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Performance of Dual-tracer PET-CT for Staging Post-Liver Transplant Hepatocellular Carcinoma Recurrence

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Background. Precise staging is essential in the management of patients with recurrent hepatocellular carcinoma (HCC) after liver transplantation. There is no current consensus on the optimal staging strategy. We conducted this study to evaluate the performance of dual-tracer positron emission tomography-computed tomography (PET-CT) for this purpose and to investigate whether the results of dual-tracer PET-CT affected patient management. **Methods.** A retrospective study was conducted. Patients who underwent dual-tracer PET-CT for suspected or confirmed HCC recurrence after liver transplant were included. The lesion-based sensitivity and positive predictive value of dual-tracer PET-CT were determined. **Results.** Fifty-six patients and 189 recurrent tumors were included. The lesion-based sensitivity and positive predictive value of dual-tracer PET-CT were 94.7% and 90.4%, respectively. The sensitivity of dual-tracer PET-CT was better than the standard imaging in the surveillance protocol (82.5% versus 94.7%, $P < 0.001$), especially for detecting liver recurrence (71.0% versus 96.8%, $P < 0.001$). Half of the dual-tracer PET-CT detected additional recurrence ($n = 26$, 46.4%) and one-third led to a change in management ($n = 19$, 33.9%). Ten patients (17.9%) with inconclusive standard imaging had metabolic recurrence confirmed on PET-CT and treatment was commenced early. Four patients (7.1%) had revised locoregional treatment, and 5 (8.9%) had to withdraw from locoregional treatment after the detection of additional metastatic disease. **Conclusions.** Dual-tracer PET-CT is effective for staging posttransplant HCC recurrence. It often provides valuable information to guide clinical management.

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Despite stringent patient selection, recurrence occurs after 20% of liver transplantations performed for hepatocellular carcinoma (HCC).^{1,2} Historically, posttransplant HCC recurrence was associated with dismal survival.^{3,4} However,

treatment of HCC recurrence has been evolving and survival outcomes have improved thanks to better immunosuppression and anticancer treatments.⁵⁻⁷ Patients with oligorecurrence (ie, limited disease in terms of location and numbers) have been selected for radical treatment involving a combination of systemic and locoregional therapies. Precise staging is essential for selecting the optimal treatment for patients with posttransplant HCC recurrence.

Positron emission tomography-computed tomography (PET-CT) with 18-fluorodeoxyglucose (FDG) has emerged as an effective staging modality for various visceral malignancies.⁸ However, FDG is not sensitive for HCC.⁹⁻¹¹ The high level of glucose-6-phosphatase in hepatocyte metabolizes FDG and resulted in reduced tracer accumulation in well-differentiated HCC.⁹ Dual-tracer PET-CT with 11acetate (ACT) and FDG is a better modality for metastatic workup in patients with HCC.^{12,13} For posttransplant HCC recurrence, there is currently no consensus for the optimal staging strategy. Concurring with most centers, we performed contrast computed tomography (CT) of the thorax and abdomen, because of its availability.¹⁴⁻¹⁶ Bone scan was reserved for patients with symptoms suggestive of skeletal metastasis. In line with promising experience in primary HCC, dual-tracer PET-CT was also offered to patients with recurrence as an option at cost. We observed that dual-tracer PET-CT often provided valuable additional information to guide treatment

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decision. Therefore, the current study is conducted to review the performance of dual-tracer PET-CT for staging recurrent HCC after liver transplantation. The objective is to assess whether dual-tracer PET-CT is effective in this context; and whether performing dual-tracer PET-CT affects treatment decision for these patients.

