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REVIEW ARTICLE **CME**

Update on Positron Emission Tomography for Hepatocellular Carcinoma

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ABSTRACT

Hepatocellular carcinoma (HCC) is conventionally evaluated with ultrasonography, computed tomography, and magnetic resonance imaging. Positron emission tomography (PET) using the commonest radiotracer fluorine-18 fluorodeoxyglucose ([^{18}F]FDG) has only a moderate sensitivity in detecting the primary tumour. This leads to the use of other radiotracers with better sensitivity for HCC, including carbon-11 acetate, carbon-11 choline, and fluorine-18 fluorocholine. PET using dual tracers (FDG complemented with a non-FDG tracer) can optimise the diagnostic performance. Although [^{18}F]FDG PET has a limited role in detecting the primary tumour, it is more accurate in diagnosing extrahepatic metastases, which may affect treatment planning. Pre-treatment [^{18}F]FDG PET also has a potential role in predicting prognosis and treatment outcomes, and supplementing established criteria to select patients for liver transplantation. Post-treatment PET may evaluate therapeutic response or detect tumour recurrence but supporting data remain relatively limited. There has been rapid advancement in the usage of PET for HCC; this warrants further prospective studies to confirm the role of PET in clinical management.

Key Words: *Carbon-11 acetate; Carbon-11 choline; Carcinoma, hepatocellular; Fluorodeoxyglucose F18; Positron-emission tomography*

中文摘要

正電子發射斷層掃描用於肝細胞癌的更新

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肝細胞癌（HCC）的成像評估通常通過超聲檢查、電腦斷層掃描和磁共振成像進行。在檢測原發性HCC的應用上，正電子發射斷層掃描（PET）配合常用的氟-18氟脫氧葡萄糖（[^{18}F]FDG）只有中度的靈敏性，因此需要使用其他對HCC有較高靈敏性的放射性示蹤劑，包括碳-11乙酸酯、碳-11膽鹼、氟-18氟膽鹼。組合性使用放射性示蹤劑能相互取長地提高PET在診斷HCC的成像精度。儘管[^{18}F]FDG PET對於原發性HCC檢測的價值有限，但對於檢測肝外轉移則具有較高的精確性，藉此或能影響制訂治療方案。療前的[^{18}F]FDG PET更在預測HCC患者的預後和治療結果具有潛在作用，亦可能幫助選擇患者接受肝移植。療後PET可以監測HCC治療反應和檢測腫瘤復發，但確證的數據是相對有限的。PET在HCC的應用迅速發展，有待進一步的前瞻性研究以確立其在臨牀治療過程中的應用。

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INTRODUCTION

In Hong Kong, hepatocellular carcinoma (HCC) is the dominant histopathologic type of primary liver cancers, which rank as the fourth most common cancer and the third most common cause of cancer-related deaths.[1] The incidence of HCC is on a downward trend, partly related to vaccination against predisposing hepatitis B virus infection, but it continues to be a highly prevalent disease with high mortality in East Asia including China.[2] The diagnosis and evaluation of HCC is primarily based on laboratory tests, contrast-enhanced computed tomography and / or magnetic resonance imaging and when necessary, tissue biopsy.[3,4] Although positron emission tomography (PET) has wide oncological application, its use in prevailing clinical management guidelines and staging systems for HCC is limited.[3-6] In recent years, there has been a surge of clinical PET studies related to HCC. This review article aims to provide an update on the emerging role of PET in management of HCC.

DETECTION OF PRIMARY LESION

Ultrasonography is commonly used for surveillance of HCC in high-risk patients, whereas computed tomography and magnetic resonance imaging are the standard imaging modalities for diagnosing HCC, with pooled per-lesion sensitivity of 72% and 79%, respectively.[3,4,7] Fluorine-18 fluorodeoxyglucose ([^{18}F]FDG) is the first commonly used PET radiotracer for detection of HCC.[8,9] It is a glucose analogue that enters the living cell via glucose transporters, and is phosphorylated by hexokinase to 2-deoxyglucose-6-phosphate, which is then retained within the cell. In tumour cells, increased expression of glucose transporters forms the basis of FDG accumulation.[10] For detection of primary HCC, [^{18}F]FDG PET has a pooled sensitivity of 52% (95% confidence interval [CI] = 47-56%) on a per-patient basis and 47% (95% CI = 43%-51%) on a per-lesion basis (Table 1).[8,9,11-31] The modest sensitivity is due to a high dephosphorylation rate of 2-deoxyglucose-6-phosphate by glucose-6-phosphatase in well-differentiated HCC, which is similar to that in normal hepatocytes, leading to a decrease in tumoural FDG retention.[8,27,30] Contrarily, poorly differentiated HCC tends to increase glycolytic enzymes and decrease glucose-6-phosphatase expression, thereby increasing the detectability by [^{18}F]FDG PET.[12,17,24,27,30-32] Semi-quantitatively, the standardised uptake value (SUV) of FDG was significantly higher in poorly differentiated HCC than in well-differentiated and

Table 1. Studies related to fluorine-18 fluorodeoxyglucose positron emission tomography for detection of primary hepatocellular carcinoma.

