

Prediction of Microvascular Invasion and Recurrence Using Preoperative ¹⁸F-FDG PET/CT Metabolic Parameters in Hepatocellular Carcinoma

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Abstract

Background: Microvascular invasion (MVI) is very important in the evaluation of hepatocellular carcinoma (HCC), but diagnosis is determined by postoperative pathology; thus, preoperative non-invasive methods will play an active role. The purpose of this study was to assess the performance of metabolic parameters of preoperative ^{18}F -fluorodeoxyglucose positron emission tomography/computerized tomography (^{18}F -FDG PET/CT) in the prediction of MVI and postoperative recurrence in primary hepatocellular carcinoma.

Methods: We retrospectively collected 72 patients with HCC who have performed ^{18}F -FDG PET/CT scan before partial hepatectomy between 2016 and 2019. We used both normal liver tissue and inferior vena cava as the reference background, and combined with clinicopathological features, ^{18}F -FDG PET/CT metabolic and volumetric indices to predict MVI and postoperative recurrence of primary HCC before surgery.

Results: Twenty-one of the 72 patients recurred, in recurrent cases showed higher maximum standard uptake value (SUV_{max}), TNR (ratio of tumor SUV_{max} to mean SUV [SUV_{mean}] of the background tissue), metabolic tumor volume (MTV) and total lesion glycolysis (TLG) than nonrecurrence cases ($p < 0.001$). All ^{18}F -FDG PET metabolic and volumetric indices for predicting postoperative HCC recurrence were significant on receiver-operating-characteristic (ROC) curve analyses ($p < 0.05$). TNR_{IVC} , TNR_{NL} , MTV, TLG_{IVC} , and TLG_{NL} were significant factors for predicting MVI in HCC ($p < 0.05$). On multivariate analyses, MVI, SUV_{max} , TNR_{IVC} , TNR_{NL} , MTV, TLG_{IVC} , and TLG_{NL} ($p < 0.05$) are independent risk factors for predicting postoperative HCC recurrence. TNR_{IVC} is the most relevant PET/CT parameter for predicting MVI in HCC, and MTV is the most valuable for predicting postoperative HCC recurrence. Moreover, the PET/CT parameters are more accurate for prognosis with inferior vena cava as a reference background than with normal liver tissue.

Conclusion: ^{18}F -FDG PET/CT metabolic and volumetric indices are effective predictors, and could non-invasively provide more comprehensive predictive information on MVI and postoperative recurrence of primary HCC before surgery.

Background

Hepatocellular carcinoma (HCC) accounts for 85–90% of all primary liver cancers. Radical resection is the first choice for liver cancer. However, the 5-year recurrence rate is approximately 70% even with R0 resection [1]. Therefore, early diagnosis and accurate prediction of postoperative liver cancer recurrence is of great significance. It has been reported that the main risk factors for the recurrence of liver cancer include liver function, hepatitis, tumor size, stage, grade, microvascular invasion (MVI), and treatment [2–3]. As an indicator of tumor aggressiveness, MVI is very important for postoperative evaluation. However, MVI is determined by postoperative pathological examination. Preoperative non-invasive diagnosis of

MVI will play an active role in the determination of surgical resection range and other treatment planning, which can effectively reduce the recurrence rate.

As an important molecular imaging technique, positron emission tomography/computerized tomography (PET/CT) plays a unique role in the diagnosis and therapeutic decision of HCC. ^{18}F -fluorodeoxyglucose (^{18}F -FDG) PET/CT reflects the metabolic activity and differentiation of HCC based on variable parameters, and has the ability for tumor staging, re-staging, evaluation of therapeutic effect, and determination of malignant potential and prognosis [4–7]. Metabolic tumor volume (MTV) and total lesion glycolysis (TLG) of ^{18}F -FDG PET/CT have been concerned as measures of tumor volume and burden with high glucose metabolism [8]. However, they have been mostly studied in lymphoma, lung cancer and intestinal cancer, and rarely in HCC. In addition, most of the published studies are based on liver background. As the uptake in normal liver tissue is unstable due to susceptibility to hepatitis, cirrhosis, and other factors, this study intends to use the inferior vena cava as a reference background to overcome the shortcomings of the existing methods. At present, no studies have been conducted to investigate whether multiple metabolic parameters of ^{18}F -FDG PET-CT could provide more comprehensive predictive information for preoperative evaluation of MVI and the tumor activity of HCC using the inferior vena cava as a reference background.

This study intends to use the inferior vena cava as a reference, instead of the commonly used PET/CT reference background, to assess the prognostic value of the following PET/CT metabolic parameters for preoperative evaluation of MVI and postoperative recurrence of primary HCC: maximum standard uptake value (SUV_{max}), TNR (ratio of tumor SUV_{max} to mean SUV [SUV_{mean}] of the background tissue), MTV, and TLG.

Materials And Methods

Patients

Written informed consent for PET/CT was obtained from all patients in this study. This study was approved by the Ethics Review Committee of Fudan University Shanghai Cancer Center. A retrospective analysis was performed on 72 patients (58 males and 14 females) with HCC diagnosed after partial hepatectomy in the Department of Hepatobiliary Surgery, Fudan University Shanghai Cancer Center from January 2016 to February 2019.

Inclusion criteria

1) age > 18 years; 2) HCC was suspected on preoperative enhanced CT or MR or PET/CT, and confirmed by postoperative pathological analysis; 3) whole-body ^{18}F -FDG PET/CT was performed within two weeks before the operation, and resectability was confirmed preoperatively; 4) laboratory tests (heart, kidney, and blood etc.) were within normal limits; 5) no other antitumor treatment before and during the operation, and no other tumor history; 6) no postoperative complications (e.g., liver failure, bile leakage,

upper gastrointestinal bleeding, hepatorenal syndrome, abdominal abscess, lung infection, and other infections); and 7) complete medical records and follow-up data.