MATERIALS AND METHODS

Patients and Surveillance Protocol

Retrospective review of a prospectively maintained database identified patients who developed posttransplant HCC recurrence at Queen Mary Hospital, the University of Hong Kong between January 2005 and December 2019. It is the tertiary referral center and the only liver transplant center in Hong Kong. Outpatient assessment was arranged every 3 mo for patients transplanted for HCC, during which clinical examination and blood test for liver function and alpha-fetoprotein (AFP) were performed. A contrast-enhanced CT scan of the thorax and abdomen was performed at 6-mo interval. Additional imaging (eg, bone scan or MRI of spine) was performed when clinically indicated. For patients with suspected or confirmed radiological recurrence, dual-tracer PET-CT was offered as a self-financed option for the purpose of comprehensive staging. Patients who were willing to pay USD 2500 for dual-tracer PET-CT would undergo the examination. All patients with dual-tracer PET-CT performed upon diagnosis of posttransplant HCC recurrence during the study period were included. Ethics board approval was exempted because this study was retrospective and no patient management was affected.

Dual-tracer PET-CT

Dual-tracer PET-CT was performed with ACT and FDG. ACT was prepared using modification of technique reported by Norenberg et al.¹⁷ Imaging commenced with a plain whole-body tomography. Scanning was repeated 20 min after intravenous ACT administration (550–740 MBq) with identical position and acquisition settings. Fifteen minutes following ACT scan, FDG was injected (370–550 MBq), followed by repeated scanning 60 min later. The details of the examination methods were described elsewhere.¹⁸ The reconstructed images were interpreted by an experienced radiologist specialized in nuclear medicine. Metabolic assessment of a lesion was conducted with visual judgment supplemented by quantitative evaluation using standard uptake value. In general, a maximum standard uptake value >2.0 was regarded as the criterion of metabolic avidity.

Definition of Recurrence

A lesion satisfying one or more of the following criteria was defined as recurrence (Table 1): (1) histological confirmation, (2) radiological diagnosis by standard imaging, and (3) unequivocal radiological progression on standard modality or PET-CT. For thoracic lesions, plain or contrast CT thorax was the standard. For intraabdominal lesions, contrast CT and contrast MRI were regarded as the standard. For bone metastasis, bone scan and MRI spine were both considered standard modalities. When more than 5 metastatic lesions were detected in one organ, only 5 of them would be counted to avoid statistical bias induced by counting multiple lesions in patients with innumerable metastases. Lesions not fulfilling the preset criteria were regarded as nonrecurrence.

TABLE 1.

Criteria to define a recurrent tumor and the proportion of tumor satisfying each criterion

Criteria	Tumors, n (%)
Histological confirmation	13 (6.9)
Radiological diagnosis by standard imaging	136 (72.0)
Thorax: plain/contrast CT	
Abdomen: contrast CT/contrast MRI	
Bone: bone scan/MRI spine	
Unequivocal radiological progression on standard imaging or PET-CT	40 (21.2)

CT, computed tomography; PET-CT, positron emission tomography-computed tomography.

Performance of Imaging

All lesions appearing metabolically avid (FDG or ACT) on dual-tracer PET-CT or fulfilling the definition of true recurrence were included for analysis. PET-CT findings were evaluated to determine its sensitivity and positive predictive value. The sensitivity was compared with standard imaging performed within 3 mo from the index PET-CT. Standard imaging performed beyond this time interval was not included for comparison. Specificity and negative predictive value were not determined because true negative could not be quantified (any tissues uninvolved by recurrence were true negatives). Statistics were analyzed on lesion basis because one patient might have multiple recurrent tumors with different radiological properties.

Definition of Change in Management

Management of posttransplant HCC recurrence depends on disease status. Patients with disseminated disease were palliated with systemic therapy or best supportive care, whereas patients with oligorecurrence were treated with a combination of systemic and locoregional therapy.⁶ Patients diagnosed with oligorecurrence on standard imaging were planned for curative treatment. When dual-tracer PET-CT detected additional recurrences, the locoregional therapy might be altered (eg, resection of additional lesions). When disseminated disease was noted on dual-tracer PET-CT, locoregional therapy would be withheld and the treatment would be systemic therapy. These were considered changes in management. Patients with inconclusive standard imaging were planned for serial imaging. When dual-tracer PET-CT confirmed metabolic recurrence, treatment would be commenced. This was also considered a change in management.

