

Predicting tumor recurrence using metabolic indices of ^{18}F -FDG PET/CT prior to orthotopic liver transplantation for hepatocellular carcinoma

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Abstract. The present study analyzed the ability of metabolic burden indices from ^{18}F -fluorodeoxyglucose (^{18}F -FDG) positron emission tomography/computed tomography (PET/CT) to predict tumor recurrence following orthotopic liver transplantation (OLT) in patients with hepatocellular carcinoma (HCC). Seven major metabolic indices were measured by ^{18}F -FDG PET/CT in 93 patients with HCC, prior to OLT. The Mann-Whitney U test was then used to predict the association of metabolic indices, including the maximum standardized uptake value (SUVmax), tumor-to-mediastinum SUV ratio, tumor-to-normal-liver SUV ratio, SUV normalized to lean body mass metabolic tumor volume (MTV), total lesion glycolysis (TLG) and uptake-volume product (UVP), with the recurrence risk. The Deauville-like scoring system was used to quantify the recurrence risk. Univariate and multivariable Cox regression models were performed to determine survival rate.

The results showed that Deauville-like score (PET-negative vs. -positive), MTV (cutoff value, 13.36), TLG (cutoff value, 62.21) and UVP (cutoff value, 66.60) had high prediction performance for tumor recurrence ($P < 0.05$). TLG had the highest receiver operating characteristics area under the curve of 0.725. Among the clinical factors, high level of α -fetoprotein (AFP, ≥ 144 ng/ml), Milan criteria, tumor number (> 3), involvement of both right and left lobes, and tumor size (> 5 cm) were found to be significant predictors of tumor recurrence. Patients in the low metabolic group had longer recurrence-free survival (RFS) times compared with those in the high metabolic group, regardless of whether they met the Milan criteria or not. AFP, uptake-volume product according the SUV mean of mediastinum (UVP-M), Milan criteria, lymph node metastasis, and the number of tumors were significant prognostic factors for RFS ($P < 0.05$) in both univariate and multivariate survival analyses. Additionally, the MVI was a significant prognostic factor based on univariate survival analyses. Overall, the present study demonstrated the metabolic burden indices measured by PET/CT, Deauville-like score, MTV, TLG and UVP as significant prognostic factors in patients with HCC following OLT. The combination of metabolic indices measured by PET/CT and the existing criteria, such as the Milan criteria, may play an important role in evaluating the suitability of OLT in specific patients.

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Abbreviations: HCC, hepatocellular carcinoma; RFS, recurrence-free survival; CI, confidence interval; AFP, α -fetoprotein; ^{18}F -FDG, ^{18}F -fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; SUV, standardized uptake value; SUL, SUV normalized to lean body mass; TLR, tumor-to-normal-liver SUV ratio; TMR, tumor-to-mediastinum SUV ratio; MTV, metabolic tumor volume; TLG, total lesion glycolysis; UVP, uptake-volume product; MVI, microvascular invasion; OLT, orthotopic liver transplantation; TACE, transarterial chemoembolization

Key words: PET/CT, metabolic indices, OLT, HCC, prognosis

Introduction

Orthotopic liver transplantation (OLT) is an effective treatment for various types of end-stage liver disease and is the most appropriate alternative for treating HCC associated with liver cirrhosis (1). However, tumor recurrence following OLT is a common cause of poor prognosis and poor long-term survival. Due to the high costs and limited organ donors, the application of OLT requires accurate evaluation of a patient's condition to guarantee the recipient benefits from OLT without recurrence.

The Milan criteria (2) or the University of California San Francisco (UCSF) criteria (3), which are based on the tumor size and number, are the main criteria for selecting recipients in numerous LT centers. The prognosis is evaluated according to these criteria. However, it has been observed that a number of

patients with similar clinical features display a different prognosis profile according to the Milan criteria (4,5). Therefore, the biological characteristic of tumors must be considered when evaluating patient prognosis. Pathological differentiation is generally accepted as predictive of recurrence and was internalized in the Hangzhou criteria for transplantation (6). Microvascular invasion (MVI), which represents tumor aggressiveness, is another predictor of HCC recurrence (7). However, the biological properties of tumors can only be evaluated accurately by histological examination, which is limited by the invasive nature of tumors and the high risk of sampling errors caused by intra-tumoral heterogeneity (8).

In HCC, glucose metabolism is correlated with tumor grade and aggressiveness, which is assessed by ^{18}F -fluorodeoxyglucose (^{18}F -FDG) positron emission tomography/computed tomography (PET/CT). Glucose metabolism was found to be a significant prognostic factor of survival in patients with hepatic tumors undergoing curative surgical resection (9). The maximum standardized uptake value (SUVmax), which represents a single pixel showing maximal metabolic uptake and reflects the degree of FDG uptake, was shown to influence the survival of patients with several different types of cancer, including HCC (10). In addition, metabolic tumor volume (MTV) and total lesion glycolysis (TLG) reflected the metabolic activity and volume of tumors, and were associated with the recurrence risk of patients with HCC (11-13). However, the incorporation of the metabolic burden indices and candidate selection criteria for OLT remains controversial.

The aim of the present study was to analyze the association between ^{18}F -FDG PET/CT metabolic burden indices or clinicopathological factors and the recurrence risk in patients with HCC, following OLT. The Deauville-like scoring system was used to classify the recurrence risk using the most important metabolic indices as the input factors. Furthermore, univariate and multivariate survival analyses were performed to determine the influence of these metabolic indices on recurrence-free survival (RFS) and to identify a priority candidate order based on metabolic criteria.