Exclusion criteria

1) liver cancer with unresectable distant metastases; 2) liver cancer with clear Portal vein tumor thrombosis (PVTT); 3) a history of other malignant tumors or other anti-tumor treatments; 4) active infections; 5) elevated fasting blood glucose or any abnormal safety laboratory findings; 6) perioperative death, very early relapse, and loss to follow-up (2 and 12 months); and 7) incomplete follow-up data. All patients were followed up for a minimum of 12 months. Liver function tests, alpha fetoprotein (AFP) measurement, and enhanced CT were performed every 3–6 months after hepatectomy to exclude recurrence.

¹⁸F-FDG PET/CT PET/CT

A Siemens Biograph 16 HR PET/CT scanner was used. ¹⁸F-FDG with a radiochemical purity of >95% was produced by a cyclotron and its synthesis module in our department. All patients were fasted for at least 6 h, rested in the supine position for 60 min, and injected intravenously with ¹⁸F-FDG at a dose of 7.4 MBq/kg before the scanning. Blood glucose levels were controlled to be equal to or less than 7.78 mmol/L. The scanned area was between the calvarium and the top of the thighs. The CT parameters were as follows: voltage 120 kV, current 100 mA, slice thickness 3.75 mm, helical pitch 3.6, and tube rotation time 0.5 s. Immediately after CT, PET was performed with the same machine for the same scanned area as that of CT. 3D-PET emission data were acquired for 2 min/bed position for a total of 6–7 bed positions (data for the head and trunk were acquired separately). CT data corrected for attenuation were fused with images reconstructed by the iterative method to obtain PET/CT fusion images.

Image Processing

The PET/CT data was imported into the Siemens workstation, and read by two experienced PET/CT physicians independently. Standardized uptake value (SUV) was automatically calculated from manually drawn regions of interest (ROI) as follows: $SUV = \text{lesion concentration (kBq/ml)} / \text{injected FDG dose (MBq)} / \text{body weight (kg)}$. SUV_{max} was measured. MTV was measured automatically using an absolute threshold of SUV 2.5. SUV_{meanNL} and $SUV_{meanIVC}$ were defined as the mean SUV of three ROIs with the same area as the lesion placed at the level of normal liver tissue and normal inferior vena cava, respectively. The ratio of tumor to background SUV was calculated as follows: $TNR_{NL} = SUV_{max} / SUV_{meanNL}$; $TNR_{IVC} = SUV_{max} / SUV_{meanIVC}$. TLG was calculated as follows: $TLG_{NL} = MTV \times SUV_{meanNL}$; $TLG_{IVC} = MTV \times SUV_{meanIVC}$.

Statistical analysis

Statistical analysis was performed using SPSS 19.0 (SPSS, Inc., Chicago, IL, USA). The variables examined in this study were gender, age, hepatitis B status, tumor size, number, serum AFP, bilirubin,

histological grade, MVI, and ^{18}F -FDG PET/CT parameters (SUV_{max} , TNR_{NL} , TNR_{IVC} , MTV, TLG_{NL} , TLG_{IVC}). Quantitative data are expressed as $\bar{x} \pm s$. T test was used for comparison. Enumeration data were expressed as percentage. The first relapse after hepatectomy for HCC was taken as the endpoint. Recurrence-free survival (RFS) was defined as the time between surgical resection and the first relapse after surgery. The sensitivity, specificity, and cutoff values of SUV_{max} , TNR_{NL} , TNR_{IVC} , MTV, TLG_{NL} , and TLG_{IVC} in predicting tumor recurrence were determined using receiver operating characteristic (ROC) curve analysis. The area under the curve (AUC) was divided into three categories: low accuracy (0.50–0.70), medium accuracy (0.70–0.90), and high accuracy (0.90–1.00). Factors for the presence of MVI were carried out using univariate logistic regression analysis. Factors with statistically significant differences in univariate analysis were included in multivariate logistic regression analysis. RFS curves were constructed using the Kaplan-Meier method for the factors affecting recurrence. Differences between groups were analyzed by the univariate analysis. Factors with statistically significant differences in univariate analysis were included in the Cox multivariate regression model to further analyze their effects on postoperative recurrence of HCC. $P < 0.05$ was considered statistically significant.

Results

Clinical characteristics and PET/CT findings

Seventy-two patients with HCC were enrolled, including 58 males (80.56%) and 14 females (19.44%), aged from 18 to 77 years, with an average age of 56 ± 9 years. All patients were followed up for 12 to 49 months, with a median follow-up time of > 24 months. Twenty-one of the 72 patients recurred. The overall postoperative recurrence rate was 29.17% (21/72), and the RFS rate was 70.83% (51/72) (Table 1). Quantitative analysis of PET/CT metabolic parameters revealed higher SUV_{max} , TNR_{NL} , TNR_{IVC} , MTV, TLG_{NL} , and TLG_{IVC} in recurrent cases (all $p < 0.001$) (Table 2).

Table 1
Clinicopathologic characteristics of patients with hepatocellular carcinoma.