Data Analysis and Statistics

Categorical variables were compared with chi-square test. Continuous variables were presented as median and interquartile range (IQR). Parametric and nonparametric variables were compared using t-test and Man-Whitney U test where appropriate. Sensitivities of diagnostic tests were compared with Fisher exact test. Data were analyzed using Statistical Package for the Social Sciences 16.0 (SPSS) for Windows (SPSS Inc., Chicago, IL). Statistical significance was defined by $P < 0.05$.

RESULTS

Patient and Recurrence Characteristics

During the study period, 127 patients developed recurrent HCC after liver transplantation. Fifty-eight patients

(45.6%) underwent dual-tracer PET-CT upon diagnosis of recurrence. The imaging records were not available in 2 patients, and they were excluded. The remaining 56 patients (44.1%) formed the basis of this study (53 men, 3 women; median age 59) (Figure 1). There was a male predominance (94.6%) as hepatitis B was the primary etiology for HCC in our locality (Table 2). The median time to recurrence was 13 mo from transplant (IQR 5–27). The majority of the patients underwent CT thorax (n = 52, 92.9%) and CT abdomen (n = 47, 83.9%) as per our surveillance protocol. Eight patients (14.3%) underwent MRI abdomen, usually for delineating equivocal liver lesions detected on CT scan. Five (8.9%) and 6 patients (10.7%) underwent bone scan and MRI spine, respectively, for clinical suspicion of bone metastases.

Upon recurrence, there were a median of 2 tumors (IQR 1–5) measuring up to 2.1 cm (IQR 1.2–3.4 cm). Most patients had recurrence limited to one organ (median 1, IQR 1–1), most frequently in the liver (n = 34, 60.7%), followed by the lung (n = 24, 42.9%) and bone (n = 11, 19.6%). The median AFP level upon recurrence were 11 ng/mL (IQR 3–295).

Lesion Characteristics

Two-hundred twenty recurrent tumors were identified. Thirty-one were excluded because there were >5 tumors in the corresponding organ. The remaining 189 true recurrences formed the basis of this study. The proportion of tumors satisfying each criterion was listed in Table 1. There were 13 (6.9%) histologically confirmed recurrence after

surgical resections (10 lung resections and 3 adrenalectomies). The majority (n = 136, 72.0%) were diagnosed with standard imaging. The remaining 40 tumors (21.2%) were confirmed based on subsequent radiological progression. The median tumor size was 1.5 cm (IQR 1.0–2.3 cm) (Table 3). The majority were liver (n = 62, 32.8%), lung (n = 63, 33.3%), bone (n = 34, 18.0%), and lymph node (n = 21, 11.1%) recurrences. There were also 5 peritoneal recurrences (2.6%) and 4 adrenal metastases (2.1%).

There were 229 metabolically avid lesions on dual-tracer PET-CT. Two hundred ten of them were true recurrences. The remaining 19 lesions did not fulfill the criteria of true recurrence. They were included as nonrecurrences (ie, false positive).

Dual-tracer PET-CT Versus Standard Imaging

Dual-tracer PET-CT was performed at a median of 13 d after the standard imaging revealing the recurrence. The performance of dual-tracer PET-CT is summarized in Table 4. The lesion-based sensitivity was 94.7%. The positive predictive value of a metabolically avid lesion was 90.4%. The sensitivity compared favorably over standard imaging (82.5% versus 94.7%, $P < 0.001$), especially when detecting liver recurrence (71.0% versus 96.8%, $P < 0.001$) (Table 5). The sensitivity of FDG PET-CT was lower than that of standard imaging (82.5% versus 60.8%, $P < 0.001$), most noticeably for liver (71.0% versus 51.6%, $P = 0.04$), lung (88.5% versus 73.0%, $P = 0.04$), and bone recurrence (96.0% versus 55.9%, $P < 0.001$).