Study	Design	No. of patients / lesions	Patient-based sensitivity (%)	Lesion-based sensitivity (%)
Li et al.,[11] 2017	Prospective	22 / 70	45	23
Bailly et al.,[12] 2016	Retrospective	34 / -	29	-
Castilla-Lièvre et al.,[13] 2016	Prospective	28* / 43	36	30
Chotipanich et al.,[14] 2016	Prospective	9 / 9	67	67
Wang et al.,[15] 2015	Prospective	22 / 37	-	57
Cheung et al.,[16] 2013	Retrospective	43 / 58	40	33
Ijichi et al.,[17] 2013	Retrospective	53 / 67	-	43
Larsson et al.,[18] 2012	Retrospective	44 / -	30	-
Cheung et al.,[19] 2011	Retrospective	58 / -	43	-
Wu et al.,[20] 2011	Prospective	76 / -	63	-
Talbot et al.,[21] 2010	Prospective	34* / 70	68	67
Wolfort et al.,[22] 2010	Retrospective	20 / -	70	-
Hwang et al.,[23] 2009	Prospective	10 / -	40	-
Park et al.,[24] 2008	Prospective	90 / 110	-	61
Yamamoto et al.,[25] 2008	Retrospective	12 / 16	-	50
Talbot et al.,[26] 2006	Prospective	9 / -	56	-
Ho et al.,[27] 2003	Prospective	32 / 55	-	47
Jeng et al.,[28] 2003	-	36 / -	56	-
Wudel et al.,[29] 2003	Retrospective	67 / -	64	-
Khan et al.,[30] 2000	Retrospective	20 / -	55	-
Trojan et al.,[31] 1999	Prospective	14 / -	50	-
Delbeke et al.,[9] 1998	Prospective	23 / -	70	-
Okazumi et al.[8] 1992	-	20 / -	55	-

* Including a small proportion (<6%) of patients with combined hepatocellular-cholangiocarcinoma.

moderately differentiated HCC.[32] Other factors associated with high FDG uptake include large tumour size, multiple tumours, high serum alpha-fetoprotein (AFP) levels, advanced tumour stage, and vascular invasion.[13,17,22,24,31,33] The specificity of [^{18}F]FDG PET for HCC was seldom reported; one study reported it to be 94% on a per-patient basis and 91% on a per-lesion basis.[21] False-positives or other potentially FDG-avid lesions include infective or inflammatory lesion, focal nodular hyperplasia, hepatic adenoma, other hepatic primary or secondary tumour, and isolated cases of angiomyolipoma and focal hepatic steatosis.[21,24,34-38]

Owing to suboptimal detectability of HCC by [^{18}F]FDG alone, the use of other radiotracers with or without combination of [^{18}F]FDG was suggested. Carbon-11 acetate ([^{11}C]acetate) was one of the non-FDG radiotracers tested for hepatic lesions.[27] The mechanism of acetate uptake in tumours is related to its contribution to free fatty acid synthesis.[39] The pooled sensitivity of [^{11}C]acetate PET is 82% (95% CI = 77%-87%) on a per-patient basis and 71% (95% CI = 66%-75%) on a per-lesion basis (Table 2).[11,16,18,19,23,24,27,40,41] [^{11}C]acetate and [^{18}F]FDG are complementary; well-differentiated HCC is more readily detected by [^{11}C]acetate PET, whereas poorly differentiated HCC is more readily detected by [^{18}F]FDG PET.[23,24,27] Dual-tracer (FDG + acetate) PET has a pooled sensitivity of 88% (95% CI = 80%-93%) on a per-patient basis and 82% (95% CI = 77%-86%) on a per-lesion basis.[11,16,18,24,27] The specificity of

Table 2. Studies related to non-fluorodeoxyglucose positron emission tomography for detection of primary hepatocellular carcinoma.

Study	Design	No. of patients / lesions	Patient-based sensitivity (%) by single tracer / combined with fluorodeoxyglucose	Lesion-based sensitivity (%) by single tracer / combined with fluorodeoxyglucose
Carbon-11 acetate				
Li et al.,[11] 2017	Prospective	22 / 70	68 / 73	51 / 57
Cheung et al.,[16] 2013	Retrospective	43 / 58	93 / 95	93 / 95
Roivainen et al.,[40] 2013	Prospective	14 / 59	50 / -	44 / -
Larsson et al.,[18] 2012	Retrospective	44 / -	77 / 89	- / -
Cheung et al.,[19] 2011	Retrospective	58 / -	93 / -	- / -
Hwang et al.,[23] 2009	Prospective	12 / 25	83 / -	64 / -
Park et al.,[24] 2008	Prospective	90 / 110	- / -	75 / 83
Li et al.,[41] 2006	Prospective	18 / 46	78 / -	78 / -
Ho et al.,[27] 2003	Prospective	32 / 55	- / -	87 / 100
Fluorine-18 fluoroacetate				
Takemoto et al.,[45] 2014	-	5 / -	60 / 60	60 / 60
Ho et al.,[46] 2012	-	5 / -	0 / -	0 / -
Carbon-11 choline				
Castilla-Lièvre et al.,[13] 2016	Prospective	28* / 43	75 / 93	67 / 81
Chotipanich et al.,[14] 2016	Prospective	9 / 9	78 / -	78 / -
Lopci et al.,[48] 2015	Prospective	50 scans / 79	88 / -	59 / -
Wu et al.,[20] 2011	Prospective	28† / -	71 / 89‡	- / -
Yamamoto et al.,[25] 2008	Retrospective	12 / 16	- / -	63 / 100
Fluorine-18 fluorocholine				
Kwee et al.,[49] 2017	Prospective	37 / 37	84 / -	84 / -
Bieze et al.,[50] 2014	Prospective	29 / 50	- / -	88 / -
Talbot et al.,[21] 2010	Prospective	34* / 70	88 / 94	84 / 90
Talbot et al.,[26] 2006	Prospective	12 / -	100 / -	- / -
Fluorine-18 fluorothymidine				
Eckel et al.,[51] 2009	Prospective	16 / -	69 / -	- / -
Carbon-11 metomidate				
Roivainen et al.,[40] 2013	Prospective	14 / 59	43 / -	46 / -
2-[^{18}F]fluoro-2-deoxy-D-galactose				
Horsager et al.,[52] 2016	-	10 / 15	40 / -	53 / -
Sørensen et al.,[53] 2011	-	23 / -	74 / -	- / -
(4*S*)-4-(3-[^{18}F]fluoropropyl)-L-glutamic acid				
Kavanaugh et al.,[54] 2016	Prospective	11 / 16	73 / -	75 / -
Baek et al.,[55] 2013	-	5 / 5	100 / 100	100 / 100

* Including a small proportion (<6%) of patients with combined hepatocellular-cholangiocarcinoma.
† Comprised primary tumours with negative fluorodeoxyglucose positron emission tomography.
‡ Derived from 48 fluorodeoxyglucose-positive and 20 choline-positive tumours in 76 patients.

