ASTR

ORIGINAL ARTICLE

pISSN 2288-6575 • eISSN 2288-6796
https://doi.org/10.4174/astr.2020.99.1.8
Annals of Surgical Treatment and Research

^{18}F-fluorodeoxyglucose PET/CT as an independent predictor for patients with hepatocellular carcinoma combined with major portal vein tumor thrombus

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Purpose: Hepatocellular carcinoma (HCC) patients with major portal vein tumor thrombosis (mPVTT) complications were generally characterized by extremely poor prognoses. The aim of this study was to explore the role of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET/CT imaging in predicting HCC complicated by mPVTT.
Methods: Five hundred one HCC patients received surgery in our hospital during November 2008 to December 2014, among which 32 patients (6.4%) were diagnosed as HCC complicated by mPVTT. Six cases were excluded for reasons of complex medical conditions, including 2 cases of salvage liver transplantation, 2 cases of re-resection, 1 case of mPVTT combined with inferior vina cava tumor thrombosis, and 1 case of residual portal vein tumor thrombosis. Ultimately, 26 cases were enrolled in this study. The maximal tumor standardized uptake value (SUVmax) was identified as a predictive factor and detected. The univariate and multivariate regression analyses were performed to identify the prognostic factors for recurrence-free survival (RFS) and overall survival (OS) of HCC patients complicated by mPVTT.
Results: Our results showed that the median OS was 16 months. The 1-, 3-, and 5-year cumulative OS was 55.6%, 31.7%, and 31.7%, respectively. The multivariate regression analysis revealed that SUVmax ≥ 4.65 was the only independent risk factor for RFS and OS.
Conclusion: SUVmax was an independent predictor for RFS and OS of patients suffering from both HCC and mPVTT. Low SUVmax could serve as an effective factor for selecting candidates with low recurrence risks and for helping with improving patient survival after surgical resection.
[Ann Surg Treat Res 2020;99(1):8-17]

Key Words: Hepatocellular carcinoma, Portal vein, Positron emission tomography computed tomography, Thrombus

INTRODUCTION

Major portal vein tumor thrombosis (mPVT) refers to tumor thrombus invasion in the first branch or the main portal vein, or the opposite side portal branch [1]. Patients with hepatocellular carcinoma (HCC) complicated by mPVTT

Received December 2, 2019, **Revised** March 7, 2020,
Accepted April 7, 2020

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generally have unfavorable prognoses due to severe intrahepatic and/or extrahepatic metastases, portal hypertension, jaundice, and ascites. Research on the medical history of HCC patients with mPVTT indicated that the median survival of untreated patients was 2.7–4 months [2,3]. Meanwhile, the incidence of mPVTT was considerably higher than expectation. According to a nationwide follow-up survey conducted in Japan, 7.4% patients were diagnosed as having mPVTT when first diagnosed with HCC and more than half of them (3.8%) then underwent liver resection [4]. Liver resection is a promising therapeutic strategy for large cohorts and for patients with advanced conditions. Another nationwide multicentral study from Japan also showed survival benefits from liver resection in portal vein invasion associated HCC [5]. However, the postoperative outcomes of the HCC patients complicated by mPVTT were unsatisfactory and debatable in view of the postsurgical median survival ranging from 6 months to 20 months [6-8].

With the evolution of surgical techniques and perioperative management, liver resection has become a reliable and safe treatment option with an acceptable mortality of less than 2% [9,10]. However, tumor recurrence is the most critical factor that shortens the long-term survivals of HCC patients with mPVTT. Notably, portal vein tumor thrombosis (PVTT) itself is the most important independent risk factor for early postoperative recurrence of HCC [11]. Currently, there are few clinicopathological prognostic factors for predicting the tumor recurrence of HCC patients complicated by mPVTT. Positron emission tomography with fluorine-18-fluorodeoxyglucose (^{18}F-FDG PET) has been widely used in detecting the glucose metabolic activity of tumors, thus it could be used as an indicator for tumor aggressiveness. Torizuka et al. [12] reported that ^{18}F-FDG uptake in high-grade HCC was significantly higher than that in low-grade HCCs. Recently, several clinical studies showed that preoperative ^{18}F-FDG PET measurement could predict tumor differentiation and postoperative outcomes of HCC patients [13-15].

So far, few studies have focused on the application of ^{18}F-FDG PET in predicting recurrence-free survival (RFS) and overall survival (OS) of HCC patients with mPVTT based on the maximum standard uptake value (SUV_{max}). Thus, in this retrospective study, we calculated the optimal cutoff value of SUV_{max} by drawing receiver operating characteristic (ROC) curves in order to predict the prognoses of HCC patients with mPVTT after liver resection.

METHODS

Patients

A total of 501 HCC patients underwent surgery in our hospital during November 2008 and December 2014, among which 32 HCC patients (6.4%) had mPVTT complications of Vp3 or Vp4 stage according to the classification method described in the study by Ikai et al. [1].