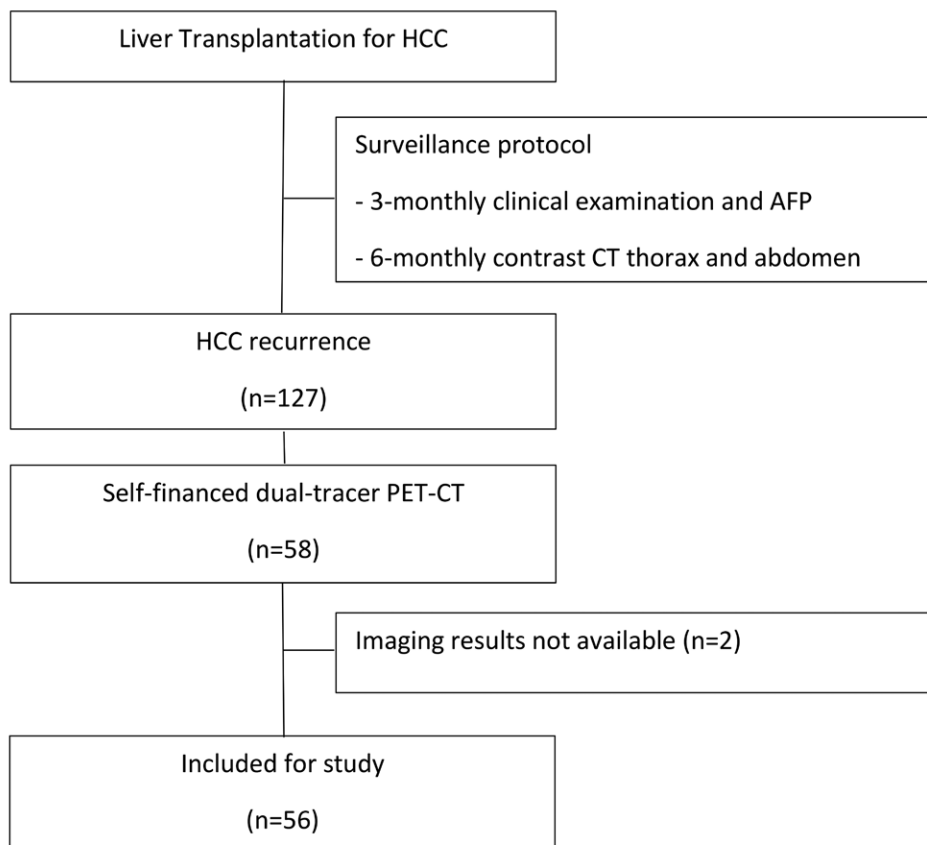


FIGURE 1. Flow diagram showing the enrollment of subjects in the current study. AFP, alpha-fetoprotein; CT, computed tomography; HCC, hepatocellular carcinoma; PET-CT, positron emission tomography-computed tomography.

TABLE 2.
Patient demographics and recurrence status

Patient demographics	
Gender, M/F (% M)	53/3 (94.6)
Age at recurrence, median (IQR), y	59 (54–66)
Time from transplant, median (IQR), mo	13 (5–27)
Staging conventional modality, n (%)	
CT thorax	52 (92.9)
CT abdomen	47 (83.9)
MRI abdomen	8 (14.3)
Bone scan	5 (8.9)
MRI spine	6 (10.7)
Number of tumors, median (IQR)	2 (1–5)
Size of largest tumor, median (IQR), cm	2.1 (1.2–3.4)
Number of organs involved, median (IQR)	1 (1–1)
Location of recurrence, n (%)	
Liver	34 (60.7)
Lung	24 (42.9)
Bone	11 (19.6)
Peritoneum	4 (7.1)
Adrenal	4 (7.1)
Lymph node	6 (10.7)
AFP upon recurrence, median (IQR), ng/mL	11 (3–295)

AFP, alpha-fetoprotein; CT, computed tomography; F, female; IQR, interquartile range; M, male.