Patients and methods

Patients. The present study included a total of 752 patients who underwent OLT at Tianjin First Central Hospital (Tianjin, China) between September 2013 and April 2017. Among these patients, 196 patients underwent a PET/CT examination. In total, 93 patients (83 men and 10 women; mean age \pm SD, 51.37 \pm 8.43 years; range, 29-70 years) were included in this retrospective analysis according to the following criteria: i) No macrovascular invasion and no distant metastasis, as confirmed by CT, magnetic resonance imaging (MRI) or ^{18}F -FDG PET/CT; ii) patients who underwent PET/CT before and after OLT; iii) patients who received OLT within 4 weeks of PET/CT scan; iv) HCC confirmed by clinical diagnosis or histopathological results; and v) patients who did not experience recurrence following OLT were followed up for at least 12 months. The following criteria were used to exclude patients: i) Patients who received OLT only for liver cirrhosis or intracholangio cellular carcinoma; ii) patients who did not undergo PET/CT following OLT, whose recurrence could

not be confirmed and iii) patients whose follow-up data was missing.

Enhanced CT or MRI was performed to confirm the site, size and number of tumors. In most patients, PET/CT was performed to assess the presence or absence of metastasis. Candidates for LT were selected mainly based on the Milan criteria (2). However, if there was neither major vascular invasion nor extrahepatic metastasis, OLT was still performed in some patients. Patients with different types of hepatitis, along with clinical histopathological features, including treatment history, serum α -fetoprotein (AFP) level, cell differentiation, tumor number, tumor location, tumor size, liver cirrhosis, lymph node metastasis, satellite nodules, microvascular invasion (MVI) and interstitial vessel tumor embolus, were recorded. Among the 93 patients, 91 had a clinical history of hepatitis, including 84 cases with hepatitis B, 5 with hepatitis C, 1 with hepatitis B and D, and 1 with autoimmune hepatitis. The other 2 patients were diagnosed with alcoholic liver cirrhosis without a history of hepatitis.

Patients were routinely examined by ultrasound (US) at days 7, 14 and 28 following OLT, in order to monitor the progress of the transplanted liver. The AFP level was measured every 2-3 months. CT or MRI scans were performed 3 months after OLT. An ^{18}F -FDG PET/CT scan was performed every 6 months or complementarily used when serum AFP was increased, or other suspicious symptoms or signs were observed, including pain, fever and cough. The recurrence of lesions was confirmed by the ^{18}F -FDG PET/CT examination or other imaging tools.

The study design was approved by the Institutional Clinical Research Ethics Committee of Tianjin First Central Hospital (approval no. 2018N103KY). No organs from executed prisoners were used. Each organ donated or transplanted was allocated by the China Organ Transplant Response System.

^{18}F -FDG PET/CT examination. All patients fasted for at least 6 h. Blood glucose concentration was confirmed to be <7.1 mM in each patient prior to administering ^{18}F -FDG. ^{18}F -FDG was purchased from Tianjin Atom High Science Isotopes Medicine Co., Ltd. The radiochemical purity of ^{18}F -FDG was 98%, which was tested by the manufacturer. At 1 h post-intravenous injection of ^{18}F -FDG [5.55 MBq/kg (0.15 mCi/kg)], whole-body PET/CT examination was performed using a Biograph mCT 64 system (Siemens Healthineers) in the supine position. CT images were acquired from the skull base to the upper thigh area for attenuation map and lesion localization (94-140 mAs, 120 kVp, 5-mm wide section). A 3.0-mm thick section was reconstructed for attenuation correction followed by subsequent image fusion. PET images of the same area were acquired following CT scans in 3-dimensional mode, with 6-7 bed positions. Images were reconstructed using an iterative algorithm and were transported to a dedicated workstation (syngoMMWP VE40A; Siemens Healthineers) and analyzed using the syngo TrueD software (TRUED_SYSLATEST_VE10A40; Siemens Healthineers).

PET/CT image analysis. All images were visually analyzed independently by two experienced nuclear medicine specialists, and differences of opinion were resolved by another

PET/CT expert. For quantitative analysis, the SUV_{max} and SUV_{mean} based on body weight, and SUV normalized to lean body mass (SUL) in the primary tumor, were measured. For non-FDG-avid tumors, the enhanced CT scans were used to determine the location and extent of the primary tumor on PET/CT images. For FDG-avid tumors, the MTV, referring to the volume of the tumor with the SUV in a given range on the image (based on tumor volume), was manually measured by 3-dimensional globular region of interests (ROIs). The SUV_{max} of 40% was used as the margin threshold for volumetry, as previously described (14,15). The SUV_{mean} of the mediastinum (M_{suv}) was measured as from 1 cm³ volumetric globular ROIs in the descending aorta. The SUV_{mean} of the liver background (L_{Bsuv}) was measured as from 20 cm³ volumetric globular ROIs, which were drawn in locations where HCC was not detected in the liver. The tumor-to-normal liver SUV ratio (TLR) and the tumor-to-mediastinum SUV ratio (TMR) were calculated with the following equation: $TLR \text{ or } TMR = \frac{SUV_{max} \text{ of the tumor}}{SUV_{mean} \text{ of the normal liver or mediastinum}}$. TLG is a parameter that reflects the average status of glycolysis in tumors, indicating the tumor burden by incorporating MTV and SUV_{mean} in the calculation process. TLG was calculated as the product of MTV and SUV_{mean} . For each patient, if there were multiple tumors in the liver with (<5 lesions) the MTV and SUV_{mean} of all tumors were calculated. If the number of lesions was >5, the 5 biggest tumors were calculated. MTV and SUV_{mean} of the whole liver were measured for diffuse tumors. For multiple tumors, MTV or TLG was the sum of all lesions. The uptake-volume product (UVP) (12), another metabolism burden index, was reported to be a significant prognostic factor, which exhibits a higher predictive power compared with other indices. In the present study, UVP was calculated as the product of MTV and mean TMR.