[^{11}C]acetate PET for HCC was 79% on a per-patient basis in one study.[40] False-positives or other potentially acetate-avid lesions include focal nodular hyperplasia, high grade dysplastic nodule, hepatic adenoma, angiomyolipoma, cholangiocarcinoma, and isolated cases of intrahepatic lymphoid hyperplasia and hepatic splenosis.[16,24,35,40,42-44] Fluorine-18 fluoroacetate ([^{18}F]FAC) was tested because ^{18}F radionuclide has a longer half-life than ^{11}C radionuclide (110 minutes vs. 20 minutes). One study reported positive [^{18}F]FAC uptake in three out of five HCC patients, similarly detected by [^{18}F]FDG, but in another study, none of the [^{11}C]acetate-avid primary lesions showed [^{18}F]FAC-avidity (Table 2).[45,46]

Carbon-11 choline ([^{11}C]CH) targets choline metabolism which is essential for cell membrane phospholipid synthesis.[47] Cancer cells incorporate choline actively to facilitate rapid cell duplication. Fluorine-18 choline derivatives, notably fluorine-18 fluorocholine ([^{18}F]FCH), has also been used (Table 2).[13,14,20,21,25,26,48-50] The pooled sensitivity of [^{11}C]CH PET and [^{18}F]FCH PET is 83% (95% CI = 77%-88%) on a per-patient basis and 75% (95% CI = 69%-79%) on a per-lesion basis. Similar to acetate, CH and FCH appear to be complementary with FDG and tends to have higher sensitivity in detecting well-differentiated HCC.[13,14,20,21,25,26] Dual-tracer (FDG + CH or FCH) PET has a pooled sensitivity of 91% (95% CI = 85%-95%) on a per-patient basis and 88% (95% CI = 82%-93%) on a per-lesion basis (Table 2).[13,20,21,25] The specificity of [^{11}C]CH or [^{18}F]FCH PET for HCC was 47% to 90% on a per-patient basis and 62% to 86% on a per-lesion basis.[21,48] Reported false-positives were cholangitis, focal nodular hyperplasia, hepatic adenoma, and cholangiocarcinoma.[21,48]

Other PET radiotracers were also studied (Table 2).[40,51-55] Fluorine-18 fluorothymidine, the uptake of which is based on metabolism within the DNA synthesis pathway, was reported to have a sensitivity of 69% in detecting HCC.[51] Carbon-11 metomidate that binds to gamma-aminobutyric acid receptors yielded a sensitivity of 43% for HCC.[40] 2-[^{18}F]fluoro-2-deoxy-D-galactose that targets the hepatic galactose metabolism was reported to have a sensitivity of 40% to 74%.[52,53] (4*S*)-4-(3-[^{18}F]fluoropropyl)-L-glutamic acid is an imaging biomarker for the cystine / glutamate antiporter system x_c^- that exchanges intracellular L-glutamate for extracellular L-cystine or L-glutamate; it was reported to detect all five HCC in a pilot study and resulted in 73% sensitivity in a subsequent study.[54,55]

In addition to non-FDG and dual-tracer methods, a few studies proved the possibility to achieve a better sensitivity in detecting HCC by a single radiotracer, [^{18}F]FDG, but with a dual-time-point method incorporating an early dynamic imaging of hepatic perfusion plus a standard imaging of FDG metabolism,[15,56,57] and this may also have an add-on delayed imaging.[58] This warrants further comparative studies regarding not only diagnostic accuracies but also the incurred costs and radiation doses.[59]

DETECTION OF EXTRAHEPATIC METASTASES

In a meta-analysis of three [^{18}F]FDG PET studies with 239 patients, the pooled sensitivity and specificity for detection of extrahepatic metastases were 77% and 98%, respectively.[60] The relatively higher sensitivity of [^{18}F]FDG PET for detecting extrahepatic metastases of HCC as compared with primary lesions could be explained by an increased likelihood for metastases to occur in poorly differentiated type of HCC, which tends to have a higher level of FDG uptake.[61] [^{18}F]FDG PET was reported to be more sensitive than bone scintigraphy in detecting bone metastases.[62] Although [^{18}F]FDG PET is relatively sensitive in detecting extrahepatic metastases, it is not yet included as a routine modality for pre-treatment staging of HCC. There are also PET studies using various non-FDG radiotracers to detect extrahepatic metastases.[24,40,48,50,53,61,63]

Large tumour size and high FDG uptake in primary lesions were independent predictors for FDG-avid extrahepatic metastases; selective use of PET in high-risk patients to detect metastases was thus suggested.[64,65] In a study of 64 HCC patients, treatment in 16 patients (25%) were changed (mostly from a curative treatment to sorafenib therapy) when PET upstaged the HCC according to the Barcelona Clinic Liver Cancer (BCLC) classification.[65] In another study of 457 HCC patients, 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 PET might be appropriate for A to B stages especially before resection or transplantation.[66] The reported data on PET for HCC staging have yet to reach a wider consensus on when to perform PET to detect extrahepatic metastases.