TABLE 3.
Recurrent tumor characteristics

Tumor characteristics	
Tumor size, median (IQR), cm	1.5 (1.0–2.3)
Location, n (%)	
Liver	62 (32.8)
Lung	63 (33.3)
Bone	34 (18.0)
Peritoneum	5 (2.6)
Adrenal	4 (2.1)
Lymph node	21 (11.1)

IQR, interquartile range.

TABLE 4.
The performance dual-tracer PET-CT

		Nature of lesion	
		Recurrence	Nonrecurrence
Dual-tracer PET	Avid	179	19
	Nonavid	10	–
Sensitivity	94.7%		
Positive predictive value	90.4%		

PET, positron emission tomography.

Out of the 189 true recurrences, 146 (77.2%) were detected by the standard surveillance protocol. Thirty-one tumors (16.4%) were missed by standard imaging despite it had been performed (Figure 2). They included 18 hepatic, 7 pulmonary, 5 distant lymphatic, and 1 bone recurrences. The remaining 12 (6.3%) was only detected by PET-CT because the corresponding standard imaging had not been performed. The majority were bone metastases (n = 9).

Clinical Implications

Compared to the surveillance protocol, dual-tracer PET-CT detected 29.5% more tumors (n = 43). Figure 3 concludes the clinical implications of the 56 dual-tracer PET-CTs performed in our study. Half of the dual-tracer PET-CT detected additional recurrence (n = 26, 46.4%). One-third led to a change in management (n = 19, 33.9%) (Figure 3). Ten patients (17.9%) had inconclusive results on standard imaging and serial imaging was planned. Subsequent dual-tracer PET-CT confirmed metabolic recurrence and treatment was commenced early. Among them, 3 (5.4%) received surgical treatment. Four patients (7.1%) had revised locoregional treatment, and 5 (8.9%) had to withdraw from locoregional treatment after detection of additional metastatic disease. The average number of scans needed to perform for detection of additional recurrence and change in management was 2.2 and 2.9, respectively.

DISCUSSION

The optimal staging strategy for posttransplant HCC recurrence has not been described in the literature. Most centers perform contrast CT of the thorax and abdomen, with additional bone scan when patients develop symptoms suggestive of skeletal metastasis.^{14–16} Our results indicate that dual-tracer PET-CT is sensitive for detecting recurrent tumors after transplantation. Additional lesions were detected in 46.4% of the scans, and management was affected by scan results in 33.9% of the patients.

Comprehensive and precise staging is essential for selecting the optimal treatment for posttransplant HCC recurrence. The ideal staging modality should identify all recurrence (high sensitivity) without error (high positive predictive value). In concordance with previous reports, our data suggested that FDG was not sensitive for detecting HCC recurrence (sensitivity 60.8%).^{9–11} In contrast, the sensitivity of dual-tracer PET-CT compared favorably over standard imaging (82.5% versus 94.7%, $P < 0.001$). The positive predictive value of dual-tracer PET-CT was 90.4%. This was a conservative estimation. The nature of additional lesions detected required serial imaging to confirm. Some patients responded to treatment, whereas some did not undergo reassessment. In either case, these lesions were regarded as false positive. Our results supported that dual-tracer PET-CT was effective for staging posttransplant HCC recurrence. Previously, we recommended either dual-tracer PET-CT or a combination of contrast CT and bone scan for staging posttransplant HCC recurrence.⁶ Considering its simplicity and enhanced sensitivity, dual-tracer PET-CT is probably the better modality to guarantee comprehensive and precise staging.