Vp3 refers to the formation of tumor thrombi in the first-order branches of the portal vein. Vp4 refers to the formation of tumor thrombi in the main trunk of the portal vein or a portal vein branch contralateral to the primarily involved lobe (or both). Six cases were excluded due to the following reasons; 2 cases receiving living donor liver transplantation, 2 cases undergoing re-resection after recurrence of tumor with mPVTT, 1 case with both HCC and inferior vena cava thrombosis, and 1 case with residual PVTT. Ultimately, 26 HCC patients including 23 males and 3 females with a median age of 50 years (range, 31 to 72 years) were enrolled in this study. Serological testing showed positive expression of serum hepatitis B surface antigen in 23 cases and positive expression of anti-hepatitis C viral antibody in 1 case. The detailed clinicopathological

Table 1. Clinical-pathologic characteristics of the patients in the present study (n = 26)

Variable	Value
Age (yr)	50 (31–72)
Male sex	23 (88.5)
Platelet count (×1,000/mm^3)	178 (64–315)
Serum total bilirubin (mg/dL)	0.9 (0.4–2.4)
Serum AST (U/L)	52.5 (21.0–243.0)
Serum ALT (U/L)	38.0 (17.0–340.0)
Serum albumin (g/dL)	4.3 (3.2–4.8)
PT-INR	1.1 (0.88–1.5)
Serum α-FP (ng/mL)	483.3 (2.6–60,500.0)
Serum α-FP (>400 ng/mL)	13 (50)
ICG R15 (%)	14.5 (4.2–36.4)
ICG R15 (%) (≤15%)	15 (57.7)
Child-Pugh stage A	25 (96.2)
PET-SUV_{max}	6.2 (2.6–15.1)
Preoperative TACE	4 (15.4)
Tumor size (cm)	9.3 (1.4–20.0)
Tumor number	1 (1–6)
Multiple tumor number	6 (23.1)
Liver cirrhosis (fibrosis stage 4)	17/26 (65.4)
Bile duct involvement	7/24 (29.2)
Hepatic vein involvement	3/23 (13.0)
Resection margin positive	11 (42.3)
Microvascular invasion	25/25 (100)
Ig/Eg	20 (76.9)/6 (23.1)
Intrahepatic Metastasis	20/24 (80.3)
90-Day mortality (OP mortality)	0 (0)
Disease-free survival (mo)	3 (1–88)
Overall survival (mo)	16 (4–88)

Values are presented as median (range) or number (%).
PT-INR, prothrombin time-international normalized ratio; ICG R15, indocyanine green retention rate at 15 min; PET-SUV_{max}, positron emission tomography-the maximum standard uptake value; TACE, transcatheter arterial chemoembolization; OP, operation.

characteristics of the 26 patients were listed in Table 1. All the data retrospectively analyzed in the study were retrieved from the database of our hospital that prospectively stored clinical data. The protocol of this study was approved by the medical ethics committee of our hospital (AJIRB-MED-MDB-19-448).

Operating procedure and portal vein thrombectomy

Patients received specific operations according to the sites and the sizes of PVTT. Five cases received right trisectionectomy. Fifteen cases received right or extended right hemihepatectomy and 6 cases underwent left hemihepatectomy. The tumor embolisms in the first branch of the left portal vein (Vp3) were *en bloc* removed with the tumor. The tumor embolisms in the first branch of the right portal vein and/or the main portal vein were removed by open resections under the occlusion of the main glissonean pedicle and the first branch of the contralateral glissonean pedicle. The occlusion was achieved by using extra fascial access but not dissecting the glissonean pedicle. The detailed procedures of the thrombectomies were shown in Fig. 1. Portal vein dissection was performed after the parenchyma had been divided. The hepatic artery and the bile duct were ligated and divided separately. Then, the anterior wall of the portal vein where tumor embolisms invaded was transversely incised. The PVTT was peeling off from the portal vein lumen. Any residual tumor thrombus, if existing, in the caudate branch could be removed by meticulously suction. After removing the gross PVTT, the lumen was flushed with heparinized saline and back-bleeding to remove potentially cancerous residual tissue. The posterior wall of the portal vein was dissected using scalpels and the stump was closed with 6/0 prolene continuous sutures. To prevent portal vein stenosis, a distance of 3–5 mm was reserved from the incision site to the bifurcation of the right and left portal veins.

Follow-up strategy, recurrence, and treatment pattern

The median duration of follow-up was 12 months (range, 4 to 88 months). All the patients in our hospital were followed up in strict accordance with the standard protocol. In detail, these patients underwent enhanced CT scan of the upper abdomen at day 7 postoperatively. After discharge from the hospital, all patients were followed up monthly by detecting tumor markers (i.e., α-FP) and analyzing laboratory data (i.e., CBC, AST, ALT, albumin, total bilirubin) during the first 6 months after surgery. Thereafter, the patients were followed up every 2–3 months by measuring the tumor markers, evaluating liver function and performing radiological examinations (i.e., chest X-ray). An enhanced CT scan was performed every 6 months. In addition, more specialized, accurate examinations such as magnetic