The tumors were semi-quantitatively scored based on the Deauville 5-point scoring system (16). The scoring system is as follows: 1, no uptake above the background; 2, uptake ≤mediastinum; 3, uptake >mediastinum but ≤liver; 4, uptake moderately increased compared with the liver at any site; and 5, uptake markedly increased compared with the liver at any site. The SUV_{max} of the lesions in the liver were measured and assigned a Deauville-like score as follows: 1-3, PET-negative group (n=22/93; 23.66%); 4, PET-weakly positive group (n=30/93; 32.26%); and 5, PET-markedly positive group (n=41/93; 44.09%).

Statistical analysis. The IBM SPSS statistics software (version 20.0; IBM Corp.) was used for statistical analysis. The χ^2 test was performed to compare clinicopathological factors and recurrence states. Data are expressed as the mean ± SD. M_{suv} and L_{Bsuv}, SUV_{max} and SUL, TMR and TLR were calculated and analyzed using Pearson's correlation analysis. (P≤0.05 was considered to indicate a statistically significant difference). An unpaired Mann-Whitney U test was used to compare differences between the metabolic indices, including SUV_{max} , TMR, TLR, SUL MTV, TLG and UVP of the two groups with or without recurrence. Recurrence-free survival (RFS) time was defined as the interval between the date of OLT and the date when recurrence was detected by follow-up imaging modalities. Receivers operating characteristic (ROC) curve analyses were performed to predict recurrence based on quantitative indices of PET/CT

examination. Given the specificity value, the cutoff values with the highest sensitivity for quantitative factors were determined by an algorithm for optimal cutoff determination (12). In the survival analyses, the Kaplan-Meier method was used to assess the cumulative RFS, and the log-rank test was performed to test the statistical significance of the differences between groups. Cox proportional hazards regression model was used to determine predictors of RFS. Hazard ratios were calculated with corresponding confidence intervals (CIs) set to 95%. P<0.05 was considered to indicate a statistically significant difference.

Results

Follow-up information. The follow-up and other clinical information of the patients are listed in Table I. The mean follow-up time for all patients was 18.31±16.91 months (range, 1-60 months; 95% CI, 12.57-17.66). Among the 93 patients, 30 showed no recurrence during the follow-up period of at least 12 months, with a mean follow-up time of 37.13±14.69 months (range, 13-60 months; 95% CI, 20.00-29.14). A total of 63 patients had a recurrence during the follow-up period, with a mean follow-up time of 10.90±10.30 months (range, 1-55 months; 95% CI, 8.29-13.20). The average recurrence period was 9.23±8.11 months (range, 1-35 months; 95% CI, 8.29-13.20).

A total of 12 patients had intrahepatic recurrence, 16 patients had combined intrahepatic and extrahepatic recurrence and 35 patients had extrahepatic recurrence. The sites of recurrence were the liver (n=30), lung (n=24), lymph nodes (n=23), adrenal gland (n=8), peritoneum (n=7), diaphragm (n=4), bone (n=4), cancer embolus (n=4), spleen (n=1), face (n=1), pleura (n=1) or widespread (n=1).

In total, 29 patients had early recurrence (≤6 months), with mean and median RFS times of 2.93±0.26 months (95% CI, 2.42-3.44) and 3.00±0.217 months (95% CI, 2.57-3.43), respectively. A total of 34 patients had a late recurrence (>6 months), with mean and median RFS times of 14.29±1.34 months (95% CI, 11.67-16.92) and 12.00±0.472 months (95% CI, 11.07-12.93), respectively (P<0.05).

During the follow-up, 7 patients died at 3, 4, 12, 15, 26 and 27.7 months, respectively. Since the number of patients who died was low, the median overall survival (OS) was not determined.

Association between clinicopathological features and recurrence. Clinicopathological features were examined, following the division of patients into different subgroups, to assess their association with recurrence. ROC analyses were performed, which indicated the cutoff values for age and AFP level to be 60 years and 144 ng/ml, respectively. The subgroups of tumor number and size were based on the Milan criteria.

Analysis by χ^2 test revealed that elevated AFP (≥144 ng/ml), Milan criteria, tumor number >3, involvement of both right and left lobes, and tumor size >5 cm were significant predictors of tumor recurrence. Patients with poorly differentiated tumors, positive satellite nodules, MVI and interstitial vessel tumor embolus had a higher recurrence rate (P<0.05; Table I).

