A dual-tracer approach using 11C-CH and 18F-FDG in HCC clinical decision making.

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Purpose

Early detection of recurrent or progressive tumour in HCC remains the strongest prognostic factor for survival. Dual tracer PET/CT imaging with 11C-CH and 18F-FDG can be used to further increase detection rates as both tracers relate to different metabolic pathways involved in HCC tumour development. This case series aims to evaluate the role of dual-tracer PET imaging with 18F-FDG and 11C-CH in clinical decision making with HCC patients suspected of recurrent or progressive HCC.

Background/Methods

We included all HCC patients who underwent both 11C-CH and 18F-FDG PET/CT in our institute from February 2018 to December 2021. No exclusion criteria were applied. Patients were included if they received both 11C-CH and 18F-FDG PET/CT within 4 weeks of each other and had at least 6 months of follow-up. These patients underwent dual tracer PET/CT scanning in cases of unexplained and suspicious CT/MRI anatomical imaging and sudden rise of serum tumour markers without anatomical imaging evidence. A detected lesion found was considered critical when the finding had prognostic consequences leading to treatment changes.

Results

Nineteen patients who underwent 11C-CH and 18F-FDG PET/CT examinations were included in which all but six patients were previously treated for HCC (MWA; n = 9, SIRT; n = 2, resection; n = 3, TACE; n= 1, and SABR; n= 1). Combined critical finding detection rate for both tracers was 95%, with 18F-FDG 68%, and 11C-CH 84%. Non-critical findings were found in 63% by 18F-FDG and 50% with 11C-CH. Intrahepatic HCC recurrence finding rate was 65% for both tracers. 18F-FDG found more ablation site recurrences (4/5) compared to 11C-CH (2/5). T two needle tract metastases were only by 11C-CH. Extrahepatic finding rate was 75% for positive lymph nodes for both tracers. Two new primary tumours were found, one by 18F-FDG and both by 11C-CH.

Conclusions

Our study favours a dual-tracer approach in HCC staging in high-risk patients or when conventional imaging is non-conclusive.

Keywords: dual-tracer PET/CT imaging, hepatocellular carcinoma, 18F-FDG, 11C-CH, clinical decision making

List of abbreviations: hepatocellular carcinoma (HCC), Barcelona-Clinic Liver Cancer (BCLC), transarterial chemoembolization (TACE), selective internal radiotherapy (SIRT), 18F-fluoro-2-deoxy-d-glucose (18F-FDG), 11C-Choline (11C-CH), microwave ablation (MWA), alpha-fetoprotein (AFP), des-gamma-carboxy-prothrombin (DGCP), stereotactic ablative radiotherapy (SABR), non-alcoholic steatohepatitis (NASH), orthotopic liver transplantation (OLT), maximum intensity projection (MIP).

Declarations

Ethics approval and consent to participate and consent for publication

According to the Dutch Medical Research Involving Human Subject Act, the local medical ethical committee exempted approval without additional procedures in view of the retrospective nature of the study and all the procedures being performed were part of the routine care. No additional informed consent was required.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by E.B. Veenstra and W. Noordzij. The first draft of the manuscript was written by E.B. Veenstra and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Background

Hepatocellular carcinoma (HCC) is a major cause of global morbidity and mortality with rising incidence (1). Therefore, early detection of recurrent or progressive tumour remains the strongest prognostic factor for survival (2,3). Currently, diagnostic imaging with dynamic CT and MRI are currently advised in detecting progression of HCC according to ESMO clinical guidelines (4).

The Barcelona clinic liver cancer (BCLC) staging system currently divides therapeutic options for HCC into: curative treatments (surgical resection, ablation, and liver transplantation) in case of very early or early stage HCC (A), transarterial chemoembolization (TACE) or selective internal radiotherapy (SIRT) for intermediate stage HCC (B), sorafenib for advanced stage HCC (C), and best supportive care for terminal stage HCC (D) (5). Imaging after treatment with dynamic CT or MRI can be complicated by fibrosis and heterogenous residual tumour appearance and extrahepatic metastasis (4,6). Histological analysis of tumour differentiation is often not performed, but is a major predictive factor of post-operative recurrence in HCC (7). This motivated the use PET imaging as non-invasive marker of tumour differentiation with the potential to be a more sensitive method for localizing tumour recurrence (8).