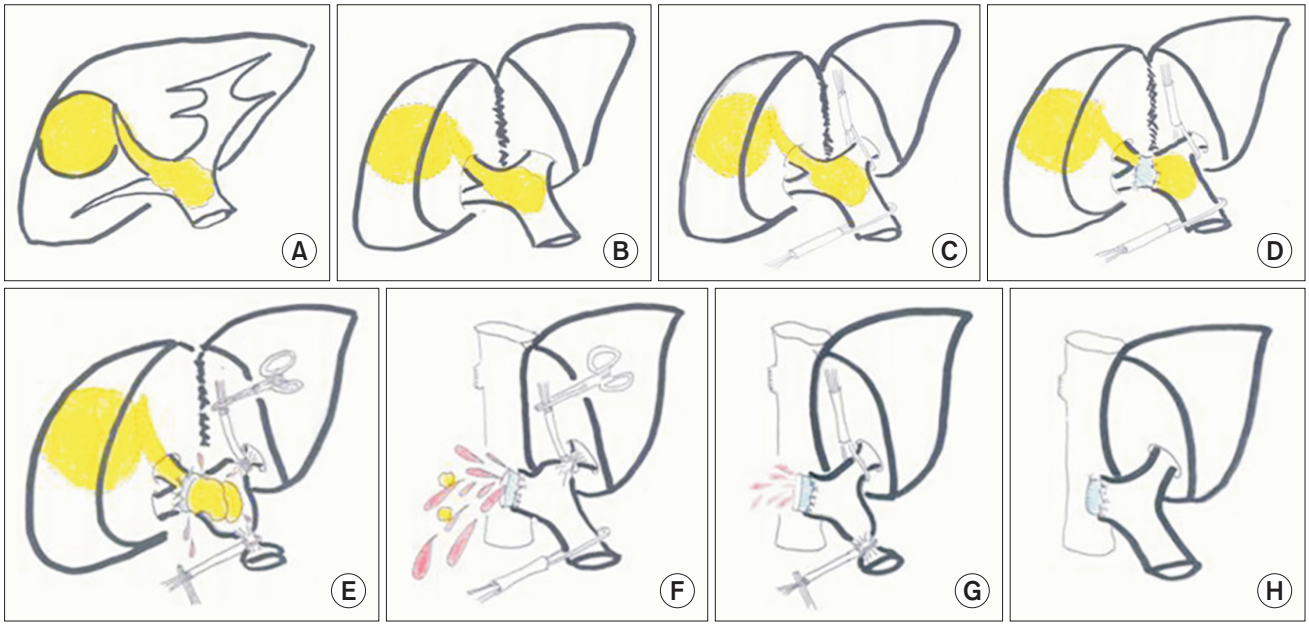


Fig. 1. The surgical procedures for thrombectomy. (A) Schema showing a right liver hepatocellular carcinoma (HCC) and HCC-derived portal vein tumor thrombous (PVTT) extending to the main portal vein. (B) Exposure the hilar structure after the liver parenchyma divided. (C) Extra fascial access to tape the main and the left glissonean pedicle. (D) The hepatic artery and the bile duct were ligated and divided separately. (E) While clamping the main and left portal glissonean pedicle, the anterior wall of the portal vein was transversely incised. The PVTT was peeling off from the portal lumen. (F) The lumen was flushed with heparinized saline and main portal bleeding to remove potentially cancerous residual tissue. (G) Left portal back-bleeding to remove potentially cancerous residual tissue. (H) The posterior wall of the portal vein was dissected by scalpel and the stump was closed with 6/0 prolene by continuous suture.

resonance imaging or PET/CT would be performed once there existed a high risk of recurrence.

During the follow-up period, tumor recurrences were observed in 21 cases. Among these cases, there were 11 cases of multiple intrahepatic recurrences, 5 cases of multiple intrahepatic recurrences combined with PVTT recurrence, 2 cases of multiple intrahepatic recurrence with lung metastasis, 2 cases of single intrahepatic recurrence, and 1 case of multiple lung metastasis. Thus, 4 different therapeutic strategies were developed for treating tumor recurrences according to hepatic function and recurrence patterns of the patients. Twelve patients received transcatheter arterial chemoembolization (TACE) treatment. Four patients received treatment with multikinase inhibitor of sorafenib; Two patients received palliative radiotherapeutic treatment and 3 patients received conservative management.

^{18}F-FDG PET/CT acquisition, analysis, and the determination of the optimal cutoff value of SUV_{max}

Patients were fasted for at least 6 hours before the examination. The blood glucose levels of these patients were normal (range, 74 to 106 mg/dL) before ^{18}F-FDG administration. Then, these patients were injected with 370 MBq of ^{18}F-FDG and rested for 1 hour before scanning. Emission PET data were acquired from the vertex to the upper thigh using a Discovery ST scanner (GE Healthcare, Milwaukee, WI, USA). Noncontrast CT scans were also performed for reconstruction (tube rotation time 1 s/rev, 120 kV, 60 mA, 7.5 mm/rotation, ordered subset expectation maximization, 2 iterations, 30 subsets).

The characteristics of liver tumors including ^{18}F-FDG uptake and extrahepatic metastasis were analyzed. Volumes-of-interest were placed on the tumor and the background (contralateral lobe of liver). The amounts of ^{18}F-FDG uptake were expressed by standardized uptake values (SUV, g/mL), which were calculated based on the radioactivities in volume-of-interest, injection dosages, and patient's body weight. Maximum SUV (SUV_{max}, the hottest single voxel) was used for analysis in the present study.