Prognostic value of metabolic indices in preoperative PET/CT for tumor recurrence. M_{suv} and L_{Bsuv} were positively corre-

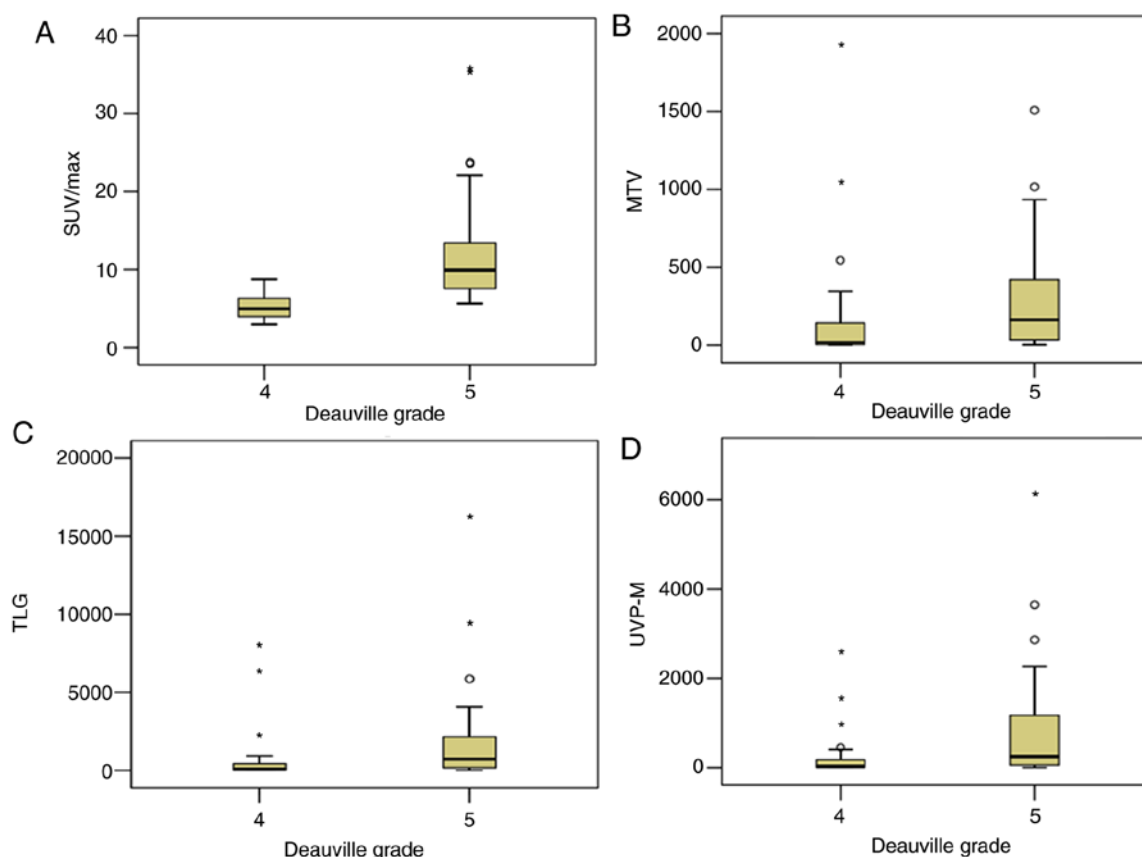


Figure 1. Metabolic indices, including (A) SUVmax, (B) MTV, (C) TLG and (D) UVP-M, were higher in PET-markedly positive groups compared with PET-weakly positive groups, according to Deauville-like criteria grades 5 and 4, respectively. The asterisks and circles in the figure represent the extreme values and outliers, respectively. SUVmax, maximum standardized uptake value; MTV, metabolic tumor volume; TLG, total lesion glycolysis; PET, positron emission tomography; UVP-M, uptake-volume product according the SUVmean of mediastinum.

lated ($P<0.05$; $r=0.867$; data not shown). SUV_{max} and SUL, as well as TMR and TLR, were positively correlated (both $P<0.001$; $r=0.995$ and $r=0.942$, respectively; data not shown). The MTV, TLG and UVP of the non-recurrence group were significantly lower compared with those of the recurrence group, ($P=0.018$, $P=0.009$ and $P=0.028$, respectively; data not shown). However, SUV_{max} , TMR, TLR and SUL were not significantly different between the recurrence group and the non-recurrence group (data not shown).

Association between Deauville-like score and recurrence. The Deauville-like score in preoperative PET/CT was summarized. Higher Deauville-like score was associated with higher metabolic indices ($P<0.05$). The most important metabolic indices including SUV_{max} , MTV, TLG and uptake-volume product according the SUV_{mean} of mediastinum (UVP-M) were selected and are presented in Fig. 1.

According to the Deauville-like score, 22 patients had PET-negative lesions prior to OLT, with 6 patients (27.3%) experiencing a recurrence at 9, 11, 16, 16, 25 and 35 months, respectively, following OLT. The mean recurrence period was 18.67 ± 9.73 months (range, 9-35 months; 95% CI, 8.46-28.88).

In the PET-weakly positive group, 23 of 30 (76.7%) patients had a recurrence, with a mean recurrence period of 9.83 ± 7.62 months (range, 1-31 months; 95% CI, 6.53-13.12). In the PET-markedly positive group, 33 of 41 (80.5%) patients had a recurrence, with a mean recurrence period of 6.97 ± 7.04 months

(range, 1-34 months; 95% CI, 4.47-9.47 months) ($P<0.001$). The recurrence period in the PET-markedly positive group was shorter than that of the PET-weakly positive group, and the recurrence periods of the two groups were shorter than that of the PET-negative group. Therefore, the corresponding recurrence risks for patients in the PET-negative (score 3), PET-weakly positive (score 4) and PET-markedly positive groups (score 5) were low, medium and high, respectively ($P<0.05$; Fig. 2A).