18F-fluoro-2-deoxy-d-glucose (18F-FDG) PET/CT evaluates tumour viability based on glycolytic activity. Success has been achieved in HCC with sensitivity ranging from 36% to 70% after treatment (9–11). Less success has been realized for multifocal HCC and non-bone extrahepatic metastases (10,12). The sensitivity of 18F-FDG PET/CT for well-differentiated intrahepatic HCC is similar to

conventional imaging (13–18). To overcome this lack of sensitivity for certain extrahepatic and intrahepatic metastases, the 11C-Choline (11C-CH) tracer of cell membrane lipid metabolism is used. HCC may show a high proliferation and increased metabolism of cell membrane components, which will lead to an increased uptake of choline (15). Clinical studies of 11C-CH show better detection rates than 18F-FDG PET/CT for well to moderately differentiated HCC lesions (84%) (11).

As both tracers relate to different metabolic pathways involved in tumour development, it is hypothesized that poorly differentiated HCC could be better evaluated with 18F-FDG and well-differentiated HCC with 11C-CH (19,20). This led to the consideration of dual-tracer imaging in HCC as tumour differentiation of lesions within a given patient may vary, some taking up only one tracer. Variability of uptake can also be seen between separate portions of a single HCC lesion. Due to high background uptake of liver parenchyma of 18F-FDG, intrahepatic lesions might more difficult to detect, further complicated by the display of significant treatment effects seen on PET/CT in post-therapy HCC cases (21). Therefore, this study aims to evaluate the role of dual-tracer PET imaging with 18F-FDG and 11C-CH PET/CT in diagnosed HCC patients with suspicion of recurrent or progressive HCC in clinical decision making.

Methods

This case series study included HCC patients who underwent both 11C-CH and 18F-FDG PET/CT in our institute from February 2018 to December 2021. No exclusion criteria were applied. HCC patients were included if they received both 11C-CH and 18F-FDG PET/CT within 4 weeks of each other, had at least 6 months of follow-up, and were suspected of intra- and extrahepatic recurrence of HCC on conventional imaging or elevated serum tumour markers. Individual informed consent was not required, according to the Dutch Act on Medical Scientific Research involving Human Beings (WMO).

A multidisciplinary team consisting of a hepato-pancreato-biliary surgeon, radiologist, and nuclear medicine physician discussed follow-up status of HCC patients, often with a history of treatment, such as microwave ablation (MWA), selective internal radiotherapy (SIRT) or transarterial

chemoembolization (TACE), and surgical resection. These patients underwent dual-tracer PET/CT scanning in cases of unexplained and suspicious CT/MRI anatomical imaging or sudden rise of serum tumour markers without anatomical imaging evidence. General patient characteristics, medical imaging, relevant histopathology, BCLC stage, and follow-up therapy were extracted from patient medical records. Laboratory serum sampling of alpha-fetoprotein (AFP) and des-gamma-carboxy-prothrombin (DGCP) were recorded.

PET/CT images were examined by author EBV and related to radiologist's report of both tracer studies and noted whether a lesion was detected by any of the tracers. No case discrepancies were encountered. A lesion was considered malignant if there were non-physiological foci of high uptake, unless the imaging context concluded benign origin. A clinical finding was considered critical when the finding had prognostic consequences leading to treatment changes. On the contrary, non-critical findings were defined as findings not altering treatment strategy, for example in case of a novel extrahepatic metastasis in patients with already known extrahepatic disease.

PET/CT and FDG/CHOLINE

All images were taken on a Biograph mCT40 PET/CT (Siemens Healthcare, Erlangen, Germany). Before both PET/CT studies, patients were instructed to fast for at least 6 hours. The 11C-CH had a scheduled activity of 400 MBq, irrespective of body mass. 11C-CH or 18F-FDG (3 MBq/kg of body mass) administered intravenously in an infusion line connected to saline. Low-dose CT was acquired first, followed by PET acquisition 5 minutes after 11C-CH injection or 60 minutes after 18F-FDG injection, covering a field of view from the skull to mid thighs.