The ROC curve has demonstrated in this cohort study a value of 4.65 as the best cutoff value of SUV_{max} for tumor recurrence after hepatectomy. The area under the curve was 0.948. The P-value was 0.002 (Fig. 2).

Statistical analysis

All data were processed and analyzed using IBM SPSS Statistics ver. 19.0 (IBM Co., Armonk, NY, USA). The continuous variables were expressed as median (range) deviation and compared by the Student t-test. The categorical data were presented as frequency and were analyzed using the Fisher chi-square test. The multivariate analysis was performed with Cox regression for significant variables on the univariate analysis.

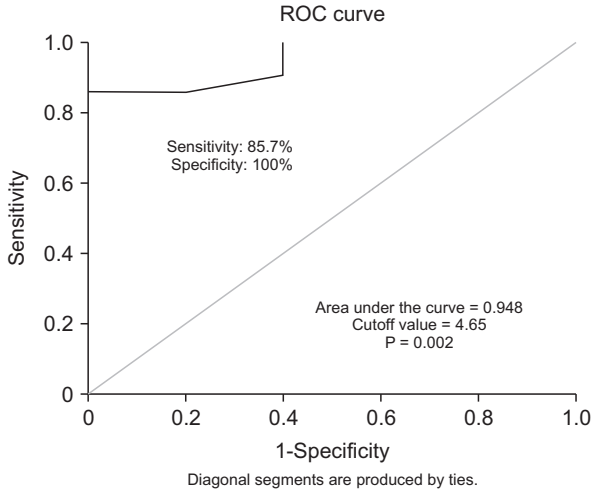


Fig. 2. Receiver operating characteristic (ROC) curve to assess the optimal cutoff value of SUV_{max} for tumor recurrence (4.65). ROC curve to assess the optimal cutoff value of SUV_{max} for tumor recurrence (4.65). SUV_{max}, maximum standard uptake value.

OS and RFS were analyzed using the Kaplan-Meier method and compared by the log-rank test. Confidence intervals were constructed at 95%, and P-values < 0.05 were considered statistically significant.

RESULTS

The characteristics of HCC patients complicated by mPVTT

As the last follow-up time was March 2017, the median duration of follow-up in the present study was 12 months (range, 4 to 88 months). Hepatitis B was the most common etiological factor. These patients were relatively young with a median age of 50 years, as well as having relatively normal liver function. According to the Child-Pugh classification, 25 patients belonged to grade A and one patient belonged to grade B. Most of the patients possess aggressive tumor characteristics which presented by microvascular invasion, intrahepatic metastasis, and infiltrative growth type. The postoperative pathological examinations indicated that the median tumor size was 9.3 cm (range, 1.4 to 20 cm), and the median number of tumors was 1 (range, 1 to 6). Four patients had a history of treatment with TACE. Three patients had complications by hepatic vein involvement, and 7 patients had complications by bile duct involvement. The median SUV_{max} was 6.2, ranging from 2.6 to 15.1. Hospital mortality was defined as any death within 90 days after surgery. Notably, there were no hospital mortalities in this study. The clinicopathological characteristics of these patients were shown in Table 1.

Survival outcomes and characteristics of patients with long-term survivals

The Kaplan-Meier plot of OS for these patients showed that 1-, 3-, and 5-year OS were 55.6%, 31.7%, and 31.7%, respectively (Fig. 3). The median OS was 16 months. Six patients experienced long-term survival of more than 3 years. The characteristics of these long-term survival patients were shown in Table 2, among which relatively low SUV_{max} (range, 2.1 to 4.4) was the most common characteristic. Among the 6 cases, there were 2 cases of recurred intrahepatic tumor within 1 year; among which, 1 had single intrahepatic recurrence and the other had 5 intrahepatic recurrences. However, both of them survived for a long period after TACE treatment.

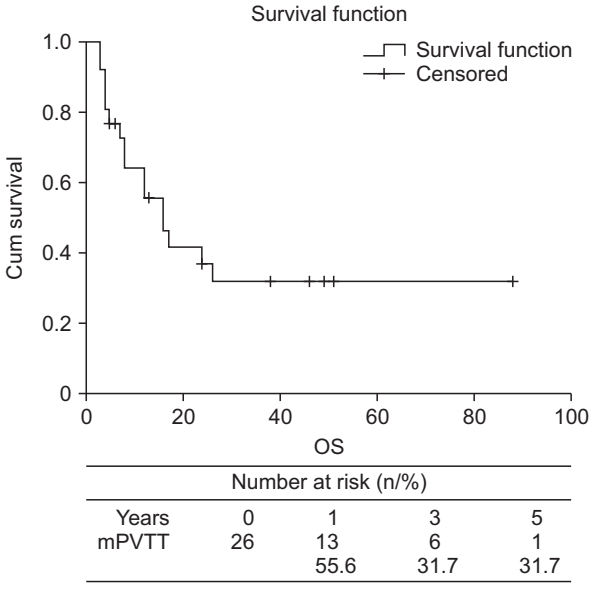


Fig. 3. Kaplan-Meier survival analysis shows the overall survival cure of the hepatocellular carcinoma (HCC) patients with major portal vein tumor thrombosis (mPVTT) in the present study. The 5-year overall survival (OS) of the patients with mPVTT in this study was 31.7%.