Characteristic	Overall	Recurrence	Nonrecurrence
Patients(n)	72	21(29.17%)	51(70.83%)
Sex(n)	58 M:14 F	16 M:5 F	41 M:10 F
Age, mean(y)	56 ± 9(18–77)	57 ± 11(18–77)	55 ± 8(24–72)
Follow-up time, mean(mo)	30.2 ± 16.1(13.3–48.8)	24.7 ± 11.2(13.3–35.8)	35.2 ± 12.4(20.4–48.8)
HBV+(n)	56(77.78%)	15(71.43%)	41(80.39%)
Tumor size(cm)			
≤ 3	11(15.28%)	2(9.52%)	9(17.65%)
≥3, ≤5	24(33.33%)	6(28.57%)	18(35.29%)
≥5, ≤ 10	29(40.28%)	9(42.86%)	20(39.22%)
≥10	8(11.11%)	4(19.05%)	4(7.84%)
Tumor number(n)			
Single	63(87.5%)	16(76.19%)	47(92.16%)
Multiple	9(12.5%)	5(23.81%)	4(7.84%)
AFP≥25 ng/mL(n)	25(34.72%)	13(61.90%)	12(23.53%)
Bilirubin≥10 mg/L(n)	49(68.06%)	17(80.95%)	32(62.75%)
Tumor grade(n)			
I	3(4.17%)	2(9.52%)	1(1.96%)
II	29(40.28%)	6(28.57%)	23(45.10%)
III	34(47.22%)	9(42.86%)	25(49.02%)
IV	6(8.33%)	4(19.05%)	2(3.92%)
Vascular invasion(n)			
No	49(68.06%)	7(33.33%)	42(82.45%)
Yes	23(31.94%)	14(66.67%)	9(17.65%)
HBV hepatitis B virus			

Table 2
PET/CT characteristics of patients with HCC according to recurrence and MVI

Characteristic	MVI(n = 23)	nonMVI(n = 49)	<i>p</i>	Recurrence(n = 21)	Nonrecurrence(n = 51)	<i>p</i>
SUV _{max}	5.31 ± 2.53	3.14 ± 1.63	0.276	6.76 ± 2.19	3.73 ± 1.05	< 0.001*
TNR _{IVC}	3.27 ± 1.84	2.53 ± 1.12	0.423	4.21 ± 1.34	2.19 ± 0.71	< 0.001*
TNR _{NL}	3.09 ± 1.91	2.21 ± 1.34	0.532	3.13 ± 1.56	1.94 ± 0.57	< 0.001*
MTV(cm ³)	209.44 ± 130.11	30.26 ± 23.65	< 0.001*	253.71 ± 179.94	27.64 ± 28.35	< 0.001*
TLG _{IVC}	427.39 ± 237.56	41.89 ± 38.72	< 0.001*	478.45 ± 254.31	48.32 ± 32.71	< 0.001*
TLG _{NL}	542.32 ± 206.45	56.53 ± 49.66	< 0.001*	631.77 ± 217.63	61.34 ± 47.69	< 0.001*
SUV _{max} maximum standard uptake value; TNR _{IVC} maximum standard uptake value of the tumor -to-mean uptake value of the inferior vena cava ratio; TNR _{NL} maximum standard uptake value of the tumor -to-mean uptake value of the normal liver tissue ratio; MTV Metabolic tumor volume; TLG _{IVC} total lesion glycolysis with the inferior vena cava as a reference background; TLG _{NL} total lesion glycolysis with the normal liver tissue as a reference background.						
*:p < 0.05						

Predictive Factors of logistic regression analysis for MVI in HCC

The average SUV_{max} in patients with MVI and without MVI was 5.31 ± 2.53 and 3.14 ± 1.63, respectively, and there was no statistically significant association between SUV_{max} and MVI (*p* > 0.05) (Table 2). Univariate logistic analysis showed that tumor size, tumor grade, SUV_{max}, TNR_{IVC}, TNR_{NL}, MTV, TLG_{IVC}, and TLG_{NL} have statistical significance in predicting postoperative MVI in HCC (all *p* < 0.05) (Table 3). However, multivariate logistic analysis revealed that only TNR_{IVC} (Odds ratio[OR] = 1.612, 95%CI = 1.241–1.863, *p* = 0.003), TNR_{NL} (OR = 1.583, 95%CI = 1.194–1.816, *p* = 0.005), MTV (OR = 1.155, 95%CI = 1.004–1.267, *p* = 0.041), TLG_{IVC} (OR = 1.102, 95%CI = 1.052–1.296, *p* = 0.021), and TLG_{NL} (OR = 1.093, 95%CI = 1.034–1.277, *p* = 0.024) are independent factors for predicting postoperative HCC recurrence (Table 3). In particular, the largest odds ratio and the smallest *p* value were obtained for TNR_{IVC} (OR = 1.612, 95% CI = 1.241–1.863 *p* = 0.003). It indicates that TNR_{IVC} is the most relevant PET/CT parameter for predicting MVI in HCC.

Table 3
Logistic regression analysis in predicting microvascular invasion of HCC

Characteristic	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	<i>p</i>	Odds ratio (95% CI)	<i>p</i>
AFP level(ng/mL)				
≤ 25.0	1[Reference]			
> 25.0	1.175(1.069–2.831)	0.089		NA
HBV				
No	1[Reference]			
Yes	1.004(0.672–2.351)	0.734		NA
Tumor size(cm)				
≤ 5	1[Reference]			
> 5	1.733(1.264–3.485)	0.021*		NS
Tumor number				
Single	1[Reference]			
Multiple	1.015(0.731–1.928)	0.441		NA
Bilirubin level(mg/L)				
≤ 10	1[Reference]			
> 10	1.097(0.864–2.246)	0.271		NA
Tumor grade				
0	1[Reference]			
1	1.118(0.951–1.662)	0.048*		NS
2	1.357(1.217–3.901)	0.032*		NS
3	2.044(1.538–4.389)	0.005*		NS

HBV hepatitis B virus;SUV_{max} maximum standard uptake value; TNR_{IVC} maximum standard uptake value of the tumor -to-mean uptake value of the inferior vena cava ratio; TNR_{NL} maximum standard uptake value of the tumor -to-mean uptake value of the normal liver tissue ratio; MTV Metabolic tumor volume; TLG_{IVC} total lesion glycolysis with the inferior vena cava as a reference background; TLG_{NL} total lesion glycolysis with the normal liver tissue as a reference background; CI confidence interval; NA not assessed; NS not selected as significant factor.