PET data was reconstructed with Siemens Ultra HD (TrueX and time of flight), using 3 iterations and 21 subsets with a 400-matrix size and a 9-mm Gaussian (isotropic) filter. Attenuation and scatter correction of PET emission data were achieved by a low-dose CT scan with 120 kV and 35 mAs. For 18F-FDG, SUVmax was determined according to EARL and corrected for blood glucose level.

Results

Nineteen patients who underwent 11C-CH and 18F-FDG PET/CT examinations were identified (Table 1). All patients were diagnosed with HCC by imaging (n=10) or by pathology (n=9). All but six patients were previously treated for HCC, including MWA (n = 9), SIRT (n = 2), surgical resection (n = 3), TACE

(n= 1), and stereotactic ablative radiotherapy (SABR, n= 1). Six patients had not yet been treated, as they received dual-tracer PET/CT while awaiting planned therapy, or no therapy option was available at that time. All but two patients had underlying diffuse liver disease: cirrhosis (n = 8) with one case caused by chronic hepatitis B virus and one by hereditary hemochromatosis, fibrosis (n = 1), non-alcoholic steatohepatitis (NASH, n = 6), and steatosis (n = 1). Nine patients were considered BCLC stage A, seven stage B, and three stage C. Histopathologic results of the primary HCC lesion were available in nine patients, with four well-, two moderately-, and three poorly differentiated tumours. The minimum length of follow-up was 12 months, with a maximum of 24. After one year of follow-up, nine patients had deceased.

PET/CT

Eleven patients received both scans on the same day and all patients underwent both scans within 21 days. 11C-CH and 18F-FDG PET/CT examinations of the same patient were performed in arbitrary order. In 11 cases inclusion for dual-tracer imaging was due to non-conclusive CT/MRI findings, one patient had both non-conclusive CT/MRI imaging and significant rise of tumour marker, and seven patients were considered for dual-tracer PET/CT only having unexplained rise of tumour markers.

PET Findings

Critical findings were found in 68% (13/19) of all cases by 18F-FDG and 84% (16/19) by 11C-CH (Table 2). Non-critical findings, which were often recurrent multifocal HCC, were found in 63% by 18F-FDG and 50% with 11C-CH. Critical finding detection rate for both tracers combined was 95%, as one patient had a new intrahepatic HCC recurrence that remained undetected by both PET tracers. With MRI, this patient was diagnosed with progressive disease of the known HCC lesion, which was subsequently successfully treated with SIRT.

New intrahepatic HCC recurrence was diagnosed in 65% of all cases by both tracers. One case of vascular involvement by means of a tumour thrombus of the portal vein was confirmed by 18F-FDG PET/CT only. Thirteen extrahepatic mHCC lesions were found, with a detection rate for eight lymph nodes of 75% for both tracers. Four soft-tissue lesions were found, all considered mHCC: m. abductor longus (by both PET tracers), pararectal fat (CH-only), thoracic wall (FDG-only), and lung (FDG-only). For therapy-related lesions, two needle tract metastases were found (CH-only, Figure 1) and 80% of ablation site recurrences were identified by 18F-FDG (4/5, Figure 2) and 40% by 11C-CH (2/5). Two cases of novel pathology-proven malignancy were seen: one case of novel prostate carcinoma (Gleason score 8, CH-only) and one case of bilateral lung carcinoma (both tracers).

After both PET/CT imaging studies, three patients were not considered for treatment and received best supportive care. All other patients received therapy after dual-tracer PET/CT examinations, with among them ten patients undergoing liver-directed therapy and five being treated with systemic therapy (chemotherapy and immunotherapy). A CH-only lesion in the pararectal fat was surgically resected in one patient. Histopathology was available for nine patients and 11C-CH detected critical findings in all cases. Both a needle tract metastasis in well-differentiated HCC and progression of a known primary moderately differentiated HCC lesion showed no 18F-FDG uptake.