The survival analysis of low and high SUV_{max} groups

The patients were divided into 2 groups based on the optimal cutoff value of SUV_{max} (4.65), including low SUV_{max} group (SUV_{max} values < 4.65) and high SUV_{max} group (SUV_{max} values ≥ 4.65). The RFS time of high SUV_{max} group was significantly shorter than that of the low SUV_{max} group (the log-rank test: 12.756, P = 0.000) (Fig. 4A). The 1-, 3- and 5-year of RFS in high SUV_{max} group was 0%, 0%, and 0%, respectively. However, the 1-, 3-, and 5-year of RFS in the low SUVmax group reached up to 60%, 60%, and 60%, respectively. OS time of high SUV_{max} group was significantly shorter than that of the low SUV_{max} group (the log-rank test: 7.586, P = 0.006) (Fig. 4B). In terms of OS, the 1-, 3-, and 5-year survivals of high SUV_{max} group were 46.0%, 0%, and 0%, respectively, while the 1-, 3-, and 5-year survivals of low SUV_{max} group were 75.0%, 75.0%, and 37.5%, respectively. Tumor recurrence was observed in 3 patients from low SUV_{max} group. Two of these cases were shown in Table 2, and they survived for 46 months and 51 months, respectively. One patient experienced multiple liver tumors recurrence and died 8 months after TACE treatment. Two patients in the low SUV_{max} group died during the follow-up period. Another patient died of hepatic failure after the HBV recurrence. However, all the patients in the high SUV_{max} group had tumor recurrences within 10 months, and 14 of 18 patients finally died of tumor progression during the follow-up period. The remaining 4 patients were lost to follow-up.

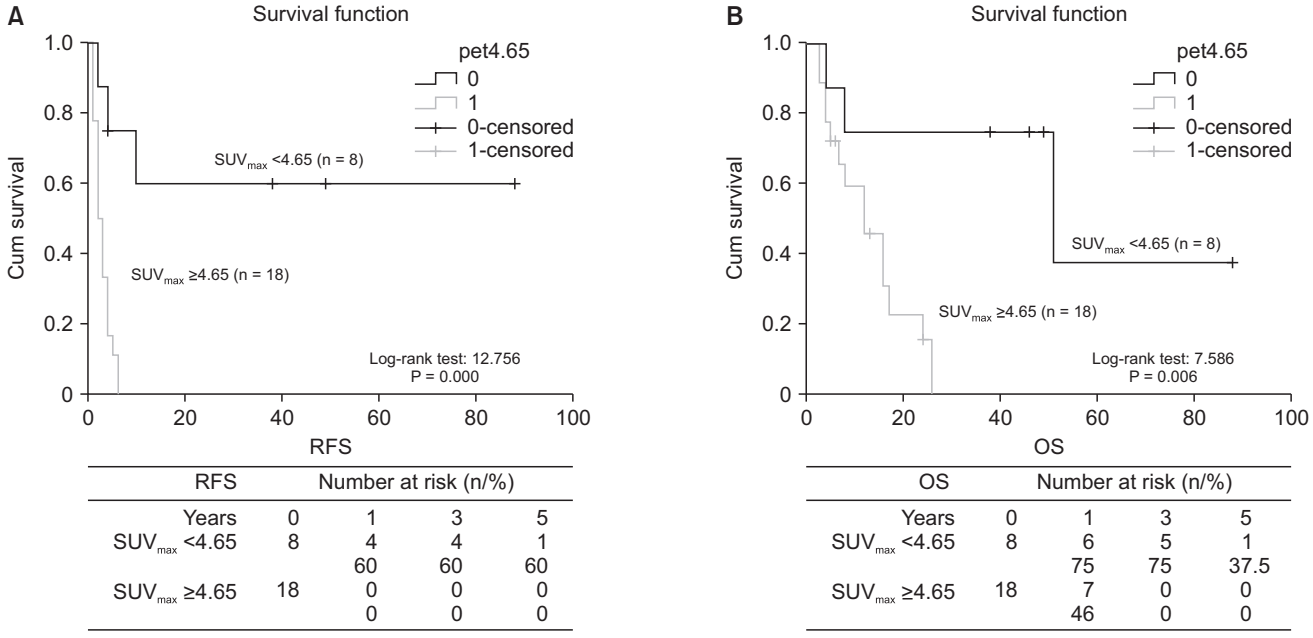
Analysis of risk factors for mPVTT patients

The comparisons of the clinicopathological characteristics between high and low SUV_{max} groups were shown in Table 3. There were no significant differences in liver function and tumor factors represented by Child-Pugh class grades, indocyanine green retention rate at 15 minutes and tumor sizes, tumor growth types, microvessel invasion, intrahepatic metastasis, and Edmondson-Steiner grades. In addition, results showed no significant difference in postoperative PVTT recurrence, despite there being no PVTT recurrence in low SUV_{max} group, though there were 5 cases with PVTT recurrence

