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Dual-tracer PET/CT in the management of hepatocellular carcinoma

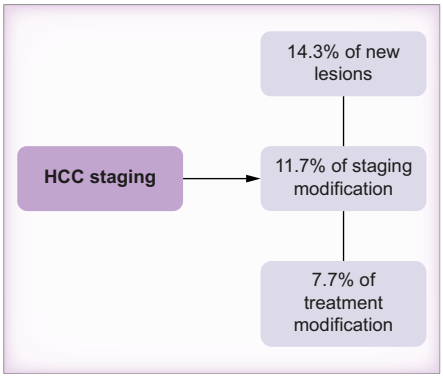
Authors

Keith Wan Hang Chiu, Chi Leung Chiang, Kenneth Sik Kwan Chan, …, Wai Kay Walter Seto, Pek-Lan Khong, Feng-Ming Kong (Spring)

Correspondence

chiangcl@hku.hk (C.L. Chiang), kong0001@hku.hk (F.-M. Kong).

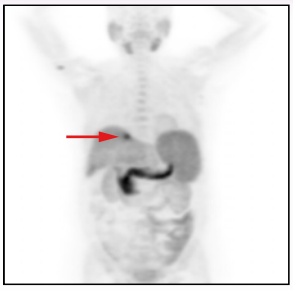
Graphical abstract



Detects HCC in patients undergoing systemic staging

	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
^{18}F-FDG PET/CT	63.6 (54.8-76.1)	95.8 (91.2-98.4)
^{11}C-Acetate PET/CT	72.6 (659.7-83.2)	96.8 (92.0-99.8)
Dual tracer PET/CT	80.7 (71.2-88.6)	94.8 (90.4-98.6)

Characterize indeterminate lesion on conventional imaging



HCC detected in 45% of patients

Identify HCC in patients with unexplained elevated AFP

Highlights:

- Dual-tracer PET/CT detects HCC in patients undergoing systemic staging.
- Dual-tracer PET/CT characterizes indeterminate lesions on conventional imaging.
- Dual-tracer PET/CT identifies HCC in patients with unexplained elevated AFP.

Impact and implications

Compared to CT or MRI, dual-tracer positron-emission tomography/computed tomography (PET/CT) led to upstaging in 12% of patients with hepatocellular carcinoma (HCC) undergoing staging, resulting in treatment modification in 8% of cases and a cost saving of US$495 per patient. It also accurately detected HCC in high-risk cases where CT or MRI were equivocal or normal. Dual-tracer PET/CT provides added value beyond conventional imaging in patients with HCC by improving staging, confirming HCC diagnosis with high accuracy in patients with indeterminate lesions, and detecting HCC in patients with unexplained elevation of serum AFP.

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Dual-tracer PET/CT in the management of hepatocellular carcinoma

Keith Wan Hang Chiu[1,†], **Chi Leung Chiang**[2,*,†], Kenneth Sik Kwan Chan[2], Yuan Hui[3], Jingyun Ren[3], Xiaojuan Wei[4], Kwok Sing Ng[5], Ho Fun Victor Lee[2], Nam Hung Chia[6], Tan-To Cheung[7], Stephen Chan[8], Albert Chi-Yan Chan[7], Kwok Chai Kelvin Ng[9], Wai Kay Walter Seto[10], Pek-Lan Khong[11], Feng-Ming Kong (Spring)[2,*]

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Background & Aims: Combined ^{18}F-fluorodeoxyglucose (FDG) and ^{11}C-acetate (dual-tracer) positron-emission tomography/computed tomography (PET/CT) is being increasingly performed for the management of hepatocellular carcinoma (HCC), although its role is not well defined. Therefore, we evaluated its effectiveness in (i) staging, (ii) characterization of indeterminate lesions on conventional imaging, and (iii) detection of HCC in patients with unexplained elevations in serum alpha-fetoprotein (AFP) levels.

Methods: We retrospectively assessed 525 consecutive patients from three tertiary centers between 2014 and 2020. For staging, we recorded new lesion detection rates, changes in the Barcelona Clinic Liver Cancer (BCLC) classification, and treatment allocation due to dual-tracer PET/CT. To characterize indeterminate lesions and unexplained elevation of serum AFP levels, the sensitivity and specificity of dual-tracer PET/CT in diagnosing HCC were evaluated. A multidisciplinary external review and a cost-benefit analysis of patients for metastatic screening were also performed.

Results: Dual-tracer PET/CT identified new lesions in 14.3% of 273 staging patients, resulting in BCLC upstaging in 11.7% and treatment modifications in 7.7%. It upstaged 8.1% of 260 patients undergoing metastatic screening, with estimated savings of US$495 per patient. It had a sensitivity and specificity of 80.7% (95% CI 71.2-88.6%) and 94.8% (95% CI 90.4-98.6%), respectively, for diagnosing HCC in 201 indeterminate lesions. It detected HCC in 45.1% of 51 patients with unexplained elevations in serum AFP concentrations. External review revealed substantial agreement between local and external image interpretation and patient assessment (n = 273, κ = 0.822; 95% CI 0.803-0.864).

Conclusions: Dual-tracer PET/CT provides added value beyond conventional imaging in patients with HCC by improving staging, confirming HCC diagnosis with high accuracy in patients with indeterminate lesions, and detecting HCC in patients with unexplained elevation of serum AFP.