*:*p* < 0.05

	Univariate analysis		Multivariate analysis	
SUV _{max}				
≤4.5	1[Reference]			
>4.5	1.334(1.182–3.742)	0.035*		NS
TNR _{IVC}				
≤4.08	1[Reference]		1[Reference]	
> 4.08	2.443(1.209–5.996)	< 0.001*	1.612(1.241–1.863)	0.003*
TNR _{NL}				
≤3.82	1[Reference]		1[Reference]	
> 3.82	2.228(1.067–5.353)	< 0.001*	1.583(1.194–1.816)	0.005*
MTV(cm ³)				
≤ 96.66	1[Reference]		1[Reference]	
> 96.66	1.436(1.152–3.419)	< 0.001*	1.155(1.004–1.267)	0.041*
TLG _{IVC}				
≤192.74	1[Reference]		1[Reference]	
> 192.74	1.845(1.263–4.313)	< 0.001*	1.102(1.052–1.296)	0.021*
TLG _{NL}				
≤215.33	1[Reference]		1[Reference]	
> 215.33	1.775(1.217–4.288)	< 0.001*	1.093(1.034–1.277)	0.024*
HBV hepatitis B virus;SUV _{max} maximum standard uptake value; TNR _{IVC} maximum standard uptake value of the tumor -to-mean uptake value of the inferior vena cava ratio; TNR _{NL} maximum standard uptake value of the tumor -to-mean uptake value of the normal liver tissue ratio; MTV Metabolic tumor volume; TLG _{IVC} total lesion glycolysis with the inferior vena cava as a reference background; TLG _{NL} total lesion glycolysis with the normal liver tissue as a reference background; CI confidence interval; NA not assessed; NS not selected as significant factor.				
*:p < 0.05				

The value of SUV_{max}, TNR_{NL}, TNR_{IVC}, MTV, TLG_{NL}, and TLG_{IVC} in predicting tumor recurrence

ROC curve analysis showed that the largest Youden index and the largest sum of sensitivity and specificity for predicting postoperative HCC recurrence were observed when the cutoff values of SUV_{max},

TNR_{IVC}, TNR_{NL}, MTV, TLG_{IVC}, and TLG_{NL} were 4.5, 4.08, 3.82, 96.66, 192.74, and 215.33, respectively. All the above parameters were statistically significant for predicting postoperative recurrence (all $p < 0.05$) and provided high accuracy (all AUC > 0.7) (Table 4). In particular, the largest AUC was found for MTV (AUC = 0.915), which provided a sensitivity and specificity of 92.8% and 85.5%, respectively, for predicting postoperative recurrence at a cutoff value of 96.66. Therefore, MTV has the greatest value in predicting postoperative HCC recurrence ($p < 0.001$). Moreover, the AUC was slightly larger for TNR_{IVC} than for TNR_{NL}, and for TLG_{IVC} than for TLG_{NL} (0.812 vs. 0.793, 0.892 vs. 0.874), and so did the sensitivity and specificity. Therefore, PET/CT parameters are more accurate in predicting postoperative HCC recurrence with inferior vena cava as a reference background than with normal liver tissue.

Table 4

Receiver-operating characteristic curve analysis of PET/CT quantitative parameters in predicting postoperative recurrence of HCC

Characteristic	Area under curve	p	Sensitivity (%)	Specificity (%)	Cutoff
SUV _{max}	0.799 (0.732-0.887)	0.001*	67.1	73.7	4.50
TNR _{IVC}	0.812 (0.792-0.853)	0.003*	81.4	86.2	4.08
TNR _{NL}	0.793 (0.746-0.824)	0.004*	77.6	82.5	3.82
MTV(cm ³)	0.915 (0.827-0.964)	$<0.001^*$	92.8	85.5	96.66
TLG _{IVC}	0.892 (0.835-0.931)	$<0.001^*$	87.5	84.4	192.74
TLG _{NL}	0.874(0.809-0.912)	$<0.001^*$	82.4	80.6	215.33

SUV_{max} maximum standard uptake value; TNR_{IVC} maximum standard uptake value of the tumor -to-mean uptake value of the inferior vena cava ratio; TNR_{NL} maximum standard uptake value of the tumor -to-mean uptake value of the normal liver tissue ratio; MTV Metabolic tumor volume; TLG_{IVC} total lesion glycolysis with the inferior vena cava as a reference background; TLG_{NL} total lesion glycolysis with the normal liver tissue as a reference background.

*: $p < 0.05$

Survival Analysis Of Prognostic Risk Factors In HCC

The univariate survival analysis showed that tumor size (cutoff value = 5 cm), MVI, SUV_{max} (cutoff value = 4.50), TNR_{IVC} (cutoff value = 4.08), TNR_{NL} (cutoff value = 3.82), MTV (cutoff value = 96.66), TLG_{IVC} (cutoff value = 192.74), and TLG_{NL} (cutoff value = 215.33) (all $p < 0.05$) have statistical significance in predicting postoperative HCC recurrence. However, multivariate survival analysis revealed that only MVI (hazard ratio [HR] = 2.441, 95%CI = 1.482–4.686, $p = 0.027$), SUV_{max} (HR = 2.054, 95%CI = 1.426–4.251, $p = 0.029$), TNR_{IVC} (HR = 2.621, 95%CI = 1.226–5.209, $p = 0.020$), TNR_{NL} (HR = 2.615, 95%CI = 1.113–4.864, $p = 0.023$), MTV (HR = 3.464, 95%CI = 1.107–5.772, $p = 0.012$), TLG_{IVC} (HR = 5.106, 95%CI = 1.472–8.113, $p = 0.001$), and TLG_{NL} (HR = 4.873, 95%CI = 1.361–9.153, $p = 0.002$) are independent risk factors for