PRE-TREATMENT PROGNOSTICATION

[^{18}F]FDG PET has a potential role in predicting

prognosis of HCC patients. In a meta-analysis drawn from 22 studies with 1721 patients, high pre-treatment tumour-to-liver SUV ratio was significantly associated with poorer overall survival (hazard ratio [HR] = 2.04, 95% CI = 1.50-2.79) and poorer disease-free survival (HR = 7.17, 95% CI = 3.58-14.4); high tumour SUV was also associated with poor overall survival (HR = 1.53, 95% CI = 1.26-1.87).[67] The median cutoff values for the SUV ratio and tumour SUV for overall survival were 1.83 and 4.9, respectively.[67]

Further retrospective multicentre studies have been reported. In a study of 195 patients with early-stage HCC amenable to curative treatments, pre-treatment tumour-to-liver uptake ratio (TLR) using 2 as cutoff was an independent prognostic factor for overall survival (HR = 2.68, 95% CI = 1.16-6.15) and recurrence-free survival (HR = 2.28, 95% CI = 1.15-4.52).[68] In a study of 214 patients who received transarterial chemoembolisation (TACE) or concurrent intra-arterial chemotherapy with radiotherapy, TLR was also an independent factor for overall survival and progression-free survival.[69] In a study of 291 subjects with more advanced disease (138 of whom had extrahepatic metastases), high TLR was independently associated with poorer overall survival for both intrahepatic disease group (cutoff = 3.0, HR = 1.89, 95% CI = 1.30-2.73) and extrahepatic disease group (cutoff = 3.2, HR = 1.69, 95% CI = 1.13-2.51).[70] In a study of 166 patients with portal vein tumour thrombosis, FDG uptake of the thrombosis was another independent prognostic factor for overall survival and progression-free survival.[71] In a study of 182 subjects who underwent living donor liver transplantation, PET-positive status was one of the independent risk factors for HCC recurrence.[72] Prognostic value of other PET parameters in patients receiving curative surgical resection, stereotactic ablative radiotherapy, yttrium-90 (^{90}Y) selective internal radiation therapy (SIRT) or sorafenib therapy has also been reported.[73-76]

PRE-TRANSPLANTATION EVALUATION

Liver transplantation is a curative treatment for HCC. The Milan criteria are the benchmark for selection of patients with underlying cirrhosis for liver transplantation.[3] These criteria use the size and number of the tumours as parameters (presence of a tumour ≤5 cm in diameter in patients with single HCC, or no more than 3 tumour nodules, each ≤3 cm in diameter, in patients with multiple tumours) in the absence of macrovascular invasion or extrahepatic involvement.[77] Nonetheless, standard imaging methods underestimate or overestimate the extent of HCC in about 20% to over 30% when compared with pathological findings of the explanted liver.[78-81] In a study of 22 transplanted patients, dual-tracer (FDG + acetate) PET achieved higher accuracy than standard computed tomography alone (95% vs. 50%) in classifying the Milan-criteria status.[16] Nonetheless, it has not yet been compared with modern magnetic resonance imaging methods.

The Milan criteria, albeit widely recognised, are rather restrictive in selecting patients. Many adapted criteria, notably the University of California San Francisco criteria with expanded morphometric parameters, have been adopted to enable more patients to be considered for transplantation.[4,80,82] [^{18}F]FDG PET provides additional metabolic parameter and has been evaluated regarding its potential value in assisting patient selection for liver transplantation (Table 3).[72,81,83-90] PET-positivity is an independent predictor of tumour recurrence and shorter recurrence-free survival; it is based on visual qualitative assessment and / or semi-quantitative index with cutoff derived from receiver operating characteristic curve analysis. Subgroup analyses showed that patients beyond the Milan criteria but were PET-negative had similar survival compared with those within the criteria.[81,83,87,88] PET-negativity may support liver transplantation in patients beyond the Milan criteria, whereas PET-positivity may be a contraindication to liver transplantation especially when accompanied by further risk factors such as a high AFP level.[6,91] All these retrospective studies are consistent about the prognostic value of [^{18}F]FDG PET, proven with statistical significance. [^{18}F]FDG PET has a potential role of supplementing established criteria in patient selection for liver transplantation, despite lacking prospective, randomised studies to confirm.

Microvascular invasion and histologic grading are independent prognostic factors of post-transplantation outcomes.[92-94] Pre-operative tumour biopsy has a risk of tumour seeding, which was estimated to be 2.7% in a meta-analysis.[95] In addition, different tumour grades or histologic heterogeneity is not uncommon within a single tumour especially for large lesions, thus biopsy results often show poor concordance with final tumour grades.[96,97] Pre-operative [^{18}F]FDG PET for prediction of microvascular invasion has a wide range of sensitivity (30%-90%), specificity (37%-92%), and positive predictive value (35%-88%), whereas

Table 3. Studies related to fluorine-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) for prediction of prognosis after liver transplantation for hepatocellular carcinoma.