Figure 1 This 75-year-old female patient (#8) with HCC in segment VI and VII, both successfully treated with MWA in 2018 and 2020. Post-treatment MRI follow-up at three months revealed two new lesions in segment V and VIII and several abdominal wall lesions suspected of needle tract metastasis. Dual-tracer PET/CT showed increased uptake of 11C-CH (A) for a needle tract site metastasis near the 10th rib (arrow), not seen by 18F-FDG (B). In addition, maximum intensity projection (MIP) of 11C-CH (C) revealed several intrahepatic metastases and a lesion at fifth costovertebral junction, all not seen on 18F-FDG (D). The costovertebral lesion resulted rapidly into spinal cord injury to which patient received emergency radiotherapy. Patient received palliative pain care and died shortly after.

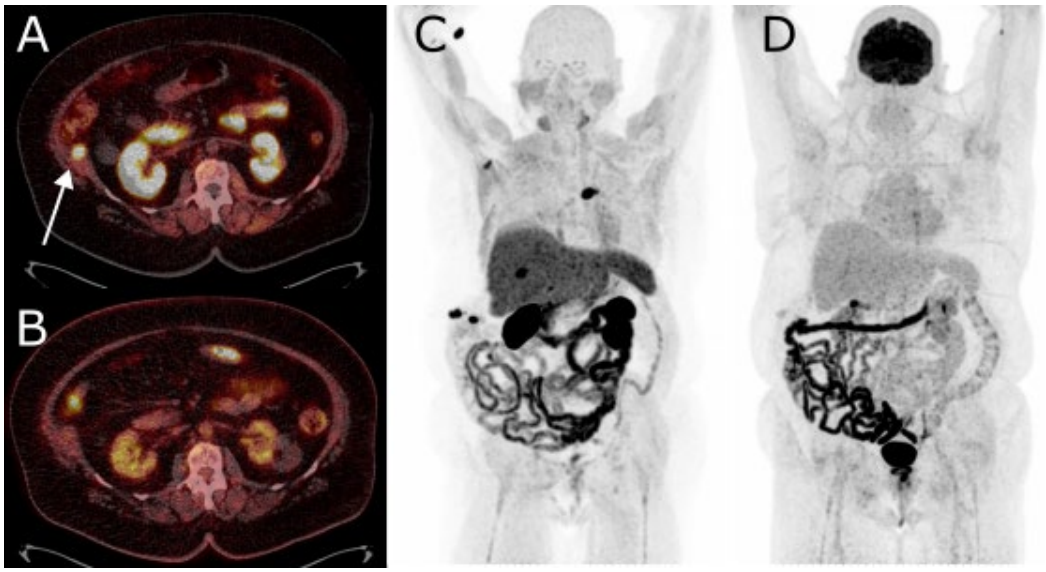

Figure 2 PET/CT imaging of a 49-year-old male patient (#1) known with hemochromatosis-related cirrhosis and multifocal HCC. Underwent MWA of solitary HCC node (32 mm) in segment VIII to ensure eligibility for orthotopic liver transplantation (OLT). Post-therapy MRI follow-up at three months displayed further progression of several intrahepatic lesions and potential tumour thrombus in v. porta, which prompted dual-tracer diagnostic with 18F-FDG and 11C-CH PET/CT. Both tracers found a metastasis in the m. adductor longus muscle (A for 11C-CH, and C for 18F-FDG, arrow), while an ablation site recurrence was only found by 18F-FDG (D) and not by 11C-CH (B). In addition, MIP images show several mediastinal lymph nodes only found by 18F-FDG (F), whereas 11C-CH (E) has physiological uptake in the same region. Due to lymphatic and extrahepatic disease patient received palliative chemotherapy.