Table 2. The characteristics for the patients with long-term survival more than 3 years (n = 6)

No.	ICG R15 (%)	T-S (cm)	T-N (n)	AFP (ng/mL)	Gr. type	Resection Margin	VP type	OS (mo)	PET-CT SUV_{max}	DFS (mo)	Recurrence site	Status
1	18.8	1.4	1	15.4	Eg	Negative	4	88	2.6	88	NA	Alive
2	14.4	11.0	1	35797.0	Ig	Negative	3	51	2.1	10	Liver-multi	Dead
3	25.2	4.0	1	378.9	Ig	Positive	4	39	4.4	39	NA	Alive
4	11.0	12.0	1	15.5	Eg	Negative	3	49	2.2	49.0	NA	Alive
5	14.5	10	1	7410	Ig	Negative	4	46	3.3	4	Liver-single	Alive
6	8.3	5.5	2	2769	Ig	Negative	3	38	3.8	38	NA	Alive

ICG R15, indocyanine green retention rate at 15 min; T-S, tumor size; T-N, tumor number; Gr. type, growth type; VP type, portal vein thrombosis type; OS, overall survival; PET-SUV_{max}, positron emission tomography-the maximum standard uptake value; DFS, disease-free survival; Eg, expanding type; Ig, infiltrate growth type.



RFS	Number at risk (n/%)			
Years	0	1	3	5
SUV_{max} <4.65	8	4	4	1
		60	60	60
SUV_{max} ≥4.65	18	0	0	0
		0	0	0

OS	Number at risk (n/%)			
Years	0	1	3	5
SUV_{max} <4.65	8	6	5	1
		75	75	37.5
SUV_{max} ≥4.65	18	7	0	0
		46	0	0

Fig. 4. Kaplan-Meier survival analysis with regard to SUV_{max}. (A) Patients with low SUV_{max} (<4.65) showed significantly longer disease-free survival than those with high SUV_{max} (≥4.65). (B) Patients with low SUV_{max} (<4.65) showed significantly longer overall survival than those with high SUV_{max} (≥4.65). SUV_{max}, maximum standard uptake value. RFS, recurrence-free survival; OS, overall survival.

Table 3. Comparison of clinical-pathologic characteristic between patients with high and low SUV_{max}

Factor	High SUV_{max} group (n = 18)	Low SUV_{max} value group (n = 8)	P-value
Age (yr)	51 (31–60)	50 (43–72)	0.461
Serum α-FP (≥400 ng/mL)	9	4	>0.999
ICG R15 (%)	14.4 (4.2–31.3)	14.5 (5.8–25.2)	0.558
MELD score	8 (6–14)	7 (6–11)	0.979
Serum abumin (g/L)	4.1 (3.2–4.8)	4.4 (4.0–4.8)	0.209
Serum T.Bilirubin (mg/dL)	0.9 (0.4–2.4)	0.8 (0.4–2.0)	0.786
PT-INR	12.3 (10.5–16.6)	11.1 (9.7–12.8)	0.229
Tumor size (cm)	8.2 (3–20)	10 (1.4–12)	0.332
Tumor size (≥6.5 cm)	12	5	>0.999
Growth type (infiltrate type)	14	6	>0.999
Microvascular invasion	18/18	7/7	>0.999
Multiple tumors	3	3	0.330
Liver cirrhosis	12	5	>0.999
Resection margin positive	9/17	2	0.234
Vp4	13	5	0.667
Introhepatic metastasis	14/17	6/7	>0.999
ES grade (grade 3 or 4)	15/16	6/7	0.526
ES grade (grade 4)	13/16	4/7	0.318
Preop TACE	4	0	0.277
Postop PVTT recurrence	5	0	0.281
PET-SUV_{max}	7.65 (4.9–15.1)	3.25 (2.6–4.4)	0.007

Values are presented as median (range) or number.
PET-SUV_{max}, positron emission tomography-the maximum standard uptake value; MELD, model for end-stage liver disease; T.Bilirubin, total bilirubin; ICG R15, indocyanine green retention rate at 15 min; Vp4, presence of a tumor thrombus in the main trunk of the portal vein or a portal vein branch contra lateral to the primarily involved lobe (or both); ES grade, Edmondson-Steiner grade; TACE, transcatheter arterial chemoembolization; PVTT, portal vein tumor thrumbosis; Preop, preoperative; Postop, postoperative.