ROC curve analysis based on metabolic indices determined by PET/CT. ROC analysis demonstrated the Deauville-like score (PET-negative vs. PET-positive), MTV (cutoff value, 13.36), TLG (cutoff value, 62.21) and UVP (cutoff value, 66.60) to be significant predictors of recurrence risk (all $P<0.05$). Among the metabolic indices, TLG had the highest AUC (0.725), with sensitivity and specificity of 79.6 and 66.7% at the cutoff value of 62.21 (Table II).

MTV=13.36 and TLG=62.21 were used as the cutoff values, and the median RFS time of the lower MTV and TLG groups was 12 months (data not shown). The median RFS time of the higher MTV and TLG groups was 5 months, and the χ^2 values were 10.826 for the MTV group and 10.211 for the TLG group ($P<0.05$; data not shown). With UVP-M=66.60 as the cutoff value, the median RFS times in the lower and higher UVP-M groups were 12 and 4 months, respectively, and the χ^2 value was 17.184 ($P<0.05$; data not shown). Fig. 3 displays the RFS

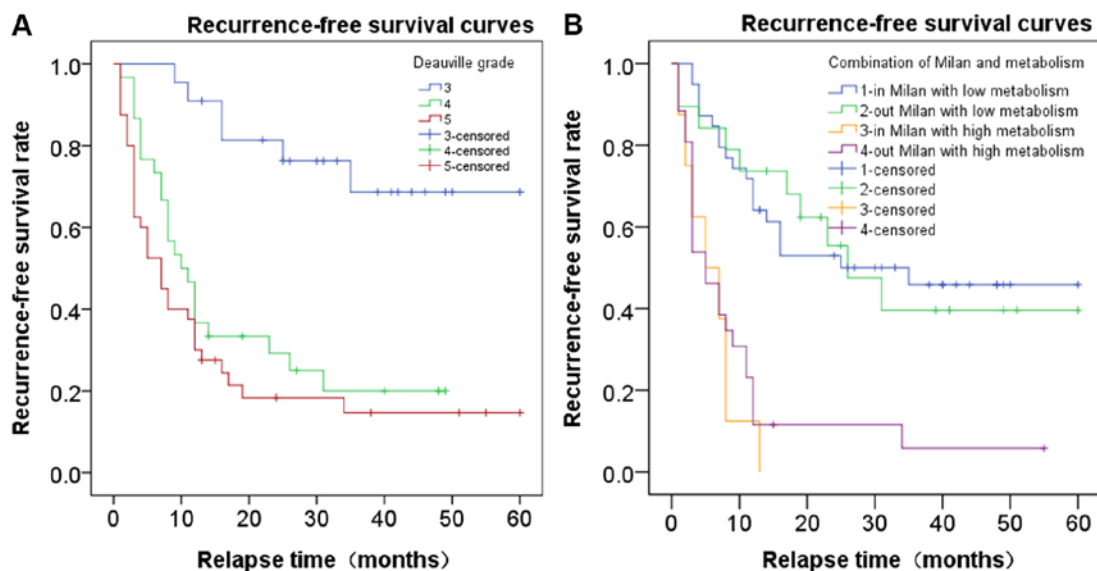


Figure 2. Kaplan-Meier analyses of recurrence-free survival according to (A) Deauville-like score and (B) the combination of metabolic status and Milan criteria (in/out).

curve based on the cutoff of MTV, TLG and UVP-M. Patients with low MTV (<13.36) exhibited significantly improved RFS than those with high MTV (≥ 13.36 ; $P<0.05$; Fig. 3A) and patients with low TLG (<62.21) exhibited significantly improved RFS than those with high TLG (≥ 62.21 ; $P<0.05$; Fig. 3B). Additionally, patients with low UVP-M (<66.60) exhibited significantly improved RFS than those with high TLG (≥ 66.60 ; $P<0.05$; Fig. 3C).

Combination of metabolic status and Milan criteria to predict the recurrence risk. To further stratify the risk of HCC recurrence, the TLG cutoff value of 62.21 was used to categorize FDG-positive patients ($n=56$) into high-metabolic ($n=45$; TLG, ≥ 62.21) and low-metabolic ($n=11$; TLG, <62.21) groups. TLG was found to be a significant predictor of late recurrence (>6 months; $P=0.04$). The RFS time in the low metabolic group (mean, 17.43 months; median, 16 months; 95% CI, 8.74-23.26) was longer compared with the high metabolic group (mean, 9.29 months; median, 12 months; 95% CI, 8.82-13.18) ($P<0.001$). However, TLG was not a significant predictor of early recurrence (≤ 6 months; $P=0.80$).

The results revealed that patients with low metabolic burden had longer RFS times compared with those with high metabolic burden, regardless of the Milan criteria. Subsequently, the patients were separated into four groups: 20 patients who met the Milan criteria with low metabolism; 10 patients who did not meet the Milan criteria with low metabolism; 8 patients who met the Milan criteria with high metabolism; and 25 patients who did not meet the Milan criteria and had high metabolism. The RFS curves of these four groups are shown in Fig. 2B. Patients with low metabolism exhibited significantly improved RFS than those with high metabolism, independently of whether they met the Milan criteria or not ($P<0.05$).