Introduction

Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related deaths worldwide, accounting for over 800,000 deaths annually.[1] Currently, CT and MRI are the imaging modalities of choice for patient work-up.[2–4] While conventional imaging provides a non-invasive method for diagnosis and treatment assessment in these patients, it has several limitations.[5] First, it often includes only the abdomen, limiting its utility in detecting distant metastasis, while extrahepatic metastases have been reported to occur in up to 42% of cases.[6] Second, many of the current diagnostic imaging criteria for HCC are extremely stringent. As there is substantial tumor heterogeneity in HCC, a significant number of patients will require additional investigations and follow-up.[7–13] Third, conventional imaging is based on morphological and anatomical assessments. Hence, HCC detection depends on the disruption of normal structures to evaluate the extent of the disease.[14] As a result, small lesions or metastatic deposits in areas not usually affected by the disease can easily be missed.

Positron-emission tomography/computed tomography (PET/CT) with combined ^{18}F-fluorodeoxyglucose (FDG) and ^{11}C-acetate (dual-tracer) is increasingly used in centers worldwide for the management of patients with HCC.[15–21] Although the validation of this imaging modality in large cohorts remains limited, studies have shown that it has excellent sensitivity and specificity for detecting HCC. Furthermore, most previous studies have not considered “real-world” practice where conventional imaging is invariably performed prior to PET/CT. Thus, substantial uncertainties remain regarding whether dual-tracer PET/CT provides additional benefits or not. This study aimed to assess the value of dual-tracer PET/CT in the context of the

* Corresponding authors. Address: Department of Clinical Oncology, LKS Faculty of Medicine, The University of Hong Kong, Room 406, Block K, Queen Mary Hospital, Pokfulam, Hong Kong; Tel.: (+852) 2255-4352.
E-mail addresses: chiangcl@hku.hk (C.L. Chiang), kong0001@hku.hk (F.-M. Kong).
† KWH Chiu and CL Chiang contributed equally to this manuscript as first authors.
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current diagnostic pathway in patients with confirmed or suspected HCC.

Materials and methods

Patients and study design

The study was approved by the Institutional Review Board in accordance with the STROBE Reporting Checklist. Consecutive adult patients with active or suspected HCC who underwent dual-tracer PET/CT were recruited from three tertiary institutions in Hong Kong SAR: Queen Mary Hospital/The University of Hong Kong between 2014 and 2020, Queen Elizabeth Hospital between 2014 and 2020, and Prince of Wales Hospital/The Chinese University of Hong Kong (PWH/CUHK) between 2018 and 2020. Dual-tracer PET/CT must be performed prior to the initiation of a new treatment regimen at the time of diagnosis, relapse, or progression. Patients without conventional imaging (CT or MRI) within 3 months of PET/CT were excluded. In total, dual-tracer PET/CT scans from 694 patients were retrospectively collected, and 169 were excluded from the current analysis for the following reasons: (i) scans were performed to assess treatment response to systemic or locoregional therapies (n = 141), (ii) no conventional imaging data were available for comparison (n = 9), or (iii) scans were performed for miscellaneous indications (not related to HCC) in patients with HCC (n = 19).

Of the 525 patients who fulfilled the inclusion criteria, the majority (n = 273, 520.0%) were evaluated for transplantation listing (n = 44), resection or other radical treatments (n = 158), and baseline assessment before palliative treatment (n = 71). Among them, 58.6% (n = 160) were treatment naïve. Dual-tracer PET/CT was performed to evaluate indeterminate lesions in 201 patients (intrahepatic lesion characterization in 158, extrahepatic lesion in 37, and both intra- and extrahepatic lesions within the same patient in six patients). An intrahepatic indeterminate lesion does not fulfil the diagnostic criteria of (i) a HCC based on either EASL or APASL guidelines or (ii) an LR 5 lesion using LI-RADS version 2018 and does not demonstrate characteristic radiological features of a benign lesion (*i.e.* LR 2-4 lesions). An indeterminate extrahepatic lesion does not demonstrate overt malignant or benign features on cross-sectional imaging. Finally, 51 scans were performed to detect HCC in patients with unexplained elevations in serum AFP concentration, defined as having a serum AFP concentration (>10 ng/ml) without a clinical or radiological cause (Fig. 1 and Fig. S1).

Patients underwent conventional imaging for a median of 26 days (IQR 14–39 days) prior to dual-tracer PET/CT. In our cohort, 474 patients underwent CT, 46 underwent MRI, and five underwent both CT and MRI prior to dual-tracer PET/CT. The patients' demographics and clinical parameters were recorded, and the cohort had a median follow-up of 35.8 (IQR 7.9–39.3) months.

Dual-tracer PET/CT scanning protocol

Although the patients underwent PET/CT from different institutions and scanners, all scans were performed using comparable protocols. A typical protocol involves fasting for at least 6 h to achieve a blood glucose concentration of <10 mmol/L before the injection of radiopharmaceuticals. ^{11}C-Acetate (0.12 mCi [4.44 MBq] per kilogram body weight) was