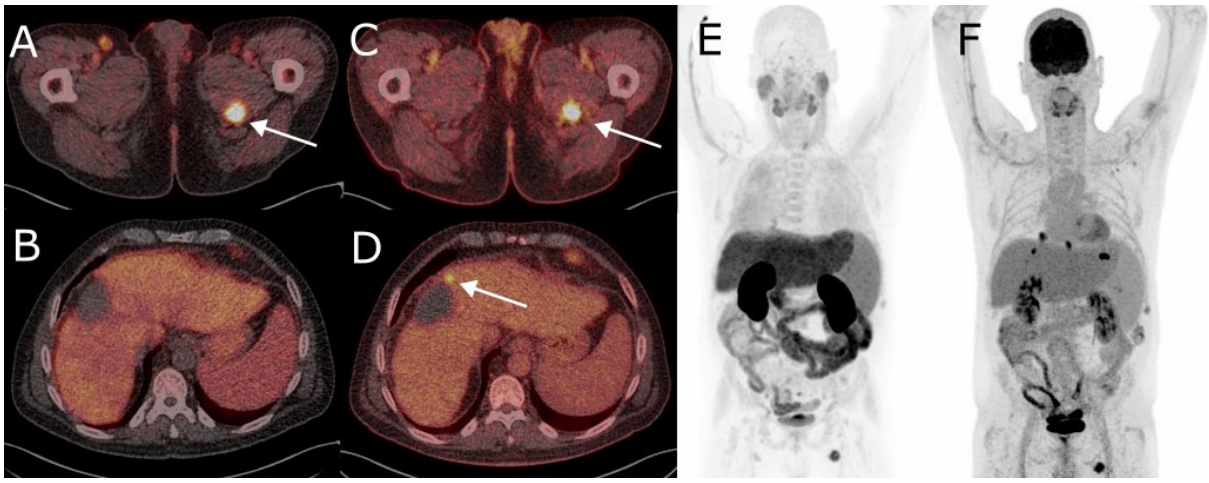
A
C
E
F
B
D

Table 1. Patient and clinical characteristics with PET/CT findings

Sex	Age (years)	Scan delay[↓] (days)	Underlying disorder liver	BCLC[1] stage	Previous therapy	Degree of differentiation at histopathology	Reason for dual-tracer examination	Critical finding	18F-FDG	11C-CH	Other findings	Follow-up therapy
M	49	2	NASH	B	MWA	N/A	Suspect CT/MRI	Recurrence ablation site, mediastinal lymph node	+	-	Both: mHCC m. adductor longus	Palliative with chemotherapy
F	71	0	Steatosis	C	MWA, Resection	Poorly	Rise of tumour marker	Recurrence ablation site, precaval lymph node	+	+	CH: needle tract recurrence, prostate carcinoma	BSC
M	72	1	NASH	0	SIRT	Poorly	Suspect CT/MRI	Retrocaval lymph node	+	+		Immunotherapy
M	77	0	None	B		Poorly	Suspect CT/MRI	HCC liver right lobe and portocaval lymph node	+	+	FDG: liver lymph node CH: HCC S1	Start systemic immunotherapy
F	64	0	NASH	B	MWA	Moderately	Suspect CT/MRI	mHCC Th6	+	+		Radiotherapy
F	74	3	Cirrhosis (HBV)	A		Moderately	Rise of tumour marker	Growth known HCC S5/6	-	+		Surgical partial liver resection
F	65	0	Cirrhosis (Alcohol)	B		Well	Suspect CT/MRI	Bilateral lung carcinoma	+	+		Surgical partial lung resection
F	75	0	Fibrosis	B	Resection	Well	Rise of tumour marker	HCC S1	+	+		TACE
F	39	12	None	B		Well	Suspect CT/MRI	Multifocal HCC liver right lobe	+	+		OLT
M	75	12	NASH	C	MWA	Well	Suspect CT/MRI	Needle tract recurrence after ablation	-	+	CH: 5th costovertebral junction	BSC
M	74	0	Cirrhosis (Alcohol)	B	TACE	N/A	Suspect CT/MRI	HCC recurrence	-	-		SIRT
M	66	0	NASH	A	MWA	N/A	Suspect CT/MRI	Lymph node lesser omentum and a. hepatica communis	-	+	FDG: mHCC ablation site S4/5	BSC
M	67	0	Cirrhosis (Alcohol)	A	MWA	N/A	Rise of tumour marker	mHCC S1, HCC recurrence ablation site S2/3	+	+	FDG: tumour thrombus v. porta	Palliative with sorafenib

