detection of primary HCC			[44]

^{18}F-FDG: ^{18}F-Fluorodeoxyglucose; ^{18}F-FLT: 18F-Fluorothymidine; EM: Extrahepatic metastases; HCC: Hepatocellular carcinoma; MI: Microvascular invasion.

detection of changes in metabolic processes may lie primarily in response assessment and aid in identifying tumor recurrence. PET imaging has shown to predict response to therapy in other tumor types as well as guide targeted therapy with better understanding of the metabolic processes of liver tumor cells.

Current search for biomarkers in HCC are in development with cross collaboration in imaging and drug development. Galectin-4, a multifunctional lectin present intra- and extra-cellularly, has recently been identified as a potential prognostic marker in HCC [65]. Another avenue of potential research is the application of mathematical modeling techniques using ^{18}F-FLT-PET to enhance the visualization of liver lesions [66].

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending or royalties.

No writing assistance was utilized in the production of this manuscript.

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