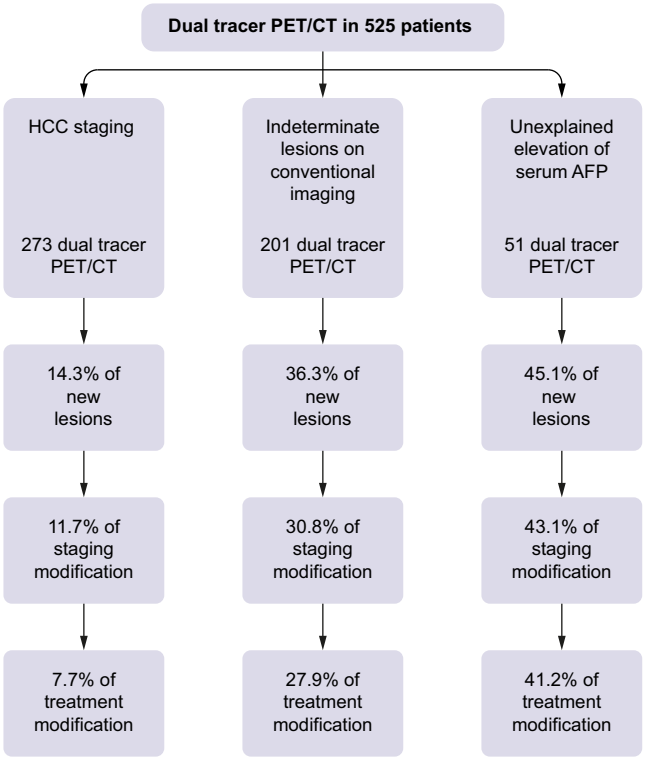

Fig. 1. Impact of dual-tracer PET/CT on identification of new lesions and modification of staging and treatment allocation (N = 559 scans in 524 patients).

administered through peripheral intravenous access, and limited whole-body imaging (from the base of the skull to the upper thighs) was performed 11 min after injection.[14,18] Fifteen minutes after the completion of ^{11}C-acetate imaging, ^{18}F-FDG was injected intravenously (0.078 mCi [2.88 MBq] per kilogram body weight), and limited whole-body imaging was performed 60 min after administration. Data acquisition was performed using an integrated in-line PET/CT scanner (GE Discovery 610 64-MSCT or GE Discovery MI 64-MSCT; GE Healthcare, Chicago, IL, USA), beginning with CT at 140 kV and 120–400 mA, a pitch of 0.984:1, and a tube rotation of 0.5 s. This was followed by PET with an emission acquisition time of 2 min per position for a 70-cm transverse field of view. Images were reconstructed with the standardized ordered-subset expectation maximization technique using 16 subsets and two iterations, with a 192 × 192 matrix for PET and a 512 × 512 matrix for CT. The reconstruction parameters were the same for both the ^{11}C-acetate and ^{18}F-FDG PET images.

Dual-tracer PET/CT analysis

PET/CT data were reviewed locally in a multidisciplinary manner by consensus between board-certified specialists of at least two specialties (*e.g.*, a radiologist and a radiation oncologist) with experience in dual-tracer PET/CT interpretation. In all cases, findings on conventional imaging were considered when interpreting the images, but the readers were blinded to patient histories and outcomes. The scans were clinically assessed by visual inspection, and focal lesions were confirmed using a semi-quantitative approach, in which a region of interest was manually contoured over the area of interest and over an area of non-

cancerous liver tissue. A lesion was considered positive for each radiotracer if the uptake was considered to be non-physiological without the context of being benign and was considered positive for dual-tracer PET/CT if it was hypermetabolic with either or both radiotracers.

To assess whether our findings were influenced by implicit bias, we selected the largest subgroup of our cohort (*i.e.*, patients who underwent dual-tracer PET/CT in the Queen Mary Hospital/The University of Hong Kong) for external review. Anonymized patient histories and the results of conventional imaging and dual-tracer PET/CT were evaluated by consensus between two nuclear medicine physicians and a radiation oncologist with working knowledge of HCC and PET/CT from the Guangdong Academy of Medical Sciences. The external reviewers were blinded to patient outcomes and the local team's interpretations. Examples of the additional benefits of dual-tracer PET/CT are shown in Fig. S2.

Statistical analysis

For tumor staging, evaluation of indeterminate lesions, and detection of unexplained elevations of serum AFP concentration, the new lesion detection rate, changes in the Barcelona Clinic Liver Cancer (BCLC) classification, and changes in treatment allocation due to dual-tracer PET/CT data were recorded. In addition, to evaluate indeterminate lesions, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were determined.

New lesions identified by PET/CT were considered to be HCC if they fulfilled any of the following criteria: (i) histological confirmation; (ii) demonstration of radiological features diagnostic of HCC based on international guidelines; or (iii) achieving threshold growth on follow-up imaging.[2–4] Lesions that were negative on dual-tracer PET/CT images but were subsequently considered to be HCC were considered false negatives, while true negatives were defined as lesions that did not fulfil the diagnostic criteria on follow-up.[22]

The performance of dual-tracer PET/CT in detecting new lesions, improving staging classification, and changing treatment allocation was compared with ^{18}F-FDG PET/CT-based reference using a two-tailed McNemar test. Categorical data were presented as numbers and percentages, and continuous variables were presented as medians and ranges. Inter-institutional agreement was determined by Fleiss' κ ranging from -1 to +1, where +1 indicates perfect agreement. A cost-benefit analysis of metastatic screening in staging patients was performed for both ^{18}F-FDG and dual-tracer PET/CT-based on the prices listed by the Hospital Authority of Hong Kong (supplemental technical notes 1).[23,24] As changes in BCLC staging due to PET/CT can result in treatment allocation from locoregional to systemic therapy, the differences between the additional costs of PET/CT and unnecessary locoregional therapies were compared (details in Appendix E1). Statistical significance was set at p <0.05 in this study. Statistical analyses were performed using R software (version 3.25).

Results

Characteristics of the patients

A description of patient characteristics is presented in Table 1. Of the 525 patients who fulfilled the inclusion criteria, 443 were males (84.4%), and the median age was 62 years (range 23–91 years). Two hundred and sixty-nine patients (51.2%) had a history of hepatitis B infection.