Study	Design	No. of patients	Median / mean±SD (range) follow-up (months)	PET parameters	Results
Takada et al.,[72] 2017	Retrospective	182	55 (1-125)	Tumour SUV_{max} > liver SUV_{max} (PET+)	PET+ vs. PET– for RR at 1 / 3 / 5 years (15% / 28% / 28% vs. 4% / 10% / 12%, p = 0.007; relative risk = 2.55, 95% CI = 1.10-5.92, p = 0.029) and OS at 1 / 3 / 5 years (77% / 64% / 58% vs. 86% / 77% / 75%, p = 0.043); Beyond MC and PET+ and / or AFP ≥115 ng/ml vs. beyond / within MC but PET– and AFP <115 ng/ml for RR at 5 years (53% vs. 8%, p < 0.001) and OS at 5 years (44% vs. 75%, p = 0.003)
Ye et al.,[83] 2017	Retrospective	103	26 (6-85)	T_{SUVmax}/L_{SUVmax} >1.35 (PET+)	PET+ vs. PET– for RR (59% vs. 28%, p = 0.007) and RFS at 1 / 3 / 5 years (70% / 39% / 22% vs. 92% / 82% / 76%, p = 0.001) and OS at 1 / 3 / 5 years (75% / 55% / 50% vs. 96% / 87% / 76%, p = 0.001; HR = 4.57, 95% CI = 1.42-14.7, p = 0.011); Within MC and PET+ vs. within MC and PET– for RFS at 5 years (65% vs. 92%, p < 0.05) and OS at 5 years (81% vs. 92%, p = 0.233); Beyond MC and PET+ vs. beyond MC and PET– for RFS at 1 / 3 / 5 years (57% / 33% / 11% vs. 90% / 79% / 66%, p = 0.002) and OS at 1 / 3 / 5 years (63% / 49% / 33% vs. 90% / 80% / 67%, p = 0.044); Beyond MC and PET– vs. within MC for RFS at 1 / 3 / 5 years (90% / 79% / 66% vs. 95% / 73% / 73%, p = 0.148) and OS at 1 / 3 / 5 years (90% / 80% / 67% vs. 98% / 83% / 83%, p = 0.123)
Hong et al.,[84] 2016	Retrospective	123	43 (3-103)	T_{SUVmax}/L_{SUVmax} ≥1.10 (PET+)	PET+ vs. PET– for DFS at 5 years (49% vs. 93%, p < 0.001; HR = 9.77, 95% CI = 3.56-26.8, p < 0.001); PET+ and AFP level ≥200 ng/ml vs. PET– and AFP level <200 ng/ml for DFS at 5 years (8.3% vs. 94%, p < 0.001; HR = 29.1, 95% CI = 8.80-96.1, p < 0.001)
Hsu et al.,[85] 2016	Retrospective	147	26 (interquartile range, 33)	Tumour FDG uptake significantly > liver FDG uptake; $T_{SUVmax}/L_{SUVmean}$ >1.20 (PET+)	PET+ vs. PET– for RR (30% vs. 7.7%) and RFS at 1 / 3 / 5 years (72% / 68% / 68% vs. 97% / 91% / 85%, p < 0.001; HR = 4.49, 95% CI = 1.78-11.3, p = 0.001); PET+ and $T_{SUVmax}/L_{SUVmean}$ ≥2.0 vs. PET– for RR (67% vs. 7.7%) and RFS at 1 / 3 / 5 years (44% / 30% / 30% vs. 97% / 91% / 85%, p < 0.001; HR = 13.5, 95% CI = 4.77-38.3, p < 0.001); PET+ and $T_{SUVmax}/L_{SUVmean}$ <2.0 vs. PET– for RR (14.3% vs. 7.7%) and RFS at 1 / 3 / 5 years (85% / 85% / 85% vs. 97% / 91% / 85%, p = 0.337; HR = 1.92, 95% CI = 0.52-7.12, p = 0.328)
Kim et al.,[86] 2016	Retrospective	110	46±18 (7-83)	Tumour classified as hypermetabolic when discernible from liver (PET+); TBR_{IVCmax}; UVP_{IVC}	PET+ vs. PET– for RR (64% vs. 7.0%, p < 0.001); TBR_{IVCmax} >1.25 reduced RFS vs. TBR_{IVCmax} ≤1.25 (HR = 4.62, 95% CI = 1.48-14.4, p = 0.009); UVP_{IVC} >14.3 reduced RFS vs. UVP_{IVC} ≤14.3 (HR = 3.39, 95% CI = 1.21-9.55, p = 0.021)
Lee et al.,[87] 2015	Retrospective	280	37±24	Tumour FDG uptake significantly > liver FDG uptake (PET+)	Within MC and PET+ vs. within MC and PET– for DFS at 1 / 3 / 5 years (91% / 76% / 76% vs. 97% / 95% / 92%, p = 0.031); Within MC and PET+ vs. within MC and PET– for OS at 1 / 3 / 5 years (95% / 89% / 67% vs. 98% / 95% / 92%, p = 0.140); Beyond MC and PET+ vs. beyond MC and PET– for DFS at 1 / 3 / 5 years (44% / 42% / 38% vs. 89% / 78% / 73%, p < 0.001; HR = 3.80, 95% CI = 1.88-7.71, p < 0.001) and OS at 1 / 3 / 5 years (81% / 51% / 51% vs. 96% / 84% / 75%, p < 0.001; HR = 2.71, 95% CI = 1.24-5.95, p = 0.013); Within MC and PET+ vs. beyond MC and PET– for mean DFS (69 vs. 79 months, p = 0.846) and mean OS (72 vs. 84 months, p = 0.728); Within MC vs. beyond MC and PET– and tumour <10 cm for mean DFS (84 vs. 94 months, p = 0.076) and mean OS (84 vs. 91 months, p = 0.235)
Kornberg et al.,[81] 2012	Retrospective	91	65±45 (5-165)	Ratio of tumour to background liver FDG uptake >1 (PET+)	PET+ vs. PET– for RR (54% vs. 3.6%, p < 0.001) and PET+ reduced RFS (OR = 21.6, 95% CI = 4.90-94.9, p < 0.001); Beyond MC and PET+ vs. beyond MC and PET– for RFS at 5 years (21% vs. 81%, p = 0.002); Beyond MC and PET– vs. within MC for RFS at 5 years (81% vs. 86%)
Kornberg et al.,[88] 2009	Retrospective	42	26 (4-108)	Tumour FDG uptake significantly > liver FDG uptake (PET+)	PET+ vs. PET– for RR (50% vs. 3.8%, p < 0.001) and RFS at 3 years (35% vs. 93%, p < 0.001); Within MC and PET+ vs. within MC and PET– for RR (33% vs. 0%, p = 0.004); Beyond MC and PET+ vs. beyond MC and PET– for RR (54% vs. 11%, p = 0.004) and RFS at 3 years (35% vs. 80%, p < 0.001); Beyond MC and PET– vs. within MC for RFS at 3 years (80% vs. 94%, p = 0.6)
Lee et al.,[89] 2009	Retrospective	59	29±17 (12-72)	T_{SUVmax}/L_{SUVmax}	T_{SUVmax}/L_{SUVmax} ≥1.15 vs. <1.15 for RR (62% vs. 2.6%, p < 0.001) and RFS at 1 / 2 years (57% / 42% vs. 97% / 97%, p < 0.001)
Yang et al.,[90] 2006	Retrospective	38	19 (5-40)	Tumour FDG uptake > liver FDG uptake (PET+)	PET+ vs. PET– for RR (62% vs. 12%, p = 0.003; OR = 7.6, 95% CI = 1.99-29.0); PET+ vs. PET– for RFS at 2 years (46% vs. 85%, p < 0.001)