Table 4. Cox proportional hazards model of risk factors for DFS in HCC patients with mPVTT

Factor	Univariate analysis			Multivariate analysis		
	OR	95% CI	P-value	OR	95% CI	P-value
Serum α-FP (≥400 ng/mL)	1.172	0.492–2.791	0.720			
ICG R15 (%) (≥15%)	0.780	0.322–1.891	0.583			
Tumor size (≥6.5 cm)	2.206	0.775–5.298	0.150			
Growth type (Ig)	1.289	0.430–3.862	0.650			
Microvascular Invasion	0.626	0.081–4.833	0.654			
Multiple tumor	0.857	0.287–2.554	0.782			
Liver cirrhosis	1.403	0.397–2.737	0.932			
Resection margin positive	1.073	0.453–2.543	0.873			
Vp4	1.138	0.440–2.942	0.790			
Introhepatic metastasis	1.297	0.434–3.878	0.642			
PET-SUV_{max} (≥4.65)	8.157	1.846–36.053	0.006			
Preop TACE	2.181	0.706–6.735	0.175			

DFS, disease-free survival; HCC, hepatocellular carcinoma; mPVTT, major portal vein tumor thrombosis; OR, odds ratio; CI, confidence interval; ICG R15, indocyanine green retention rate at 15 min; Ig, infiltrate growth type; Vp4, presence of a tumor thrombus in the main trunk of the portal vein or a portal vein branch contra lateral to the primarily involved lobe (or both); PET-SUV_{max}, positron emission tomography-the maximum standard uptake value; Preop, preoperative; TACE, transcatheter arterial chemoembolization.

Table 5. Cox proportional hazards model of risk factors for OS in HCC patients with mPVTT

Factor	Univariate analysis			Multivariate analysis		
	OR	95% CI	P-value	OR	95% CI	P-value
Serum α-FP (≥400 ng/mL)	0.978	0.361–2.649	0.965			
ICG R15 (%) (≥15%)	1.224	0.453–3.303	0.690			
Tumor size (≥6.5 cm)	4.503	1.022–19.841	0.047	3.733	0.851–16.720	0.080
Growth type (Ig)	1.493	0.424–5.250	0.532			
Microvascular Invasion	0.753	0.097–5.833	0.786			
Multiple tumor	1.193	0.381–3.734	0.762			
Liver cirrhosis	0.737	0.251–2.167	0.579			
Resection margin positive	1.927	0.703–5.285	0.202			
Vp4	1.246	0.401–3.873	0.704			
Introhepatic metastasis	0.792	0.254–2.465	0.687			
Postop PVTT recurrence	2.333	0.675–8.061	0.181			
PET-SUV_{max} (≥4.65)	6.717	1.419–31.796	0.016	5.638	1.215–26.161	0.027
Preop TACE	1.753	0.478–6.433	0.398			

OS, overall survival; HCC, hepatocellular carcinoma; mPVTT, major portal vein tumor thrombosis; OR, odds ratio; CI, confidence interval; ICG R15, indocyanine green retention rate at 15 min; Ig, infiltrate growth type; Vp4, presence of a tumor thrombus in the main trunk of the portal vein or a portal vein branch contra lateral to the primarily involved lobe (or both); PET-SUV_{max}, positron emission tomography-the maximum standard uptake value; Preop, preoperative; TACE, transcatheter arterial chemoembolization.

in high SUV_{max} group. However, SUV_{max} values were significantly different between the 2 groups. The Cox regression analysis showed that SUV_{max} was the only risk factor for RFS and OS (Tables 4, 5).

DISCUSSION

Surgical resection has been identified as an effective treatment for HCC complicated by mPVTT. However, the outcomes of the HCC patients complicated by mPVTT were unsatisfactory in terms of the limited survival ranging from 6 months to 20 months [6-8]. The poor prognosis could be potentially caused by 2 reasons. On the one hand, HCC patients complicated by mPVTT generally received large-scale anatomical hepatectomy in order to reserve safe surgical margins and prevent intrahepatic metastasis. As a result,

the remnant liver volume could not maintain normal liver function. Therefore, preserved liver function was an important risk factor for patient's OS and hospital mortality. Ikai et al. [7] performed Cox multivariate regression analysis and their results showed that damaged liver function featured by ascites and prothrombin activity were critical risk factors for OS. On the other hand, tumor recurrence significantly affected patient survival due to intrahepatic tumor aggravation and subsequent liver failure. Moreover, patients would have limited therapeutic choices due to the limited remnant liver volumes and the existence of recurrent intrahepatic tumors. Choi et al. [11] indicated that PVTT was as an important independent risk factor for early postoperative recurrence of HCC, which was in analog to the finding in this work that all the patients with recurrence (21 of 26) recurred within 10 months after surgery. Besides, most of the cases (18 of 21) had multiple intrahepatic recurrences. Four distinct therapeutic strategies were carried out to treat the tumor recurrence based on degrees of liver function and patterns of recurrence. Twelve patients received TACE; Four patients received multikinase inhibitor of sorafenib; Two patients underwent palliative radiotherapy treatment and 3 patients received conservative management.