Dual-tracer PET/CT for staging

Of the 273 patients undergoing tumor staging, 64.1%, 83.7%, and 940.0% were identified as positive for HCC by ^{18}F-FDG, ^{11}C-acetate, and dual-tracer PET/CT, respectively (p <0.001, ^{18}F-FDG *vs.* dual-tracer). ^{18}F-FDG alone and ^{11}C-acetate alone identified new lesions in 25 (9.2%) and 30 (110.0%) cases, respectively, whereas dual-tracer PET/CT identified new lesions in 39 cases (14.3%; p = 0.063, ^{18}F-FDG *vs.* dual-tracer). New lesions identified by dual-tracer PET/CT were intrahepatic alone, extrahepatic alone, and both intra- and extrahepatic lesions in 53.8%, 25.6%, and 20.5% of patients, respectively (Table 2). Extrahepatic lesions were located in the bones (55.6% of cases), lymph nodes (44.4% of cases), and lungs (22.2% of cases; Table 2). Among the 39 new lesions identified using dual-tracer PET/CT, 28 (71.7%) were confirmed as HCC based on histological findings (n = 6, 21.4%) or imaging progression (n = 22, 78.6%). False-positive results were found in four patients (9.1%), with no HCC found on biopsy in three patients, and no image progression in one patient. In six (13.6%) patients, their lesions could not be validated due to rapid deterioration, although they were clinically treated as HCC. One patient (2.3%) was lost to follow-up. The number of new lesions identified using dual-tracer PET/CT increased with increasing BCLC stage (0% for BCLC 0 to 280.0% for BCLC C2, Fig. 2A).

The BCLC classification was upstaged in 19 (70.0%), 22 (8.1%), and 32 (11.7%) cases with ^{18}F-FDG alone, ^{11}C-acetate alone, and dual-tracer PET/CT, respectively (p = 0.056, ^{18}F-FDG *vs.* dual-tracer; Table 3, Fig. 2). The treatment strategy was modified in 13 cases (4.8%) based on 18F-FDG, 15 cases (5.5%) based on ^{11}C-acetate, and 21 cases (7.7%) based on dual-tracer PET/CT (p = 0.162, ^{18}F-FDG *vs.* dual-tracer; Table 3). Treatment was modified in 6.8% (3/44), 6.3% (10/158), and 11.3% (8/71) of the cases staged for transplantation, curative interventions, and palliative treatment, respectively (Table S1). Treatment modifications in treatment-naïve cases and cases previously treated for re-staging are also shown in Table S2.

A total of the 37 patients (13.6%) underwent liver transplantation, of whom 31 (83.8%) were within Milan and six (16.2%) were beyond Milan criteria. Only one patient (3.2%) within Milan criteria compared to two (33.3%) patients outside Milan criteria had staging modification due to dual-tracer PET-CT (p = 0.013).

The median survival of patients with BCLC stage 0, A, B, and C were 74.2 months (95% CI 34.9-113.4 months), 56.2 months (95% CI 35.7-76.7 months), 30.3 months (95% CI 9.5-51.2 months), 10.4 months (95% CI 4.3-16.6 months), respectively, after PET/CT staging. Dual-tracer PET-CT did not upstage patients with initial BCLC stage 0 (n = 20). Fifteen (10.5%) patients with BCLC stage A were upstaged and there was a statistically significant difference in median survival (56.2 [95% CI 36.9-75.5] months in those who were upstaged *vs.* 28.2 [95% CI 8.5-48.8] months in those who were not, p = 0.003). Nine BCLC stage B patients (19.6%) were upstaged by dual-tracer PET-CT, although the difference in median survival was not significant: 10.4 (95% CI

Table 1. Patient and tumor characteristics (N = 525 patients in the study cohort).

	Indications		
Patients	**HCC staging (n = 273)**	**Unexplained rise in serum AFP (n = 51)**	**Indeterminate lesions on conventional imaging (n = 201)**
Gender (male)	224 (82.1)	38 (74.5)	181 (90.0)
Median age (range)	61 (23-91)	65 (37-86)	64 (27-90)
Pre-existing liver disease			
Alcohol	21 (7.7)	3 (5.9)	10 (50.0)
Hepatitis B	166 (60.8)	28 (54.9)	75 (37.3)
Hepatitis C	18 (6.6)	2 (3.9)	12 (60.0)
NASH	46 (16.8)	9 (17.6)	22 (10.9)
Multiple etiologies	48 (17.5)	10 (19.6)	28 (13.9)
Without etiology	60 (22.0)	11 (21.6)	39 (19.4)
Tumor features at the time of dual-tracer PET/CT			
Treatment naïve	160 (58.6)	30 (58.8)	93 (46.3)
AFP (ng/ml)			
<200	201 (73.6)	27 (52.9)	182 (90.5)
≥200	72 (26.4)	24 (47.1)	19 (9.5)
HCC staging based on conventional imaging			
No active lesion[†]	13 (4.8)		
BCLC 0	20 (7.3)		
BCLC A	143 (52.4)		
BCLC B	46 (16.8)		
BCLC C1 (no metastasis)	26 (9.5)		
BCLC C2 (metastasis)	25 (9.2)		
HCC staging after dual-tracer PET/CT			
No active lesion[†]	13 (4.8)		
BCLC 0	20 (7.3)		
BCLC A	126 (46.2)		
BCLC B	50 (18.3)		
BCLC C1 (no metastasis)	26 (9.5)		
BCLC C2 (metastasis)	38 (13.9)		
Treatment[*]			
Curative treatment			
Resection	71 (26.0)		
Liver transplantation	37 (13.6)		
Locoregional treatment	104 (38.1)		
Palliative treatment			
TACE	22 (8.1)		
SIRT	6 (2.2)		
Systemic therapy	13 (4.8)		
Radiotherapy	3 (1.1)		
Palliative care	15 (5.5)		
Observation	2 (0.7)		

AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma; MVA, microwave ablation; NASH, non-alcoholic steatohepatitis; PEI, percutaneous ethanol ablation; PET/CT, positron-emission tomography/computed tomography; RFA, radiofrequency ablation; SBRT, stereotactic body radiotherapy; SIRT, selective internal radiotherapy; TACE, transarterial chemoembolization.

[†]13 patients underwent staging before liver transplantation.

*Treatment finally received by the patient as decided by a multidisciplinary team after reviewing the dual-tracer PET/CT findings.

Table 2. Description of new tumor lesions per patient identified by PET/CT performed for HCC staging in 273 patients.

	^{18}F-FDG PET/CT	^{11}C-acetate PET/CT	Dual-tracer PET/CT	*p* value (FDG *vs.* dual-tracer)
Patients with new tumor lesions[*]				
Intrahepatic alone	12 (4.4)	14 (5.1)	21 (7.7)	0.110
Both intrahepatic and extrahepatic	5 (1.8)	4 (1.5)	8 (2.9)	0.400
Extrahepatic alone	8 (2.9)	12 (4.4)	10 (3.7)	0.631
Localization of new tumor lesions by PET/CT per patient				
New intrahepatic nodule	17 (6.2)	18 (6.6)	29 (10.6)	0.064
Portal tumor thrombosis	5 (1.8)	3 (1.1)	6 (2.2)	0.762
Bone metastasis	5 (1.8)	7 (2.6)	10 (3.7)	0.191
Node metastasis	6 (2.2)	7 (2.6)	8 (2.9)	0.595
Lung metastasis	3 (1.1)	4 (1.3)	4 (1.3)	0.700
Adrenal metastasis	1 (0.4)	1 (0.4)	1 (0.4)	>0.99
Others	3 (1.1)	2 (0.7)	3 (1.1)	>0.99

FDG, fluorodeoxyglucose; HCC, hepatocellular carcinoma; PET/CT, positron-emission tomography/computed tomography.

*Portal tumor thrombosis is included in 'intrahepatic'.