Abbreviations: AFP = alpha-fetoprotein; CI = confidence interval; DFS = disease-free survival; HR = hazard ratio; MC = Milan criteria; OR = odds ratio; OS = overall survival; PET+ = PET-positive; PET– = PET-negative; RFS = recurrence-free survival; RR = recurrence rate; SD = standard deviation; SUV_{max} = maximum standardised uptake value; SUV_{mean} = mean standardised uptake value; TBR_{IVCmax} = ratio of tumour SUV_{max} to background (inferior vena cava [IVC]) SUV_{max}; T_{SUVmax}/L_{SUVmax} = ratio of tumour SUV_{max} to non-tumour-liver SUV_{max}; $T_{SUVmax}/L_{SUVmean}$ = ratio of tumour SUV_{max} to non-tumour-liver SUV_{mean}; UVP_{IVC} = product of TBR_{mean} (ratio of tumour SUV_{mean} to IVC SUV_{mean}) and metabolic tumour volume.

Table 4. Diagnostic performance of fluorine-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) for prediction of unfavourable histopathologic features in explanted or resected hepatocellular carcinoma.

Study	Design	PET parameters	Prediction of microvascular invasion					Prediction of poor differentiation				
			Total no.	Sn (%)	Sp (%)	PPV (%)	NPV (%)	Total no.	Sn (%)	Sp (%)	PPV (%)	NPV (%)
Lin et al.,[33] 2017	Retrospective	$T_{SUVmax}/L_{SUVmean}$ >1.69	65	80	68	-	-	-	-	-	-	-
Ye et al.,[83] 2017	Retrospective	T_{SUVmax}/L_{SUVmax} >1.35 (PET+)	103	90	37	56	80	103	84	35	62	64
Bailly et al.,[12] 2016	Retrospective	Tumour FDG uptake > liver FDG uptake (PET+); T_{SUVmax}/L_{SUVmax} >1.15	27	75	84	67	89	27*	100	81	17	100
Hsu et al.,[85] 2016	Retrospective	Tumour FDG uptake significantly > liver FDG uptake and $T_{SUVmax}/L_{SUVmean}$ >1.20 (PET+)	147	30	86	57	67	128†‡	100	78	6.7	100
Kobayashi et al.,[98] 2016	Retrospective	Tumour FDG uptake > normal contralateral or surrounding tissue FDG uptake (PET+); T_{SUVmax} ≥3.2	60	78	75	35	95	60	75	63	13	97
Ahn et al.,[99] 2015	Retrospective	$T_{SUVmax}/L_{SUVmean}$ ≥1.2	59	64	87	-	-	-	-	-	-	-
Lee et al.,[87] 2015	Retrospective	Tumour FDG uptake significantly > liver FDG uptake (PET+)	147	58	69	67	60	147§	53	62	61	54
Ijichi et al.,[17] 2013	Retrospective	Tumour FDG uptake significantly > liver FDG uptake (PET+)	67	75	67	41	89	67ǁ	100	70	45	100
Kornberg et al.,[81] 2012	Retrospective	Ratio of tumour to background liver FDG uptake >1	91	81	91	86	88	91	76	70	37	93
Cheung et al.,[19] 2011	Retrospective	Tumour FDG uptake increased (lesion-to-liver SUV_{max} ratio >1.20)	58	55	69	64	61	58	67	-	-	-
Kornberg et al.,[88] 2009	Retrospective	Tumour FDG uptake significantly > liver FDG uptake (PET+)	42	82	92	88	88	42	83	69	31	96
Yang et al.,[90] 2006	Retrospective	Tumour FDG uptake > liver FDG uptake (PET+)	38	78	79	54	92	37†§	48	86	85	50

Abbreviations: NPV = negative predictive value; PET+ = PET-positive; PPV = positive predictive value; Sn = sensitivity; Sp = specificity; SUV_{max} = maximum standardised uptake value; SUV_{mean} = mean standardised uptake value; T_{SUVmax} = Tumour SUV_{max}; T_{SUVmax}/L_{SUVmax} = ratio of tumour SUV_{max} to non-tumour-liver SUV_{max}; $T_{SUVmax}/L_{SUVmean}$ = ratio of tumour SUV_{max} to non-tumour-liver SUV_{mean}.

* With <5% being poorly differentiated tumour. To predict poor-to-moderate differentiation: Sn = 53%, Sp = 92%, PPV = 89%, NPV = 61%.

† Excluding explanted tumours with undetermined histologic grade or necrosis after loco-regional treatment.

‡ With <5% being poorly differentiated tumour. To predict poor-to-moderate differentiation: Sn = 26%, Sp = 94%, PPV = 97%, NPV = 15%.

§ For prediction of Edmondson-Steiner grade III-IV hepatocellular carcinomas.