Univariate and multivariate survival analyses. In the univariate survival analysis, AFP, UVP-M, Milan criteria,

1 node metastasis, number of tumor and MVI were found to be significant prognostic factors of RFS ($P<0.05$). In the multivariate survival analyses, AFP, UVP-M, Milan criteria, lymph node metastasis, and number of tumors were identified as significant prognostic factors ($P=0.005$, $P<0.001$, $P=0.001$, $P=0.001$ and $P=0.002$, respectively; Table III).

Discussion

Emerging evidence indicates that the Milan criteria and radiographic up-to-seven (UTS) criteria (17), are too restrictive as selection tools for liver transplantation candidates, and therefore, it is necessary to expand these criteria (18,19). Some expanded criteria, based on tumor number and size, such as the UCSF criteria (20) or the Hangzhou criteria (21), revealed that selected patients had a similar prognosis profile compared with those who met the Milan criteria. Kornberg *et al* (18) reported that the Milan criteria can successfully select patients who are suitable for LT, and further biological tumor evaluation is necessary beyond the Milan boundaries. A number of studies have identified tumor size, capsular invasion or positive resection margin, satellite nodules, MVI, AFP, transaminase and cirrhosis as risk factors for HCC recurrence (22-24). Cell differentiation and MVI, which provide histological evidence of tumor penetration into small vessels around the primary neoplasm, have become important markers of tumor aggressiveness (25). The findings of the present study are consistent with those reported in previous studies (22,24). Additionally, both right and left lobe involvement, as well as tumor number >3 , which reflect higher tumor burden, were found to be risk factors in the present study.

A non-invasive method is required to provide standardized patient selection to ensure their suitability for LT. Previous studies demonstrated that ^{18}F FDG PET/CT is a powerful prognostic marker for patients with HCC following LT, and it was found to be strongly correlated with pathological characteristics of tumors, such as microvascular invasion

Table I. Association of clinicopathological features and recurrence.

Variable	n	Non-recurrence, n	Recurrence, n	χ^2	P-value
Gender				0.307	0.579
Male	83	26	57		
Female	10	4	6		
Age, years				0.016	0.899
<60	76	25	51		
≥60	17	5	12		
Treatment history				1.614	0.656
None	36	11	25		
Interventional therapy	30	12	18		
Excision	14	3	11		
Both	12	4	8		
Drug therapy	1	0	1		
Hepatitis B/C DNA copy				2.483	0.115
Static	67	25	42		
Active	25	5	20		
No hepatitis	1	0	1		
Hepatitis types				46.140	0.305
HBV	84	28	53		
HCV	5	2	3		
NA	4	0	4		
AFP, ng/ml				5.450	0.020
<144	57	25	32		
≥144	35	5	30		
NA	1	0	1		
Milan criteria				4.020	0.040
In	46	19	27		
Out	47	11	36		
Cell differentiation				6.172	0.046
Poorly	23	3	20		
Moderately	61	23	38		
Well	3	0	3		
NA	6	4	2		
Tumor number				17.994	<0.001
<3	54	27	27		
≥3	39	3	36		
Tumor location				17.936	<0.001
Right lobe	46	22	24		
Left lobe	10	5	5		
Both	35	2	33		
NA	2	1	1		
Tumor size, cm				17.350	0.001
<5	48	24	24		
≥5	43	5	38		
NA	2	1	1		
Liver cirrhosis				1.475	0.224
No	3	0	3		
Yes	87	29	58		
NA	3	1	2		

Table I. Continued.

Variable	n	Non-recurrence, n	Recurrence, n	χ^2	P-value
Lymph nodes metastasis				2.558	0.110
No	88	31	57		
Yes	5	0	5		
Satellite nodules				12.740	<0.001
No	63	28	35		
Yes	29	2	27		
NA	1	0	1		
Stump or incisal edge				1.501	0.221
Negative	89	30	59		
Positive	3	0	3		
NA	1	0	1		
MVI				10.874	0.001
No	52	25	27		
Yes	41	6	35		
Interstitial vessel tumor embolus				12.951	<0.001
No	59	27	32		
Yes	33	3	30		
NA	1	0	1		

NA, not available or information missing; MVI, microvascular invasion; AFP, α -fetoprotein.

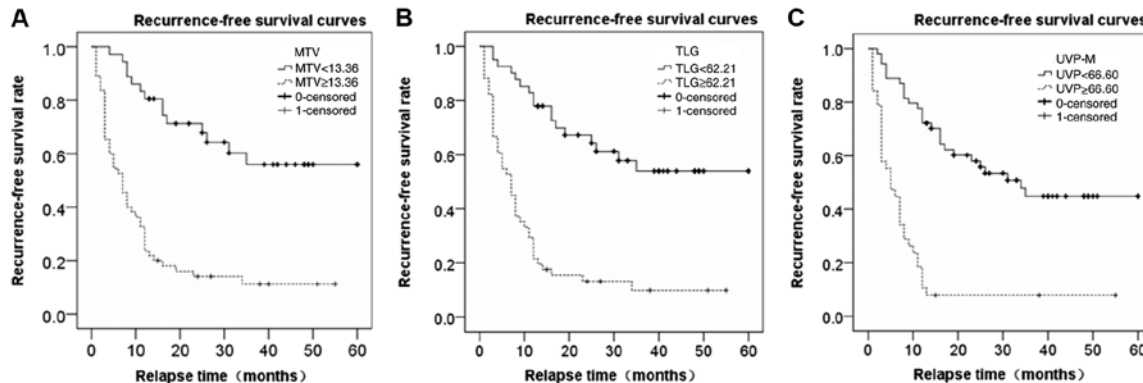


Figure 3. Kaplan-Meier analyses of recurrence-free survival based on the cutoff values of (A) MTV, (B) TLG and (C) UVP-M. MTV, metabolic tumor volume; TLG, total lesion glycolysis; UVP-M, uptake-volume product according the SUVmean of mediastinum.