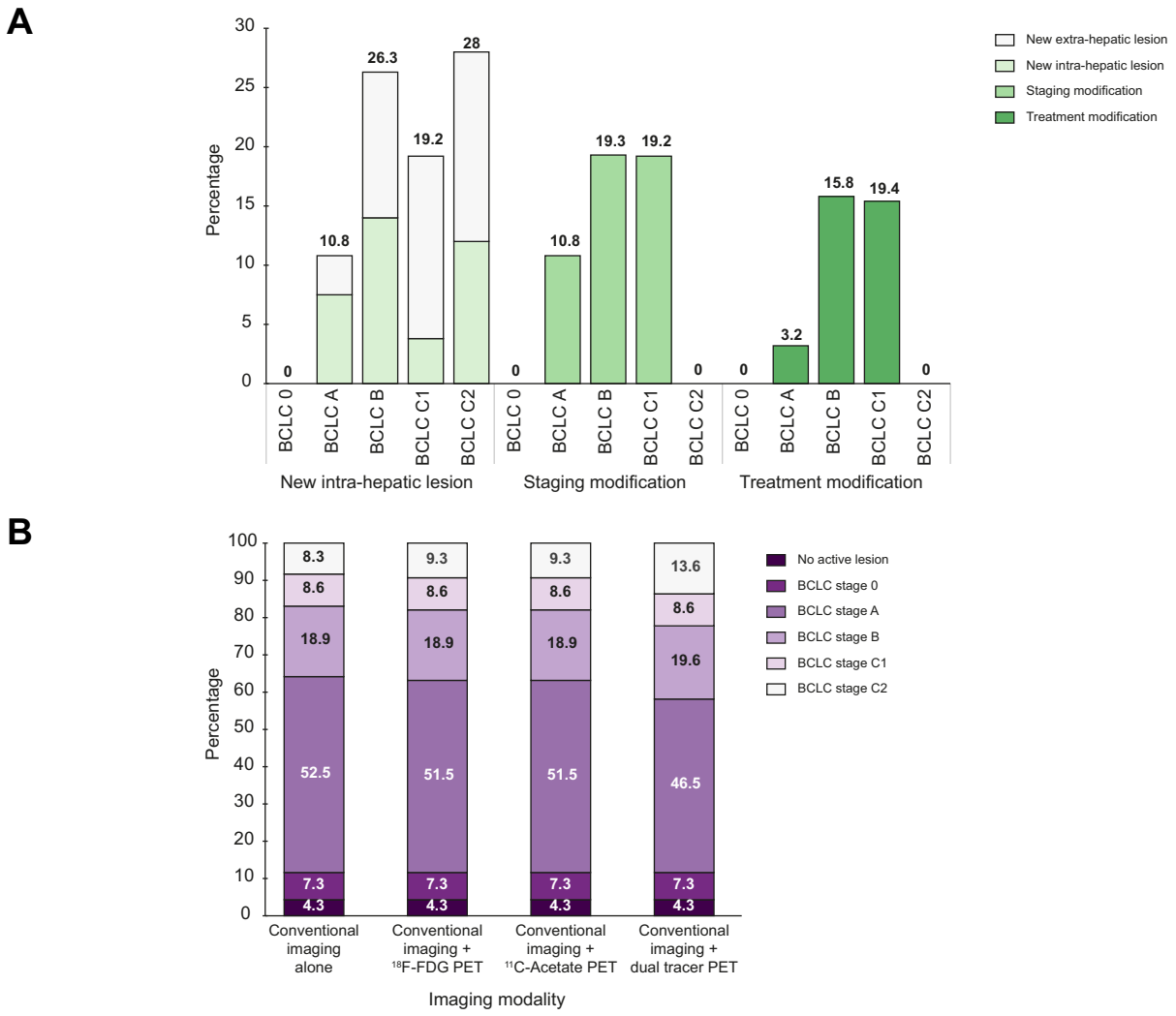

Fig. 2. Modifications in tumor staging and treatment allocation using dual-tracer PET/CT. (A) Percentages of new lesions per patient, and modifications in tumor staging and treatment allocation using dual-tracer PET/CT according to baseline BCLC classification. (B) Representation of BCLC staging based on conventional imaging alone or conventional imaging with ^{18}F-FDG PET/CT, or on conventional imaging with ^{11}C-acetate PET/CT or conventional imaging with dual-tracer PET/CT (percentages of each BCLC stage). BCLC, Barcelona Clinic Liver Cancer; FDG, fluorodeoxyglucose; PET/CT, positron-emission tomography/computed tomography.

Table 3. Patient-based statistics of diagnostic values of single-tracer and dual-tracer PET/CT for characterization of indeterminate lesions.[†]

	^{18}F-FDG PET/CT	^{11}C-Acetate PET/CT	Dual-tracer PET/CT	*p* value (FDG *vs.* dual-tracer)
Staging purpose (n = 273)[*]				
Patients with new lesions detected	25 (9.2)	30 (110.0)	39 (14.3)	0.063
Patients with BCLC staging modified	19 (70.0)	22 (8.1)	32 (11.7)	0.056
Patients with treatment allocation modified	13 (4.8)	15 (5.5)	21 (7.7)	0.162
Indeterminate lesion on conventional imaging (n = 201)				
Patients with new lesions detected	43 (21.4)	62 (30.8)	73 (36.3)	<0.001
Patients with BCLC staging modified	32 (15.9)	57 (28.4)	62 (30.8)	<0.001
Patients with treatment allocation modified	30 (14.9)	52 (25.8)	56 (27.9)	0.002
Unexplained elevation of AFP (n = 51)				
Patients with new lesions detected	13 (25.5)	18 (35.3)	23 (45.1)	0.038
Patients with BCLC staging modified	13 (25.5)	18 (35.3)	22 (43.1)	0.061
Patients with treatment allocation modified	13 (25.5)	18 (35.3)	21 (41.2)	0.093

AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma.
[*]13 patients underwent staging before liver transplantation.
[†]The performance of dual-tracer PET/CT in detecting new lesions, improving staging classification, and changing treatment allocation was compared with 18F-FDG PET/CT-based reference using a two-tailed McNemar test.

Table 4. Patient-based statistics of diagnostic values of single-tracer and dual-tracer PET/CT for characterization of indeterminate lesions (n = 201[#]).

	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Positive predictive value (%) (95% CI)	Negative predictive value (%) (95% CI)	Accuracy (%) (95% CI)
^{18}F-FDG PET/CT	63.6 (54.8-76.1)	95.8 (91.2-98.4)	85.7 (72.4-93.0)	87.2 (82.7-90.6)	86.8 (81.6-91.2)
^{11}C-acetate PET/CT	72.6 (65.9-83.2)	96.8 (92.0-99.8)	91.8 (80.9-96.8)	87.5 (82.3-91.3)	88.7 (83.2-92.3)
Dual tracer	80.7 (71.2-88.6)	94.8 (90.4-98.6)	91.8 (83.6-97.0)	87.3 (82.0-97.1)	88.9 (84.5-94.2)

AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; FDG, fluorodeoxyglucose; HCC, hepatocellular carcinoma; PET/CT, positron-emission tomography/computed tomography.
[#]Two patients were excluded as they were lost to follow-up.

4.3-16.6) months *vs.* 7.1 (95% CI 0.2-150.0) months, respectively (p = 0.088).

Indeterminate lesions on conventional imaging

Dual-tracer PET-CT had an overall sensitivity and specificity of 80.7 (95% CI 71.2-88.6%) and 94.8% (95% CI 90.4-98.6%), respectively, for diagnosing HCC in 201 indeterminate lesions on conventional imaging, leading to stage modification in 62 cases (30.8%) and treatment changes in 56 cases (27.9%, Fig. 1, Tables 3 and 4). This consisted of 51, 16, and four cases with intrahepatic only, extrahepatic only, and both intra- and extrahepatic lesions, respectively. HCC was confirmed in 67 of these 73 patients (91.8%) by biopsies (n = 39, 53.4%), demonstration of typical radiological features (n = 12, 16.4%), or reaching threshold growth on follow-up (n = 16, 21.9%).[22] There were 16 (80.0%) false-negative results (n = 4, biopsy-confirmed; n = 3, typical radiological features on follow-up imaging; n = 9, threshold growth); two patients were lost to follow-up.