ǁ Including one undifferentiated and three sarcomatous hepatocellular carcinomas with high FDG-avidity.

negative predictive value shows less variation (60%-95%) [Table 4].[12,17,19,33,81,83,85,87,88,90,98,99] The predictive values implied that [^{18}F]FDG PET was more reliable to rule out rather than rule in microvascular invasion at a prevalence of 15% to 52%; its overall accuracy was 62% to 88%. The between-study heterogeneity could result from variations in sample characteristics, microvascular invasion definition, macrovascular invasion confounder, and diagnostic thresholds.[93] Similarly, pre-operative [^{18}F]FDG PET for prediction of poorly differentiated tumour has a wide range of sensitivity (48%-100%), specificity (35%-86%), positive predictive value (7%-85%), and negative predictive value (50%-100%) [Table 4].[12,17,19,81,83,85,87,88,90,98] The overall accuracy was 57% to 81%. The heterogeneity was also due to low number of poorly differentiated tumours in some studies that recruited small or downstaged tumours; hence the prevalence became 2% to 62%. In addition, the association of PET status alone with poor histologic grade was less strong than with microvascular invasion, and did not reach statistical significance in some studies.[12,19,72,87,90,98] The clinical usefulness of [^{18}F]FDG PET per se, as compared to other imaging methods or combined with other predictors, in the prediction of unfavourable histopathologic features remains to be further defined.

Table 5. Studies related to positron emission tomography (PET) for evaluation of therapeutic response in patients with hepatocellular carcinoma.

Study	Design	Therapy (no.)	No. of patients / lesions / PET	Therapy-to-PET interval	Radio-tracer	PET parameters	Results
Cascales-Campos et al.,[100] 2015	Retro-spective	DEB-TACE	20 / - / 20	-	[^{18}F]FDG	Post-therapy T_{SUVmax}	Post-therapy T_{SUVmax} >3 vs. <3 for necrosis rate in explanted tumour (50-70% vs. 70-100%)
Hartenbach et al.,[101] 2015	Retro-spective	^{90}Y-radio-embolisation	24 / - / 33	12±3 weeks	[^{18}F]FECh	Pre-therapy $T_{SUVmean}$; ΔT_{SUVmax}; ΔTBR_{SUVmax}	Pre-therapy $T_{SUVmean}$ >12.4 predicted %ΔAFP >–20% (non-responder; PPV 82%); ΔT_{SUVmax} >–3.5 predicted non-responder (PPV 83%); ΔTBR_{SUVmax} >0.72 predicted non-responder (PPV 91%)
Song et al.,[102] 2015	Retro-spective	TACE	73 / 91 / -	41 (27-73) days	[^{18}F]FDG	Post-therapy PET+ (tumour uptake > liver uptake or = liver uptake with presence of hypodense lesion); Post-therapy $T_{SUVmax}/L_{SUVmean}$	Post-therapy PET+ vs. CECT for detection of viable tumour referenced to histology or clinicoradiology (lesion-based sensitivity 89% vs. 61%, specificity 66% vs. 77%, accuracy 80% vs. 67%, p = 0.04); Post-therapy $T_{SUVmax}/L_{SUVmean}$ ≥1.65 vs. <1.65 for median OS (35 vs. 40 months, p = 0.024; HR = 2.01, 95% CI = 1.04-3.89, p = 0.041)
Ma et al.,[103] 2014	Retro-spective	TACE	27 / - / 27	1 month (27-45 days)	[^{18}F]FDG	$\%\Delta T_{SUVmax}$ >–10% (non-responder); $\%\Delta T_{SUVmax}$ ≤–10% (responder)	Non-responder vs. responder for median time-to-progression (7 vs. 18 months, p = 0.172) and OS at 6 / 12 / 18 / 24 months (80% / 40% / 24% / 24% vs. 100% / 83% / 74% / 59%, p = 0.025; HR = 4.05, 95% CI = 1.21-13.6, p = 0.024)
Sabet et al.,[104] 2014	Retro-spective	^{90}Y-radio-embolisation	33 / - / 33	4 weeks (26-32 days)	[^{18}F]FDG	Pre-therapy T_{SUVmax}/L_{SUVmax} ≥1.2 (PET+); Pre-therapy T_{SUVmax}/L_{SUVmax} <1.2 (PET–); $\%\Delta T_{SUVmax}$ >–20% (PET+ non-responder); $\%\Delta T_{SUVmax}$ <–20% (PET+ responder)	PET+ vs. PET– for median OS (9 vs. 13 months, p = 0.010); PET+ non-responder vs. PET+ responder for median OS (5 vs. 10 months, p = 0.003); PET+ responder vs. PET– for median OS (10 vs. 13 months, p = 0.043); PET+ non-responder vs. PET– for median OS (5 vs. 13 months, p < 0.001; HR = 3.61, 95% CI = 1.9-7.0, p < 0.001)
Kim et al.,[105] 2012	Retro-spective	TACE (26), PEIT (3), RFA (2)	31 / 45 / -	9.0±8.8 (0-31) days	[^{18}F]FDG	Post-therapy PET+ (tumour uptake in eccentric, nodular or scattered pattern); PET– (tumour uptake ≤ liver uptake or in uniform rim-shaped pattern)	Post-therapy PET+ detected residual tumour referenced to clinicoradiology (lesion-based sensitivity 88%; specificity 71%; accuracy 80%; p < 0.001)
Higashi et al.,[106] 2010	Retro-spective	TAC (31), TACE (24), systemic chemotherapy (7), RFA (5)	58 / - / 67	11±11 (0-28) days	[^{18}F]FDG	Post-therapy PET+ (tumour uptake > liver uptake; metastatic lesion uptake > surrounding or contralateral normal tissue uptake)	Post-therapy PET+ detected viable hepatic tumour (sensitivity 63%, specificity 96%, accuracy 75%) and viable metastasis (sensitivity 79%, specificity 92%, accuracy 87%) referenced to histology or clinicoradiology; Post-therapy PET+ vs. PET– for mean OS (328±40 days vs. 608±30 days, p < 0.001; risk ratio = 0.212, 95% CI = 0.042-0.661, p = 0.0056)
Kim et al.,[107] 2010	Retro-spective	TACE	36 / 38 / -	74 (2-434) days	[^{18}F]FDG	Post-therapy PET+ (tumour uptake > or ≈ liver uptake)	TACE-to-PET interval <3 months: PET+ detected viable tumour referenced to histology (lesion-based sensitivity 100%, specificity 63%, accuracy 88%); TACE-to-PET interval ≥3 months: PET+ detected viable tumour (sensitivity 93%, specificity not applicable for zero non-viable tumour)
Torizuka et al.,[108] 1994	-	TOCE (20), TACE (11), PEIT (1)	30 / 32 / -	26 (3-45) days	[^{18}F]FDG	Post-therapy $T_{SUVmean}/L_{SUVmean}$	Post-therapy $T_{SUVmean}/L_{SUVmean}$ >0.6 vs. ≤0.6 for necrosis rate in resected tumour (<75% vs. 90-100%)