We studied the clinical implications of staging dual-tracer PET-CT. The higher sensitivity across different organ systems was important, because posttransplant HCC recurrence was a systemic disease. One-third of the scans resulted in change in management (number need to scan = 2.9), and this reflected the significant impact potential of dual-tracer PET-CT in this setting. From our experience, dual-tracer PET-CT was most useful under 2 circumstances. The first occasion was when standard imaging yielded inconclusive results. With regular surveillance, recurrence was often detected early. The few number (median 2) and small size of tumor (median 2.1 cm) as well as low AFP level (median 11 ng/mL) in our series reflected early disease

TABLE 5.**Sensitivity of standard imaging, FDG PET-CT, and dual-tracer PET-CT**

	Standard imaging				FDG PET-CT				Dual-tracer PET-CT			
	Sen, %	Pos, n	Neg, n	Not done, n ^a	Sen, %	Pos, n	Neg, n	P ^b	Sen, %	Pos, n	Neg, n	P ^b
All lesions	82.5	146	31	12	60.8	115	74	<0.001	94.7	179	10	<0.001
Liver	71.0	44	18	0	51.6	32	30	0.04	96.8	60	2	<0.001
Lung	88.5	54	7	2	73.0	46	17	0.04	93.7	59	4	0.36
Bone	96.0	24	1	9	55.9	19	15	<0.001	100	34	0	0.42
Peritoneum	100	5	0	0	60.0	3	2	0.44	60.0	3	2	0.44
Adrenal	100	4	0	0	100	4	0	>0.99	100	4	0	>0.99
Lymph node	75.0	15	5	1	52.4	11	10	0.20	90.5	19	2	0.24

P values < 0.05 are statistically significant.

^aNot done within 3 mo from the index PET-CT.

^bVersus standard imaging.

FDG, 18-fluorodeoxyglucose; Neg, negative; Pos, positive; PET-CT, positron emission tomography-computed tomography; Sen, sensitivity.

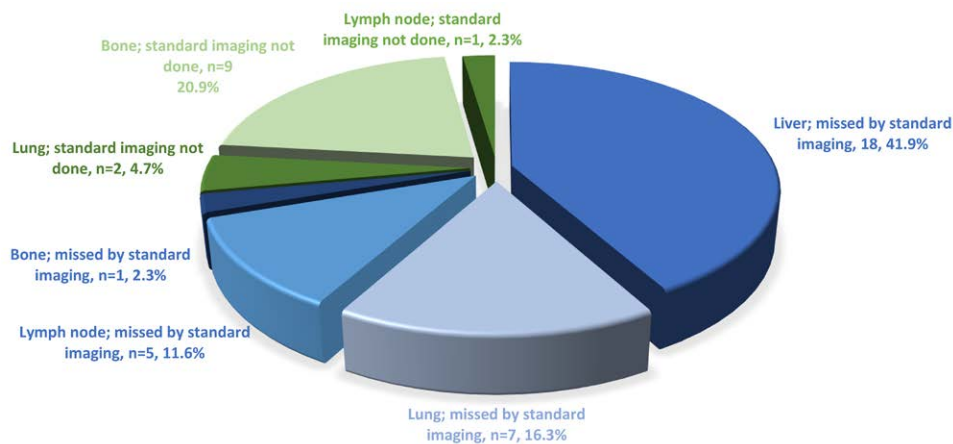


FIGURE 2. Recurrence not detected by standard surveillance protocol: location and reason (n = 43).