Unexplained elevations in serum AFP concentration

The median AFP concentration in the 51 patients with unexplained elevations in serum AFP concentration was 72 ng/ml (range: 13-23,555 ng/ml). HCC was identified in 23 (45.1%) cases (13 positive on ^{18}F-FDG alone, 18 positive on ^{11}C-acetate alone, and 23 positive on dual-tracer PET/CT). Fifteen patients had intrahepatic lesions, six had extrahepatic lesions, and two had both intra- and extrahepatic lesions (Fig. 1, Table 3). All lesions were confirmed to be HCC (histological findings, n = 9; threshold growth, n = 14). Of the 28 patients with negative PET/CT results, 20 (71.4%) remained in remission at the end of follow-up. Another eight patients were diagnosed with HCC at a minimum of 6 months after PET/CT. Patients with new lesions detected by dual-tracer PET/CT had significantly higher median AFP concentrations (405.5 ng/ml *vs.* 33 ng/ml, p <0.001). Significant differences were observed in the number of patients for whom new lesions were detected, BCLC staging was modified, and treatment allocation was modified between those with AFP concentrations <200 or ≥200 ng/ml (Table S3).

External review and discrepancies

An external review showed substantial agreement in interpreting imaging results and management in the largest subgroup of our cohort (n = 381, κ = 0.822; 95% CI 0.803-0.864), resulting in BCLC upstaging in 11.3% (22/195) and treatment modifications for staging in 8.7% (17/195). Inter-reader agreement was also substantial for the indications of indeterminate lesions and unexplained AFP elevation (Table 5). No significant differences were found in the detection of new lesions, staging modification, or treatment allocation among the three institutions (Table S4).

Cost-benefit analysis of dual-tracer PET/CT in metastatic screening

Among the 260 patients who underwent dual-tracer PET/CT for metastatic screening, 11 (4.2%) and 21 (8.1%) patients were upstaged by ^{18}F-FDG PET/CT and dual-tracer PET/CT, respectively, precluding them from planned treatment (six resections, one transplant, and four TACE [transarterial chemoembolization] procedures for ^{18}F-FDG PET/CT and 11 resections, three transplantations, and seven TACE procedures for dual-tracer PET/CT). This resulted in an estimated total cost saving of US $25,435 (US $98 per patient) by ^{18}F-FDG PET/CT and US$127,825 (US$495 per patient) by dual-tracer PET/CT (Table S5). Sensitivity analyses suggested that dual-tracer PET/CT was consistently more cost-effective than ^{18}F-FDG PET/CT (Table S6, Fig. S3).

Discussion

In this multicenter retrospective analysis, we have shown that dual-tracer PET/CT identified 15% more malignant lesions than conventional imaging for staging, had an accuracy of 95% for diagnosing HCC in indeterminate lesions on CT or MRI, and

Table 5. Independent review and discrepancies of BCLC staging and treatment modification in HCC staging (n = 195), indeterminate lesion on conventional imaging (n = 151) and unexplained elevation of AFP (n = 35) in the largest subgroup of the study cohort.

	HCC staging (n = 195)		Indeterminate lesion on conventional imaging (n = 151)		Unexplained elevation of AFP (n = 35)	
	HKU/QMH	Independent review (GAMS)	HKU/QMH	Independent review (GAMS)	HKU/QMH	Independent review (GAMS)
Patients with BCLC staging modified	23 (11.8)	22 (11.3)	46 (30.4)	39 (25.8)	14 (40.0)	13 (37.1)
Patients with treatment allocation modified	14 (7.7)	17 (8.7)	45 (29.8)	38 (25.2)	14 (40.0)	13 (37.1)
*Fleiss' κ (95% CI)						0.822 (0.803-0.864)

AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; GAMS, Guangdong Academy of Medical Sciences; HCC, hepatocellular carcinoma; HKU/QMH, University of Hong Kong/Queen Mary Hospital.
*Inter-institutional agreement was determined by Fleiss' κ ranging from -1 to +1, where +1 indicates perfect agreement.

detected HCC in 45% of patients with an unexplained increase in serum AFP levels. The interpretations of dual-tracer PET/CT were consistent among different institutions, and PET/CT was cost-effective, as it avoided unnecessary treatments in 8% of patients.

Dual-tracer PET/CT is routinely performed for patients with HCC in our institution, and our findings are consistent with those of our prior studies and the reported literature.[15,18,20,21,25,26] In a cohort of 43 patients, we previously found that dual-tracer PET has a sensitivity of 96.8% and specificity of 91.7% for the detection of HCC, which is much higher than the 41.9% and 33.0%, respectively, for CT.[18] Moreover, dual-tracer PET/CT is significantly less affected by cirrhotic changes when used for staging and liver transplant selection.[18] Similarly, in a cohort of 58 patients, ^{18}F-FDG was associated with larger tumors (>5 cm) and microvascular invasion, and the use of ^{11}C-acetate increased the overall sensitivity of the technique.[25] For surgical planning, a retrospective analysis of 152 patients showed that dual-tracer PET detected 11% more metastases than CT. While the cost-effectiveness appears meager (US$495 per patient), this is likely to be an underestimation with previous analysis showing cost savings of US$1,070 for preoperative patients from an earlier recruitment period.[23] In our study, we expanded the cohort to reflect modern clinical practice and included patients treated with non-surgical locoregional therapy (*e.g.*, by interventional radiologists with conscious sedation). Thus, we have not considered the potential costs of hospitalization or additional imaging, nor the costs for more than one episode of locoregional treatment.