predicting postoperative HCC recurrence (Table 5). In particular, TLG_{IVC} has the highest HR (HR = 5.106, $p = 0.001$), which indicates that the higher the TLG_{IVC} , the higher the probability of recurrence. Kaplan-Meier survival curve revealed a significantly higher RFS rate in patients with no MVI, $SUV_{max} \leq 4.50$, $TNR_{IVC} \leq 4.08$, $TNR_{NL} \leq 3.82$, $MTV \leq 96.6$, $TLG_{IVC} \leq 192.74$, and $TLG_{NL} \leq 215.33$ (all $p < 0.05$) (Fig. 1). PET/CT images of typical cases were presented in Fig. 2.

Table 5
Cox survival analysis for recurrence-free survival of hepatocellular carcinoma

Characteristic	Mean(mo)	Univariate analysis		Multivariate analysis	
		Hazard ratio (95% CI)	<i>p</i>	Hazard ratio (95% CI)	<i>p</i>
AFP level(ng/mL)					
≤ 25.0	44.2	1[Reference]			
> 25.0	39.3	1.437(1.218–1.646)	0.507		NA
HBV					
No	33.1	1[Reference]			
Yes	24.5	2.047(1.853–2.224)	0.252		NA
Tumor size(cm)					
≤ 5	36.3	1[Reference]			
> 5	21.7	2.533(2.051–3.124)	0.038*		NS
Tumor number					
Single	34.6	1[Reference]			
Multiple	27.5	1.554(1.287–1.763)	0.342		NA
Bilirubin level(mg/L)					
≤ 10	43.3	1[Reference]			
> 10	32.9	2.212(2.054–2.525)	0.076		NA
Tumor grade					

HBV hepatitis B virus;SUV_{max} maximum standard uptake value; TNR_{IVC} maximum standard uptake value of the tumor -to-mean uptake value of the inferior vena cava ratio; TNR_{NL} maximum standard uptake value of the tumor -to-mean uptake value of the normal liver tissue ratio; MTV Metabolic tumor volume; TLG_{IVC} total lesion glycolysis with the inferior vena cava as a reference background; TLG_{NL} total lesion glycolysis with the normal liver tissue as a reference background; CI confidence interval; NA not assessed; NS not selected as significant factor; CI confidence interval; NA not assessed; NS not selected as significant factor.

*:*p* < 0.05

		Univariate analysis		Multivariate analysis	
HBV	45.3	1[Reference]			
HBV	40.7	1.121(0.836–1.520)	0.972		NA
HBV	34.6	1.337(1.121–1.772)	0.663		NA
HBV	25.5	1.933(1.725–2.224)	0.271		NA
MVI					
No	37.3	1[Reference]		1[Reference]	
Yes	24.8	2.525(1.727–5.094)	0.042*	2.441(1.482–4.686)	0.027*
SUV _{max}					
≤4.5	29.2	1[Reference]		1[Reference]	
>4.5	28.2	2.723(1.553–4.771)	0.009*	2.054(1.426–4.251)	0.029*
TNR _{IVC}					
≤4.08	38.6	1[Reference]		1[Reference]	
>4.08	21.1	2.842(1.479–5.544)	< 0.001*	2.621(1.226–5.209)	0.020*
TNR _{NL}					
≤3.82	38.8	1[Reference]		1[Reference]	
>3.82	22.3	2.823(1.441–5.004)	< 0.001*	2.615(1.113–4.864)	0.023*
MTV(cm ³)					
≤96.66	36.4	1[Reference]		1[Reference]	

HBV hepatitis B virus; SUV_{max} maximum standard uptake value; TNR_{IVC} maximum standard uptake value of the tumor -to-mean uptake value of the inferior vena cava ratio; TNR_{NL} maximum standard uptake value of the tumor -to-mean uptake value of the normal liver tissue ratio; MTV Metabolic tumor volume; TLG_{IVC} total lesion glycolysis with the inferior vena cava as a reference background; TLG_{NL} total lesion glycolysis with the normal liver tissue as a reference background; CI confidence interval; NA not assessed; NS not selected as significant factor; CI confidence interval; NA not assessed; NS not selected as significant factor.

*:p < 0.05

		Univariate analysis		Multivariate analysis	
> 96.66	20.2	3.643(1.331–6.135)	< 0.001*	3.464(1.107–5.772)	0.012*
TLG _{IVC}					
≤192.74	37.8	1[Reference]		1[Reference]	
> 192.74	18.6	5.232(1.516–9.045)	< 0.001*	5.106(1.472–8.113)	0.001*
TLG _{NL}					
≤215.33	38.8	1[Reference]		1[Reference]	
> 215.33	19.3	4.941(1.408–9.552)	< 0.001*	4.873(1.361–9.153)	0.002*
HBV hepatitis B virus;SUV _{max} maximum standard uptake value; TNR _{IVC} maximum standard uptake value of the tumor -to-mean uptake value of the inferior vena cava ratio; TNR _{NL} maximum standard uptake value of the tumor -to-mean uptake value of the normal liver tissue ratio; MTV Metabolic tumor volume; TLG _{IVC} total lesion glycolysis with the inferior vena cava as a reference background; TLG _{NL} total lesion glycolysis with the normal liver tissue as a reference background; CI confidence interval; NA not assessed; NS not selected as significant factor; CI confidence interval; NA not assessed; NS not selected as significant factor.					
*:p < 0.05					