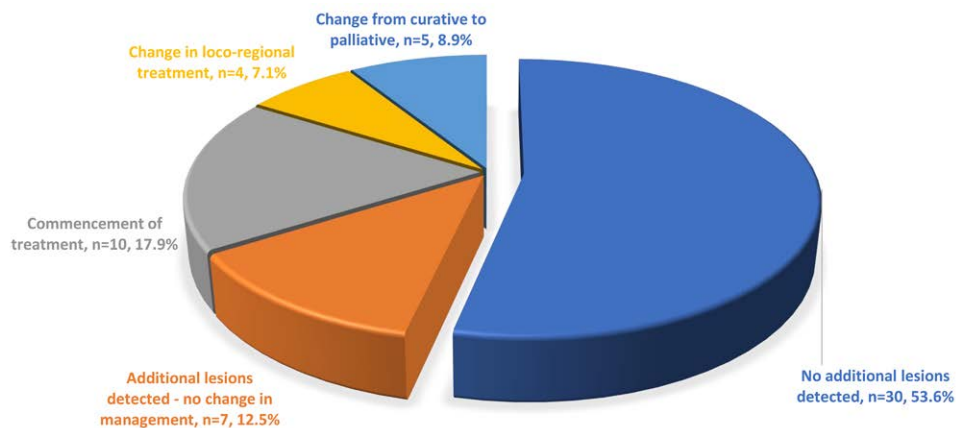


FIGURE 3. Clinical implications of dual-tracer PET-CT. PET-CT, positron emission tomography-computed tomography.

status. Anatomical assessment (ie, morphology, enhancement pattern, etc) can be limited by size of the lesion. PET-CT provided metabolic evaluation, which depends not only on size but also on tumor biology.^{9,18} A small tumor might be metabolically avid and readily detectable by PET-CT. Figure 4 shows the images of a 60-y-old man who was found to have an isolated thrombus in the retrohepatic inferior vena cava at 1 y after liver transplantation (Figure 4A). The MRI found no suspicious

lesion in the liver. However, dual-tracer PET-CT revealed intense ACT uptake from the thrombus extending to segment 7 of the liver (Figure 4C). There was another active focus at segment 6 (Figure 4D). The impression was liver recurrences with inferior vena cava invasion. Retrospective review of the MRI showed a subcentimeter lesion in segment 6 (Figure 4B). This patient received stereotactic body radiotherapy to both liver tumors. The second occasion where dual-tracer PET-CT was particularly

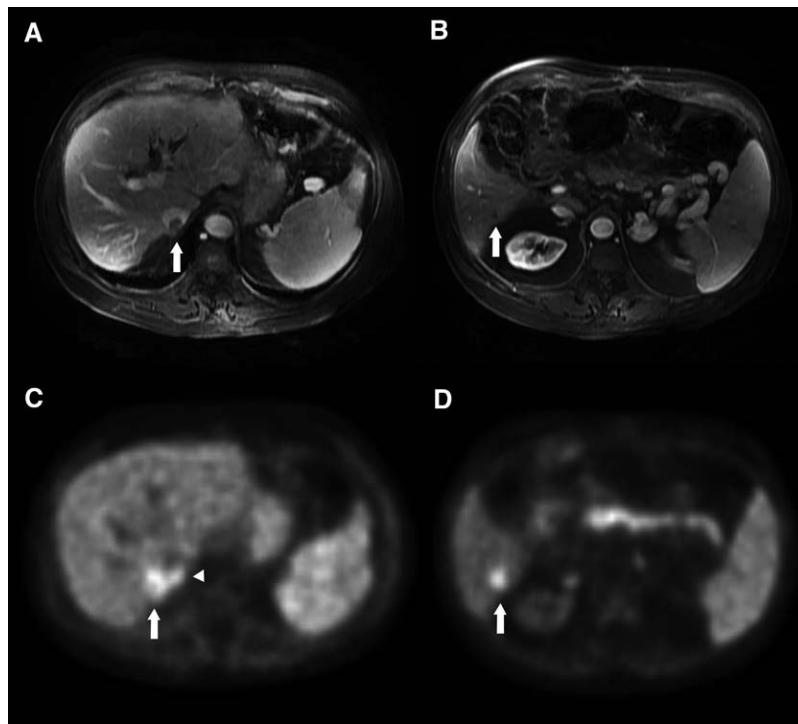


FIGURE 4. MRI and dual-tracer positron emission tomography-computed tomography (PET-CT) images of a liver transplant patient. A, MRI revealed an isolated thrombus in the retrohepatic inferior vena cava. C, Dual-tracer PET-CT revealed intense ^{11}C -acetate uptake from the thrombus (arrow head) extending to segment 7 of the liver (arrow). D, There was another focus from segment 6. B, Retrospective review of the MRI showed a subcentimeter lesion in segment 6.