M	81	1	Hemochromatosis	A	SIRT, MWA	N/A	Suspect CT/MRI	Thoracic lymph nodes	+	+	FDG: recurrence ablation site	Palliative with sorafenib
M	60	0	Cirrhosis (Alcohol)	A		N/A	Suspect CT/MRI	Known HCC S7/8	+	+		SIRT
F	76	0	Cirrhosis (Alcohol)	C		N/A	Suspect CT/MRI. Rise of tumour marker	Known HCC S7/8	+	+		SIRT
M	53	3	Cirrhosis (Alcohol)	A	MWA, Resection	N/A	Rise of tumour marker	mHCC pararectal fat	-	+		Surgical local resection
M	57	0	NASH	A		N/A	Rise of tumour marker	mHCC liver subcapsular S8	-	+		MWA
F	62	18	Cirrhosis (Alcohol)	0	MWA	N/A	Rise of tumour marker	HCC S7/8	+	-		MWA

ǂ Days between patient receiving one and the other PET/CT scan.

M; male, F; female, NASH; non-alcoholic steatohepatitis, HBV; Hepatitis B-virus; BCLC; Barcelona Clinic Liver Cancer, MWA; Microwave Ablation, SIRT; Selective internal radiation therapy, TACE; Trans-arterial chemoembolization, N/A; Not available, BSC; best supportive care, OLT; Orthotopic liver transplantation.

Table 2. PET tracer detection rates[1]

		18F-FDG	11C-CH
	Detection rate Critical finding[3]	13/19 (68%)	16/19 (84%)
	Detection rate non-critical finding	5/8 (63%)	4/8 (50%)
Differentiation[2]	Well	3/4 (75%)	4/4 (100%)
	Moderately	1/2 (50%)	2/2 (100%)
	Poorly	3/3 100%	3/3 (100%)
Multifocal HCC	Recurrence	10/16 (63%)	11/16 (69%)
	Vascular involvement	1/1 (100%)	0/1 (0%)
	Total	11/17 (65%)	11/17 (65%)
Extrahepatic HCC	Soft tissue	2/4 (50%)	2/4 (50%)
	Bone	1/1 (100%)	1/1 (100%)
	Lymph node	6/8 (75%)	6/8 (75%)
	Total	11/13 (80%)	9/13 (73%)
	New primary tumours	1/2 (50%)	2/2 (100%)
Therapy-related	Needle tract metastases	0/2 (0%)	2/2 (100%)
	Ablation site recurrence	4/5 (80%)	2/5 (40%)
	Total	4/7 (57%)	4/7 (57%)

[1] Combined detection rates were 100% for all lesions, except for one HCC recurrence, which remained undetected by both tracers.

[2] Differentiation established according to histopathology

[3] Critical finding means the tracer found a lesion which was integral in consequent clinical decision making.

Discussion

This study found detection rates of 68% for 18F-FDG and 84% for 11C-CH for lesions that were pivotal in subsequent clinical decision making in patients with HCC. In only one patient both PET tracers failed to detect the anatomical substrate for suspected disease progression, resulting in a combined radiotracer detection rate of 95%. These promising results underline the potential critical role that dual-tracer approach can have in patients with suspected progressive disease. In the current study, we identified more clinically relevant lesions when combining 11C-CH and 18F-FDG PET/CT in HCC, compared to 18F-FDG or 11C-CH alone.