and differentiation (12,26,27). In addition to FDG, other PET radioactive tracers, such as labeled choline and acetate, are frequently used in clinical practice. These factors are mainly designed to improve the specificity and sensitivity of FDG PET-CT in detecting HCC and HCC metastasis. 11C-choline is a lipid tracer with strong avidity for HCC, especially in well- and moderately-differentiated tumors (28). Several studies have described the diagnostic potential of a dual tracer approach using radiolabeled choline and ^{18}F -FDG PET/CT in HCC (29,30). 11C-ACT-PET can be used to monitor abnormal uptake of local fatty acids and is sensitive to the diagnosis of well-differentiated HCC. However, the clinical application of 11C-ACT-PET is limited due to the synthetic nature of the technology and the short half-life.

Accelerated glycolysis, determined by ^{18}F -FDG PET/CT, is highly correlated with glycolytic enzymatic activity and tumor aggressiveness in malignant tumors. ^{18}F -FDG is transported into cells via glucose transporters (GLUTs). Previous studies revealed that low ^{18}F -FDG uptake was correlated with high FDG-6-phosphatase activity, low expression of GLUT1 or GLUT2, and high expression of P-glycoprotein (31,32). High tumor uptake of FDG often indicates a poor clinical outcome (30,33). FDG-PET has been combined with the radiographic UTS criteria to select patients with HCC for LT (18). Lee *et al* (34) evaluated the accuracy of the National Cancer Center, Korea (NCCK) criteria using PET/CT (negative) and total tumor size (<10 cm). The NCCK criteria produced comparable results with preoperative PET/CT

Table II. Receiver operating characteristic analysis of metabolic burden indices for predicting recurrence.

Indices	AUC	P-value	95% CI		Sensitivity	Specificity	Youden index	Cutoff value
			Lower	Upper				
MTV	0.708	0.025	0.542	0.873	0.852	0.583	0.435	13.36
TLG	0.725	0.015	0.569	0.882	0.796	0.667	0.463	62.21
UVP	0.694	0.036	0.537	0.852	0.630	0.833	0.463	66.60

MTV, metabolic tumor volume; TLG, total lesion glycolysis; UVP, uptake-volume product; AUC, area under curve; CI, confidence interval.

Table III. Results of univariate analysis and multivariate analysis.

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	P-value	HR	95% CI	P-value
AFP	3.34	1.38-8.09	0.008	2.73	1.37-5.47	0.005
UVP-M	14.55	3.39-62.44	<0.01	5.68	2.59-12.44	<0.01
Milan criteria	0.030	0.01-0.20	<0.01	0.26	0.12-0.57	0.001
Lymph node metastasis	15.343	2.61-90.29	0.003	7.43	2.23-24.74	0.001
Number of tumor	3.648	1.55-8.62	0.003	2.58	1.43-4.66	0.002
MVI	0.228	0.06-0.95	0.042	0.325		

HR, hazard ratio; CI, confidence interval; AFP, α -fetoprotein; MVI, microvascular invasion; UVP-M, uptake-volume product according the SUVmean of mediastinum.

imaging and tumor pathological characteristics relative to the Milan criteria. Therefore, the NCCK criteria were proposed as new expanded criteria that can be used in place of the traditional Milan criteria. The present study explored the ability of metabolic indices, including MTV, TLG and UVP, measured by FDG-PET/CT to predict tumor recurrence following OLT.

SUV_{max}, TLR, MTV and TLG derived from ¹⁸F-FDG PET/CT are the most frequently used indices for staging and risk stratification of patients prior to LT. SUL is recommended for evaluating the metabolic state of SUV, based on body weight, due to the increasing frequency of obesity cases. TLR is superior to SUV_{max} in assessing tumor metabolism. Studies have shown that high TLRs reflect a poor prognosis (22,35). A study demonstrated that patients with vascular invasion exhibited significantly higher AFP levels, tumor (T) SUV_{max}, TSUV_{max}/LSUV_{max} ratio and TSUV_{max}/LSUV_{mean} ratio compared with those without vascular invasion (36). In another study, multivariate analysis revealed that peritumoral enhancement and a TSUV_{max}/LSUV_{mean} of ≥ 1.2 were significantly associated with MVI (37). TMR was compared with TLR in the present study due to the heterogeneous metabolic activities in the tissues of liver cirrhosis. The two indices showed similar performances in predicting tumor recurrence. Thus, the selection of patients by TMR rather than TLR is recommended, as the SUV_{max} of the mediastinum is more stable than the SUV_{max} of the liver with cirrhosis and hepatitis.

In a previous study, both TLR and UVP calculated by the inferior vena cava (IVC) activity were identified as significant prognostic factors of tumor recurrence in multivariate analyses (12). The descending aorta in the mediastinum was chosen as the background rather than the IVC, which is often flattened in patients with cirrhosis. Patients with low ¹⁸F-FDG uptake had significantly better survival rates than those with higher ¹⁸F-FDG uptake (38). In the present study, MTV, TLG and UVP were strong predictors of recurrence in patients with HCC following LT compared with other indices, such as SUV_{max}, TLR and SUL. UVP and TLG in PET/CT were found to be independent prognostic factors for RFS in patients with HCC following LT, demonstrating a superior prognostic value for HCC.