Discussion

The overall 5-year survival rate of liver cancer is only approximately 10%, and has not improved significantly in the past 20 years [9]. The most important reason is the high recurrence and metastasis rates of liver cancer even after satisfactory radical resection. The postoperative recurrence and metastasis of liver cancer is closely related to MVI [10–11]. Compared with traditional imaging modalities, ¹⁸F-FDG PET/CT can evaluate tumor metabolism, and is more effective in predicting tumor prognosis [12]. The results of this study showed that MVI, SUV_{max}, TNR_{IVC}, TNR_{NL}, MTV, TLG_{IVC}, and TLG_{NL} were independent risk factors for predicting postoperative HCC recurrence. In particular, TNR_{IVC} was the most relevant factor for predicting MVI, and MTV was the most valuable for predicting postoperative HCC recurrence. Patients with higher TLG_{IVC} value were likely to have a higher recurrence risk. Moreover, the PET/CT parameters are more accurate in predicting postoperative HCC recurrence when obtained with inferior vena cava as a reference background than with normal liver tissue. PET/CT non-invasively provides more comprehensive predictive information on MVI and postoperative recurrence of liver cancer before surgery, which is of great significance for improving early treatment, prolonging survival, and increase survival rate.

Patients with MVI are more likely to experience recurrence of liver cancer after surgery [13-14]. Although many studies have shown that imaging features on contrast-enhanced CT, MRI and US [15-17] could predict the microvascular invasion of HCC. However, it is still difficult to diagnose MVI based on preoperative CT, MRI or US imaging modalities. It is worth noting that MVI cannot be directly observed by PET/CT before surgery due to limited resolution. However, as an imaging technique based on tumor biological activity, PET/CT has the potential to reflect the malignant biological ability of tumors invading blood vessels [18]. SUV_{max} is the most commonly used semi-quantitative parameter of PET/CT. Several recent studies have suggested that a higher ratio of tumor SUV_{max} to normal liver mean SUV on preoperative ^{18}F -FDG PET-CT could predict the MVI of HCC [19]. Baek et al. [20] suggested that the increase of ^{18}F -FDG uptake in liver cancer was correlated with MVI and indicated a high risk of postoperative recurrence. Our results show that SUV_{max} in ROI alone is not statistically significant for predicting MVI. The reason may be that SUV_{max} only represents the highest metabolic activity within the tumor, but not the overall metabolic activity of the lesion. Hence, it has a limited predictive value for the prognosis of liver cancer. At present, other PET/CT parameters, such as SUV_{mean} , tumor-to-background ratio (TBR), MTV, and TLG, have been introduced to provide precise evidence for tumor treatment [21]. TBR represents the biological activity of tumors [22]. MTV represents the volume of the tumor with abnormally high uptake [23]. TLG is the product of MTV and SUV_{mean} in ROI and reflects tumor burden [24]. Preliminary studies have been performed to investigate the prognostic value of one or two metabolic parameters in liver cancer before or after surgery. Lee et al. [25] demonstrated that the metabolic status of HCC reflected by ^{18}F -FDG PET was an important factor in predicting long-term survival. [1]Ahn et al. [19] believed that the $TSUV_{max}/LSUV_{mean}$ ratio of > 1.2 was significantly correlated with MVI in liver cancer. Among the few studies on the use of PET/CT volumetric parameters in liver cancer, however, normal liver tissue was mainly taken as the reference background [26-27]. Single-parameter, single-background, and single-prediction approaches are unsatisfactory and incomplete in clinical applications. In this study, both normal liver tissue and inferior vena cava were used as the reference background, and combined with clinicopathological features, and PET/CT metabolic and volumetric features to predict MVI and postoperative recurrence of HCC before surgery. Our results show that TNR_{IVC} , TNR_{NL} , MTV, TLG_{IVC} , and TLG_{NL} can all independently predict MVI in HCC. A slightly higher OR was obtained for TNR_{IVC} than for TNR_{NL} , and for TLG_{IVC} than for TLG_{NL} , it suggests that TNR_{IVC} is most effective in predicting the presence of MVI in HCC. This indicates that the metabolic activity in the most malignant part of the tumor is an important prognostic factor for MVI in HCC. Moreover, a higher correlation is obtained for predicting MVI in HCC with the inferior vena cava as a reference background than with normal liver tissue.

In predicting the postoperative recurrence of liver cancer, Lee et al. [28] found that MTV was closely related to progression-free survival and overall survival in patients with HCC. Univariate analysis in this study demonstrated that tumor size, MVI, SUV_{max} , TNR_{IVC} , TNR_{NL} , MTV, TLG_{IVC} , and TLG_{NL} were all significant independent predictors of postoperative HCC recurrence, which is consistent with the results of some previous studies [29-32]. Moreover, higher sensitivity and specificity were obtained for predicting

postoperative HCC recurrence with the inferior vena cava as a reference background than with normal liver tissue. The possible reason is that liver cancer is often complicated with fatty liver, hepatitis, and cirrhosis, which results in large fluctuations in the uptake of normal liver tissue. A significantly lower RFS rate was observed in patients with PET/CT parameters higher than the cutoff values. More importantly, patients with MVI were shown to have a 1.482–4.686 times higher risk of postoperative recurrence in multivariate survival analysis. SUV_{max} , TNR_{IVC} , TNR_{NL} , MTV, TLG_{IVC} , and TLG_{NL} can all be used as independent predictors of postoperative HCC recurrence. When they are greater than the cutoff values, it highly suggests the high possibility of recurrence or incomplete treatment. In addition, MTV was more significant than SUV_{max} , TNR_{IVC} , and TNR_{NL} for predicting postoperative recurrence, and TLG_{IVC} came second. However, TLG_{IVC} had the highest HR for predicting postoperative recurrence. It indicates that tumor metabolic volume and tumor burden are important prognostic factors for postoperative HCC recurrence. Moreover, the higher the TLG_{IVC} , the larger the tumor burden, the more hazardous the tumor, and the greater the risk of recurrence. Therefore, patients with PET/CT parameters above the cutoff values should be closely followed up after surgery.