However, unlike previous studies where only histological confirmation of a lesion was used to analyze the performance of dual-tracer PET/CT, we adopted a composite outcome of clinical/radiographical confirmation of HCC, which is commonly used in other clinical studies and is more reflective of real-world practice where histological sampling is often considered unnecessary.[25–29] This allowed us to assess its performance on often underrepresented benign lesions. Our results are comparable to those of previous studies in which the specificities of ^{18}F-FDG and ^{11}C-acetate were reported to be 94% and 79%, respectively.[30,31] While many benign liver lesions, including focal nodular hyperplasia, hemangioma, and dysplastic nodules, can be ^{11}C-acetate avid, they have already been comprehensively characterized by cross-sectional imaging, thus reserving dual-tracer PET/CT as a second-line tool for problem-solving.[32]

Only a few studies have explored the use of PET/CT in detecting HCC in patients with unexplained elevation in serum AFP levels. In one small case series involving 26 patients, ^{18}F-FDG detected HCC recurrence in 71% of the patients with serum AFP concentrations >10 ng/ml. Although our results had a lower percentage of HCC recurrence detected, which may be explained by a lower mean serum AFP concentration (1,330 *vs.* 7,604 ng/dl) than the aforementioned study by Chen *et al.*,[33] the fact that HCC was found in 45% of patients further supports its use in these circumstances, as early detection and treatment of HCC recurrence are key to improving survival after locoregional interventions.[34] Further studies with larger sample sizes are required to validate this finding.

This study has several limitations. First, our study may have been affected by selection bias. However, we minimized this by including consecutive patients over a long period of time from three different tertiary centers that have different patient selection and treatment policies. Our results could have been influenced by institutional bias, as centers that routinely perform dual-tracer PET/CT may have unintentionally exaggerated its benefits. To mitigate the effects of local practice on management decision-making, we performed an external review on a subset of our cohort and showed high inter-institutional agreement between the two groups. Second, most of our patients underwent only one cross-sectional imaging modality before PET/CT. This, in particular, may affect the characterization of indeterminate lesions because two imaging modalities (*i.e.*, CT and MRI) are often recommended.[2–4] While there are differences in sensitivity and specificity between CT and MRI, a recent meta-analysis has shown that the two modalities achieve similar performance, and current international guidelines consider both imaging modalities as equivalent.[2–4,35] Third, while our results have demonstrated the unequivocal utility of dual-tracer PET/CT, the modality incurred a substantial radiation dose to patients, estimated to be around 29 mSv and 23 mSv for males and females, respectively.[36] However, we believe that the benefits of this imaging modality outweigh its potential risks, especially among the intended cohort of patients with high risks of cancer and reduced life expectancy. Nevertheless, it is worth noting that ^{11}C-acetate is not the only alternate radiotracer for the assessment of HCC. Promising results have been reported for other novel radiotracers, such as ^{18}F-fluorothymidine, ^{18}F-fluorocholine, and ^{68}Ga-PSMA for detecting and staging HCC, although direct comparison between these radiotracers remains an active area of research.[15,16,18,20,21]

In conclusion, in a large series of patients, we provided quantitative evidence for the use of combined ^{18}F-FDG and ^{11}C-acetate PET/ET in staging patients with HCC, characterizing radiologically indeterminate lesions, and detecting HCC in patients with unexplained elevations in serum AFP concentration. Further correlations of PET/CT data with morphological and anatomical appearances on conventional imaging and their relationship with underlying histological and genetic changes are being actively investigated.

Affiliations

[1]*Department of Radiology and Imaging, Queen Elizabeth Hospital, Hong Kong, China;* [2]*Department of Clinical Oncology, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong China;* [3]*Department of Nuclear Medicine, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Science, Guangdong, China;* [4]*Department of Clinical Oncology, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Science, Guangdong, China;* [5]*Department of Nuclear Medicine, Queen Elizabeth Hospital, Hong Kong, China;* [6]*Department of Surgery, Queen Elizabeth Hospital, Hong Kong, China;* [7]*Department of Surgery, LKS Faculty of Medicine, The University of Hong Kong, China;* [8]*Department of Clinical Oncology, Faculty of Medicine, The Chinese University of Hong Kong, China;* [9]*Department of Surgery, The Chinese University of Hong Kong, China;* [10]*Department of Medicine, LKS Faculty of Medicine, The University of Hong Kong, China;* [11]*NUS Clinical Imaging Research Centre (CIRC), Singapore*

Abbreviations

AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; FDG, fluorodeoxyglucose; HCC, hepatocellular carcinoma; NPV, negative predictive value; PET/CT, positron-emission tomography/computed tomography; PPV, positive predictive value.

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Conflict of interest

The authors have no conflicts of interest to declare.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Conception and design: All authors. Administrative support: KWH Chiu, CL Chiang, KSK Chan. Provision of study materials or patients: KWH Chiu, CL Chiang, KSK Chan, KKK Ng, and KS Ng. Collection and assembly of data: All authors. Data analysis and interpretation: KWH Chiu, CL Chiang, KSK Chan, YH, J Ren, X Wei, KKK Ng. Manuscript writing: All authors. Final approval of the manuscript: All authors. Accountable for all aspects of the work: All authors.

Data availability statement

All data generated or analyzed during this study are included in this article and its supplementary material files. Further enquiries can be directed to the corresponding author.

Statement of ethics

This study protocol was reviewed and approved by Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (HKU/HA HKW IRB) UW15-591. Consent has been waived given the retrospective nature of the study which was approved by IRB.

Supplementary data

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