Lee *et al* (9) retrospectively analyzed the data of 242 patients with HCC who underwent staging by FDG PET and subsequent curative surgical resection. The serum bilirubin level, MTV and TLG were found to be independent prognostic factors of overall RFS and OS ($P < 0.05$). MTV and TLG were prognostic predictors for only extrahepatic RFS ($P < 0.05$). Furthermore, serum AFP, bilirubin levels, MTV and TLG were prognostic factors of early intrahepatic RFS ($P < 0.05$), whereas hepatitis C virus positivity and serum albumin level were independently prognostic predictors of late intrahepatic RFS ($P < 0.05$). Lee *et al* (39) analyzed 191 patients who underwent FDG-PET scans and subsequent living donor LT for HCC. Based on a multivariate analysis, PET/CT-positive status was found to be an independent prognostic predictor for

disease-free survival, which influenced early recurrence. HCC recurrence occurred early (≤ 6 months) in 20 (10.5%) patients and late (> 6 months) in 18 (9.4%) patients.

Studies have evaluated the prediction ability of FDG uptake for tumor recurrence patterns. Previous studies revealed that patients with high SUV_{max} had extrahepatic recurrence and early recurrence, which reflected the aggressiveness of HCC (13,40). Such patients had a poor prognosis due to the limited therapeutic options (13,41). In the present study, MTV, TLG and UVP in pre-transplantation PET imaging were significantly higher in the recurrence group compared with that in the non-recurrence group, indicating that higher MTV, TLG or UVP were associated with shorter RFS time.

In PET-negative lesions, it is challenging to measure MTV or TLG, due to poor contrast. These patients can therefore be grouped into two types. In type-one patients, the tumor itself is non-discernible from the background due to the highly differentiated HCC in ^{18}F FDG PET/CT. In the second category, the patients received therapies such as hepatectomy or transarterial chemoembolization (TACE), which minimize the impact of disease progression and are the most frequently used to control HCC while awaiting OLT (42). These PET-negative patients had a better prognosis; a total of 22 patients with negative FDG uptake in tumors showed better prognosis or late recurrence following OLT. However, out of the PET-weakly positive group, 23/30 (76.7%) patients had a recurrence, while of the PET-markedly positive group, 33/41 (80.5%) patients had a recurrence, with a shorter mean recurrence period compared with that in the PET-negative and PET-weakly positive groups.

The Deauville-like score can be obtained from PET-positive patients by visual examination, which reflects the degree of tumor malignance. In the present study, Deauville-like score reflected the metabolic indices to some extent; a higher Deauville-like score was correlated with a higher MTV, TLG and UVP. For most patients with HCC, the prognosis can be predicted by performing visual assessment for the Deauville-like score. In patients with Deauville-like scores of 4 and 5, the metabolic indices should be evaluated during the decision-making process. TLG reflects the average level of glycolysis in tumors and is closer to the concept of tumor burden by taking into account the MTV and SUV_{mean} in the calculation process, and had the highest AUC. Thus, patients were grouped into low and high metabolic groups according to TLG in combination with the Milan criteria. Patients in the low metabolic group had a better prognosis, regardless of whether they met the Milan criteria or not.

Based on the findings of the presents study, a PET/CT examination prior to LT in all patients is recommended in order to preclude those with extrahepatic metastasis. The following metabolic criteria provide an indication for the order of priority of candidates for OLT: i) Patients with PET-negative imaging should be indicated for OLT regardless of the size and number of tumors; ii) patients meeting the Milan criteria with low metabolic indices should undergo OLT; iii) patients not meeting the Milan criteria with low metabolic indices should be considered for OLT; iv) patients meeting the Milan criteria but with high metabolic burden should undergo TACE to decrease metabolic burdens prior to LT; and v) patients not meeting the

Milan criteria with high metabolic indices should be precluded or re-evaluated following treatment to decrease metabolic burden (19). Moreover, a PET/CT examination is strongly recommended within 3 months of OLT in patients with high metabolic indices who received OLT, to detect early recurrence for timely therapy.

Apart from the intrinsic limitations of any retrospective study, there are some limitations in the present study. Firstly, the sample size was relatively small, as only patients who had PET/CT before and after LT were considered. Secondly, the recurrence rate of the patients was high due to selection bias, since some non-recurrence patients who did not undergo PET/CT examination following LT were excluded from the study. Thus, the association of metabolic and volume indices with RFS or OS following LT requires further investigation in a large sample study.

In conclusion, Deauville-like score, MTV, TLG and UVP, the metabolic indices assessed by PET/CT, are significant prognostic factors of patients with HCC who undergo OLT. Therefore, combining the metabolic indices of PET/CT examinations with the existing criteria, such as the Milan criteria, may play an important role in identifying patients who are eligible for successful OLT.

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Availability of data and materials

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

Authors' contributions

ED, conception and design, acquisition and analysis of data, manuscript preparation; DL, analysis and interpretation of data; LW, acquisition of data; XF, analysis and interpretation of data; JS, conception and design, supervision of data analysis; WX, experimental design, supervision of data analysis and manuscript revision. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study design was approved by the Institutional Clinical Research Ethics Committee of Tianjin First Central Hospital (approval no. 2018N103KY). No organs from executed prisoners were used. Each organ donated or transplanted was allocated by the China Organ Transplant Response System. All participants provided written informed consent.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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