18F-FDG appears to have low sensitivity (27-70%) for intrahepatic HCC, probably due to high background uptake of 18F-FDG in liver parenchyma (2,10). One study reported a sensitivity rate for the detection of intrahepatic HCC by choline-radiotracer of 88% (22). Our data shows moderate intrahepatic detection rates for both tracers (65%). Differences in patient selection could explain this: seven out of 19 patients in our study had a direct therapy-related critical finding, such as needle tract metastases and ablation site recurrences. 18F-FDG found most ablation site recurrences (80%) and none of the needle tract metastases, with contrasted results for 11C-CH (40% and 100%, respectively). HCC tumour aggressiveness, besides technical failure of tumour ablation procedure, is linked to lesions that require multiple bouts of locoregional therapy, of which ablation site

recurrence is indicative as well (23). Our study did not have enough histopathological data to match these results to tumour differentiation.

While both tracers detected a bilateral lung carcinoma, only 11C-CH revealed one case of prostate carcinoma (Gleason 8). Detection of extrahepatic metastasis is known to be an independent predictor of poor survival and thus critical in deciding optimal treatment, especially for OLT and liver resections work-up (24,25). In four cases out of 16, 18F-FDG missed crucial extrahepatic metastases, of which three were identified after addition of 11C-CH. Therefore, 11C-CH PET/CT scanning in patients with negative extrahepatic 18F-FDG scans may increase sensitivity in extrahepatic HCC and suspected needle-tract or local recurrence after local-regional treatment.

Lack of 18F-FDG PET/CT uptake in well-differentiated tumours may be due to low amounts of FDG-6-phosphatase activity in these tumour cells (11). Choline-tracers have shown increased uptake in well-differentiated tumours as these have increased cell membrane metabolism, of which choline is a substrate (18). It is assumed that both tracers reveal different stages of tumour differentiation, advocating for dual-tracer diagnostics (11). Although supported by recent meta-analysis, it recommends caution in accepting this rationale, as both methodological differences and lack of standardized histological grading practices were noted (26). 18F-FDG failed to identify one well- and one moderately differentiated tumour in our study: growth of known HCC lesion and a needle tract recurrence. 11C-CH identified all lesions with known differentiation. A link between elevated AFP and vascular invasion with 18F-FDG avidity has been proposed (26,27). Our study found eight cases with elevated AFP or DGCP as reason for dual-tracer PET/CT. One of these lesions was only found by 18F-FDG, three only by 11C-CH, and four lesions by both tracers. With our limited number of patients, our study does not support a link between differentiation grade or serum tumour marker elevation to 18F-FDG or 11C-CH detection rates.

Multimodal dual-tracer PET-based imaging can play a significant role in revealing changes in within-tumour metabolism, although the link between oncological changes and metabolic effects are not yet fully understood. Whereas 18F-FDG is sensitive for unexplained rise of serum levels of AFP, choline tracers appear to be not (20,22,28). Studies on unexplained serum AFP elevation following locoregional HCC treatment found that 18F-FDG PET/CT had detection rates of 64% to 98% (2,29). Our study found eight cases with unexplained AFP elevation, with seven critical lesions detected by 11C-CH and five by 18F-FDG. In all but one the finding was intrahepatic, often growth of a known tumour. Due to heterogeneity in metabolic and/or genetic traits within a single tumour and between lesions within the same patient, overlap between both tracers in their detection rates is plausible (28).

To our knowledge, the presented study is the first to look at intra- and extrahepatic distribution of HCC with a dual-tracer approach with an emphasis on post-therapy follow-up. The retrospective nature, small patient sample, and the limited amount of available histopathology are limiting our conclusions. Further studies combining histopathology, serum tumour markers, four-phase CT/MR imaging, and genetic analysis are essential to further unravel the link between HCC pathogenesis and appropriate detection techniques, such as dual-tracer PET/CT solutions.

Although PET imaging combining both 18F-FDG and Choline-radiotracers has shown its benefit in staging and therapeutic management of patients with HCC, its use is still not commonplace. Due to the intrinsic characteristics of HCC pathogenesis and the resulting metabolic differences, a negative 18F-FDG PET/CT does not exclude recurrent HCC. Our study favours a dual-tracer approach in HCC staging in high-risk patients or when conventional imaging is non-conclusive.

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