This study has the following limitations: (1) As this study is a retrospective study, there was a selection bias in the enrollment of patients. (2) The 72 patients in this study were not followed up long enough to analyze their 5-year and overall survival. (3) It is a single-center study with a small sample size, where patients with MVI and recurrence accounted for a small proportion. Therefore, the cutoff values established for the PET/CT parameters need to be confirmed by multicenter studies with a large sample size. (4) HCC recurrence was diagnosed by enhanced CT or MR instead of pathological examination. Hence, it might be underestimated in some patients, resulting in a diagnostic basis. (5) The joint diagnostic efficacy of clinicopathological indicators combined with PET/CT parameters for MVI and recurrence of HCC was not evaluated. In the future, studies will be performed with a larger sample size and longer follow-up time to investigate the value of PET/CT for predicting MVI and postoperative recurrence.

Conclusion

In summary, among the various PET/CT metabolic and volumetric parameters, TNR_{IVC} , TNR_{NL} , MTV, TLG_{IVC} , and TLG_{NL} are independent risk factors for predicting MVI and recurrence of HCC. Moreover, they are more accurate in predicting MVI and postoperative HCC recurrence before surgery when the inferior vena cava is used as a reference background as compared to normal liver tissue.

Abbreviations

AFP: Alpha fetoprotein; AUC: The area under the curve; HCC: Hepatocellular carcinoma; MTV: Metabolic tumor volume; MVI: Microvascular invasion; PVTT: Portal vein tumor thrombosis; RFS: Recurrence-free survival; ROC: Receiver-operating-characteristic; ROI: Regions of interest; SUV_{max} : Standard uptake value; TLG: Total lesion glycolysis; TNR: Ratio of tumor SUV_{max} to mean SUV_{mean}

Declarations

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Not applicable.

Authors' contributions

Chunjuan Jiang contributed to data collection and wrote an original draft. Guang Ma helped to provide data sources and follow up information. Qiufang Liu edited and analyzed data. Shaoli Song helped in the original concept generation and revised the manuscript. All authors read and agreed to be accountable for all aspects of the work.

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Availability of supporting data

Supporting data could be reached by contacting the first and corresponding author.

Ethics approval and consent to participate

Ethical approved by the Ethics Review Committee of Fudan University Shanghai Cancer Center, and participation consent was obtained from all patients in this study.

Consent for publication

Not applicable.

Competing interest

The authors declare no conflicts of interest.