useful was when standard imaging concludes oligorecurrence amenable to radical treatment. PET-CT often identified additional tumors (46.4% of the scans) that warranted specific treatment. This was especially true for hepatic recurrence given dual-tracer PET-CT was substantially more sensitive (71.0% versus 96.8%, $P < 0.001$). These patients should be considered for dual-tracer PET-CT. In case standard imaging already concluded disseminated recurrence, PET-CT would less likely alter the management.

The sensitivity of dual-tracer PET-CT was limited for peritoneal recurrence (60%). PET-CT has a lower spatial resolution (slice thickness 5 mm or higher) than CT and detection of small lesions relies on tracer avidity. In the current series, the missed peritoneal lesions ($n = 2$) were small (1.0 and 1.2 cm) and did not show C11 or FDG uptake. Tracer activity varies with biological characteristics of tumor. In gastric cancer, FDG uptake was more subtle in peritoneal metastasis because these tumors were usually poorly differentiated.¹⁹ Whether the intrinsic characteristics of HCC peritoneal metastasis affect its metabolic avidity requires further studies.

There were limitations in our surveillance protocol. The major deficiency was inadequate detection of liver recurrence (Figure 1). Employing mostly CT scan for liver (83.9%), the sensitivity compares inferiorly to dual-tracer PET-CT and under-staging might result. This is important because the liver is the most common site of recurrence (Table 2). We previously reported a series of patients with hepatic oligorecurrence treated with stereotactic body radiotherapy.²⁰ Most patients suffered regional progression (ie, in the liver away from the primary recurrence). The majority of the radiation courses (55.6%) were given without prior PET-CT. In retrospect, under-staging hepatic recurrences might have partly contributed to treatment failure. The other issue was inadequate surveillance

for bone metastasis. Bone scan was only arranged when there were symptoms. Protocolled bone scan upon recurrence would probably improve the detection rate. Alternatively, dual-tracer PET-CT can be considered for surveillance, and it offers comparable sensitivity for bone recurrence (96.0% versus 100%, $P = 0.42$). However, the current study lacks data to support this role. It must be emphasized that the positive predictive value in this study (90.4%) was obtained when PET-CT was performed for suspected or confirmed recurrence (ie, high pre-test probability). When PET-CT is performed on surveillance basis, the positive predictive value will probably depreciate. Last but not least, the cost of dual-tracer PET-CT is relatively high and it remains a concern. To maximize its benefit, surveillance program with dual-tracer PET-CT may commence on high-risk patients first (eg, with high Risk Estimation of Tumor Recurrence After Transplant score).²¹

The major limitation of this study is the retrospective methodology. Dual-tracer PET-CT was performed in patients with suspected or confirmed recurrence. This inflated the positive predictive value. The imaging sequence might enhance the sensitivity of dual-tracer PET-CT which was performed later in time, though the interval between imaging was not excessively long (median 13 d). Histological confirmation of recurrent lesions was often impractical, particularly when patients suffered multiple recurrences. Radiological diagnosis with standard imaging or serial imaging was adopted. Standard imaging was in fact by no means perfect. Serial imaging had not been performed in all patients. The number of patients and tumors were limited for subgroup analysis. We observed that dual-tracer PET-CT scan could possibly be less sensitive for peritoneal recurrence (sensitivity 60%), but the number of tumors ($n = 5$) was insufficient for analysis. Nevertheless, the current study reveals satisfactory performance of dual-tracer PET-CT

for staging posttransplant HCC recurrence. Performing dual-tracer PET-CT provides valuable information to guide clinical management. Future prospective trials might provide further insight into the role of dual-tracer PET-CT for surveillance after liver transplantation for HCC.

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