Abbreviations: [^{18}F]FDG = fluorine-18 fluorodeoxyglucose; [^{18}F]FECh = fluorine-18 fluoroethylcholine; ΔAFP = post-therapy AFP – pre-therapy AFP; ΔT_{SUVmax} = post-therapy T_{SUVmax} – pre-therapy T_{SUVmax}; ΔTBR_{SUVmax} = post-therapy tumour-to-background (spleen) SUV_{max} ratio – pre-therapy tumour-to-background SUV_{max} ratio; %ΔAFP = ΔAFP/pre-therapy AFP; $\%\Delta T_{SUVmax}$ = ΔT_{SUVmax}/pre-therapy T_{SUVmax}; AFP = alpha-fetoprotein; CECT = contrast-enhanced computed tomography; CI = confidence interval; DEB = drug-eluting beads; HR = hazard ratio; OS = overall survival; PEIT = percutaneous ethanol injection therapy; PET+ = PET-positive; PET– = PET-negative; PPV = positive predictive value; RFA = radiofrequency ablation; SUV_{max} = maximum standardised uptake value; SUV_{mean} = mean standardised uptake value; TAC = transarterial chemotherapy; TACE = transarterial chemoembolisation; TOCE = transarterial oily chemoembolisation; T_{SUVmax} = Tumour SUV_{max}; T_{SUVmax}/L_{SUVmax} = ratio of tumour SUV_{max} to non-tumour-liver SUV_{max}; $T_{SUVmax}/L_{SUVmean}$ = ratio of tumour SUV_{max} to non-tumour-liver SUV_{mean}; $T_{SUVmean}$ = Tumour SUV_{mean}; $T_{SUVmean}/L_{SUVmean}$ = ratio of tumour SUV_{mean} to non-tumour-liver SUV_{mean}.

POST-TREATMENT EVALUATION

Prospective cohort data are limited regarding post-treatment PET in evaluation of therapeutic response in HCC patients. Most were retrospective studies on patients who received TACE (Table 5).[100-108] Post-therapy tumour FDG uptake may help detecting residual tumour viability.[100,102,105-108] Positive tumour FDG uptake or related parameters after treatment was an independent predictor for shorter overall survival.[102-104,106] In a study with fluorine-18 fluoroethylcholine PET, a change in the choline uptake predicted therapeutic response using a 20% decrease in AFP as a surrogate criterion.[101] In treatment trials, a decrease in PET tracer uptake by HCC can serve as a metabolic parameter for anti-tumour activity, but this cannot imply survival benefit without proof.[11]

PET has been used as post-treatment imaging after ^{90}Y-microsphere radioembolisation or SIRT for unresectable tumours.[109,110] Post-SIRT imaging used to be performed with bremsstrahlung imaging via single photon emission computed tomography because ^{90}Y was thought of as a pure beta-emitter with secondary bremsstrahlung radiation. However, ^{90}Y does have a low abundance of positron emission which allows imaging by PET. Compared with conventional ^{90}Y-bremsstrahlung single photon emission computed tomography, ^{90}Y PET offers superior image quality with higher spatial resolution and more accurate quantitation of absorbed dose by tumour and non-target tissue.[111,112] Tumour absorbed dose evaluated by ^{90}Y PET may predict therapeutic response and outcome.[112-114] These preliminary data support further studies to define the role of ^{90}Y PET for evaluation of radiation dosimetry and therapeutic response.

DETECTION OF RECURRENCE

In a meta-analysis of five retrospective studies with 109 patients regarding [^{18}F]FDG PET for detection of recurrent HCC, the pooled sensitivity was estimated to be 82% and specificity to be 89%, although the included studies were relatively small-scale with heterogeneity.[60] In a retrospective study of 86 patients, the rates of detection were only 30% and 42% for intra- and extra-hepatic recurrences, respectively.[115] Further studies are needed to evaluate the performance of PET in the detection of HCC recurrence.

CONCLUSION

PET plays an emerging role in the management of HCC. For the detection of primary tumour, non-FDG PET using [^{11}C]acetate, [^{11}C]CH or [^{18}F]FCH has a significantly higher sensitivity than [^{18}F]FDG PET. The method of dual-tracer PET using FDG and one of these non-FDG tracers to evaluate two different types of in vivo metabolism optimises the diagnostic performance. Different HCCs show differential uptake of tracers depending on the degree of tumour differentiation. There are so far no studies directly comparing different dual-tracer combinations, or against the method of single tracer with an adjunct imaging of hepatic perfusion. [^{18}F]FDG PET is relatively more sensitive in detecting extrahepatic metastases and can be useful in evaluating high-risk patients, but is yet to reach a global consensus on when to perform PET for initial staging purpose. [^{18}F]FDG PET can also be clinically helpful for pre-treatment prognostication, including pre-transplantation evaluation hence influencing patient selection. Nonetheless, there is limited prospective validation of any stand-alone PET parameter with predefined cutoff or scale for risk stratification or prognostication. The evidence for post-treatment evaluation or detection of recurrence is relatively less and mostly also from retrospective studies, with few prospective data reported in abstracts. The complexity of HCC in terms of tumour biology, staging strategies, and treatment options warrants further prospective studies to confirm the role of PET and specific radiotracers along the course of management, and further cost-effectiveness analyses to guide healthcare decisions.

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