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Figures

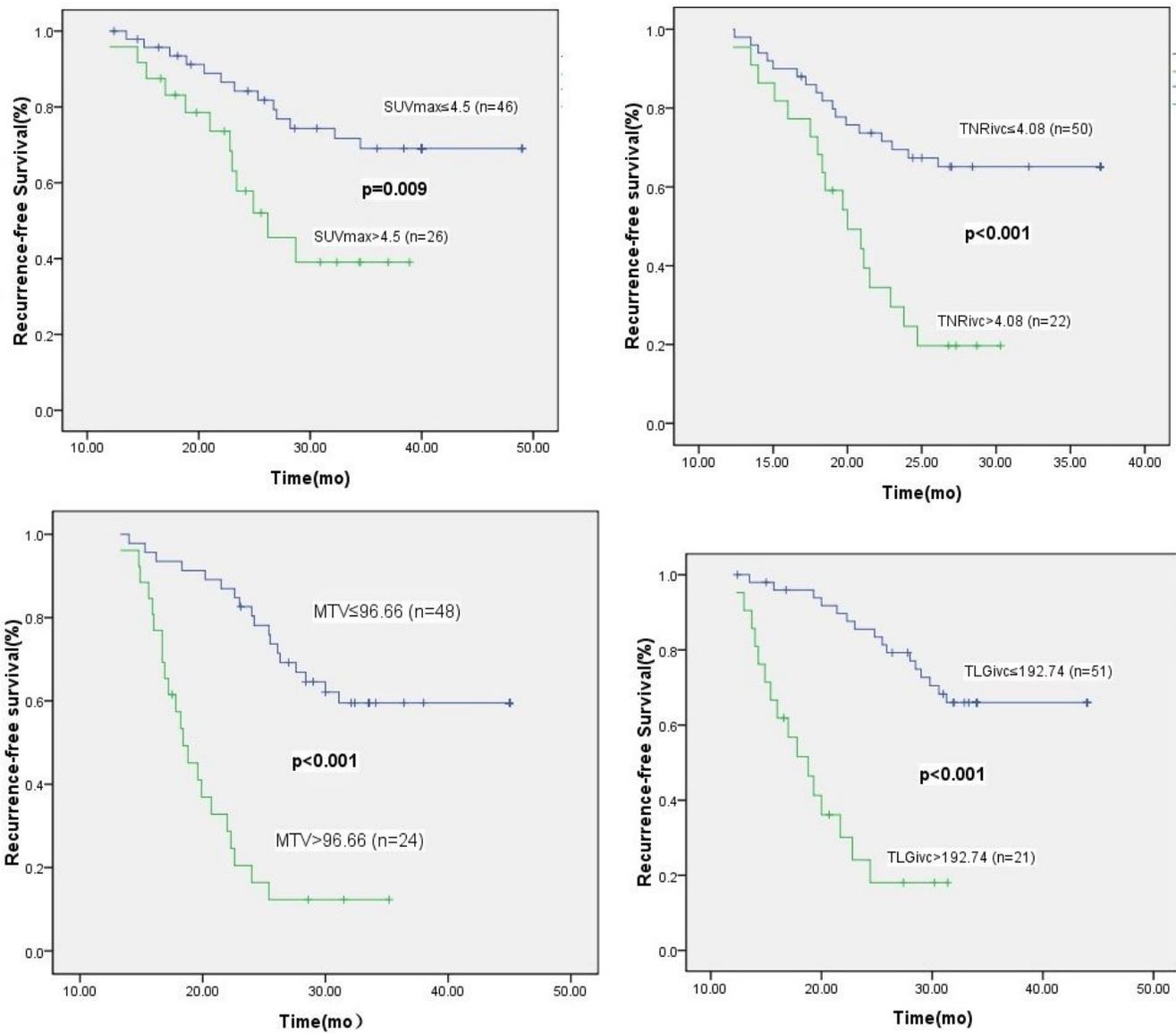


Figure 1

Kaplan–Meier survival analysis of SUVmax(cutoff=4.5), TNRIVC(cutoff=4.08), TNRNL(cutoff=3.82), MTV(cutoff=96.66)(A-D) for recurrence-free survival of hepatocellular carcinoma. Patients with low cutoff value showed significantly longer recurrence-free survival than those with high cutoff value.

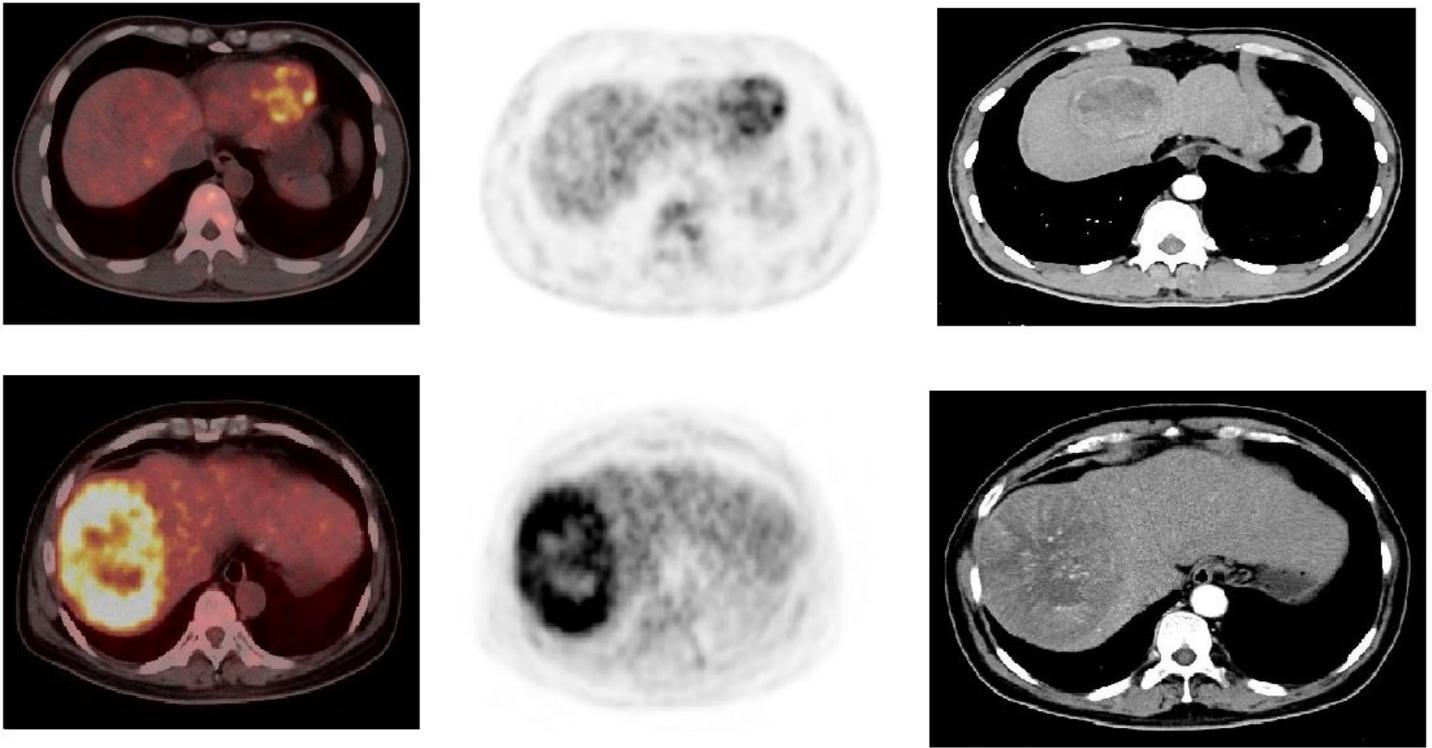


Figure 2

PET/CT images of typical cases (A–C) 63 years old with hepatocellular carcinoma on CT (arrowhead). ^{18}F -FDG PET/CT fusion images showed high TNRIVC (4.35), MTV (144.37 cm^3) and TLGIVC (279.51) (all above cutoff value). The tumor was confirmed with MVI by pathology and recurred 22.8 months after partial hepatectomy. (D–F) 55 years old with hepatocellular carcinoma on CT (arrowhead). ^{18}F -FDG PET/CT fusion images showed increased TNRIVC (2.08), MTV (23.36 cm^3) and TLGIVC (47.55) (all below cutoff value). The patient had a good outcome without MVI confirmed by pathology and with a RFS time of 38.6 months after partial hepatectomy.