PVTT itself was the most important independent risk factor for early postoperative recurrence of HCC [11]. Further, intrahepatic tumor recurrence was the most important risk factor for patient OS [7,16-18]. Thus, it was of great importance to predict the tumor recurrence for HCC patients with mPVTT. ^{18}F-FDG PET had several limitations in diagnosing primary HCC due to the variations of ^{18}F-FDG uptakes caused by heterogeneous glucose metabolism in HCC [19]. Subsequent studies further demonstrated that the phenomenon was associated with HCC progression or aggressiveness [14,15,20]. Low ^{18}F-FDG uptake was observed in well-differentiated HCC, whereas high SUV was observed in moderately- and poorly differentiated HCCs. Moreover, several studies have demonstrated that the degree of ^{18}F-FDG uptake was a significant independent and significant prognostic factor for RFS and OS of HCC patients after surgery [13,14]. Recently, preoperative positive ^{18}F-FDG PET/CT appears to be associated with better OS in HCC patients [21]. In this study, all the patients suffering both HCC and mPVTT were scanned by ^{18}F-FDG PET/CT preoperatively. The optimal cutoff value of SUV_{max} for tumor recurrence after hepatectomy was determined by ROC curve. Then, high SUV_{max} patients and low SUV_{max} patients were divided into 2 groups according to optimal cutoff value of 4.65. The SUV_{max} value was the sole risk factor that differed significantly between high and low SUV_{max} groups. The RFS and OS of the high SUV_{max} group were significantly shorter than that of the low SUV_{max} group. The recurrence period of high SUV_{max} group was relatively short in that they commonly recurred within 10 months (range, 1 to 10 months) after surgery. Besides, these patients showed aggressive recurrence patterns, characterized by multiple intrahepatic recurrences, main portal vein tumor thrombus recurrence, and multiple lung recurrences. Only 3 of 8 patients in low SUV_{max} group experienced tumor recurrence during the follow-up period. Also, the recurrent liver tumors were in accordance with Milan criteria and could be effectively controlled by TACE treatment. Notably, there were 3 deaths during the follow-up period, among which 1 case died of hepatitis B virus recurrence and subsequent liver failure at 4 months after operation, and 2 cases died of tumor recurrence and subsequent liver failure in 8 and 51 months, respectively.

There were 6 patients in low SUV_{max} group surviving more than 3 years postoperatively. The characteristics of these patients were shown in Table 2. Intriguingly, the α-FP levels of 2 patients who had liver tumor recurrence were relatively high. Herein, it could be concluded that patients with high α-FP levels deserved serious attention during the follow-up duration due to the possibility of tumor recurrence even though α-FP values were not optimal sensitivity markers for predicting tumor recurrence. Furthermore, adjuvant therapies such as adjuvant TACE, chemotherapy, and multikinase inhibitor could be applied in such cases. The application of total resection with portal vein reconstruction or thrombectomy as the radical resection for HCC complicated by mPVTT remains controversial. Debates on en bloc resection with portal vein reconstruction and thrombectomy have emerged. Theoretically, *en bloc* resection of the portal vein is a superior surgical strategy owing to no tumor thrombus exposure. Besides, thrombectomy was considered as a potentially noncurative resection because of possible dissemination of tumor cells in operative sites during decollement of the portal vein thrombus in spite of subtle manipulation. However, several previous studies showed that there were no significant differences in the hospital mortalities and morbidities between *en bloc* resection combined with portal vein reconstruction and thrombectomy for the HCC complicated by mPVTT [22,23]. In the present study, thrombectomy was performed on HCC patients complicated by PVTT extending to or beyond the main portal bifurcation, and no surgical field tumor seeding metastasis cases and no in-hospital deaths were found. However, tumor thrombus recurrences in the main portal vein were observed in 5 cases belonging to high SUV_{max} group. This finding suggested that tumor metabolism factors could be of great importance to local tumor recurrence. As for the high-risk patients with high SUV_{max} values, further clinical studies are needed to determine whether *en bloc* resection combined with portal vein reconstruction could prevent the local tumor thrombus recurrence.

In the present study, the SUV_{max} value obtained from PET/CT scan was defined as the only risk factor for DFS using univariate and multivariate analysis based on Cox proportional hazards

model (Table 4). The univariate analysis showed that both the SUV_{max} value obtained from PET/CT and the tumor diameters larger than 6.5 cm were the risk factors OS. However, according to the multivariate analysis based on Cox proportional hazards model, only the SUV_{max} obtained from PET/CT was determined as a risk factor for RFS (Table 5). The main reason could be that most of all the HCC cases complicated by mPVTT showed aggressive clinical and pathological characteristics, such as microvascular invasion, intrahepatic metastasis, and infiltrative growth type (Table. 1). A prior study revealed that the values of SUV_{max} were closely correlated with the expression of glucose transporter 1 (GLUT1), which was a key rate-limiting factor in the transport and metabolism of glucose in cancer cells [24]. Besides, the expression of GLUT1 was associated with poor differentiation and vascular invasion. Thus, our findings in this study suggested that the role of PET/CT SUV_{max} in tumor prognosis was not only limited to reflect tumor differentiation. Kitamura et al. [25] demonstrated that the proliferative activities of tumors that could predict the prognosis of HCC patients had close correlations with the glucose metabolism. However, the mechanisms of SUV_{max} to predict HCC complicated by mPVTT remained unclear and should be elucidated in future studies.

However, there were several the limitations in this study: Firstly, this study was only performed based on a single center in a retrospective manner. Secondly, the number of recruited patients was relatively limited, which could increase the selection bias in this study. Thirdly, only one surgical procedure was performed in this work. Thus, in future studies, more practical surgical procedures such as *en bloc* portal vein resection and reconstruction should be included as a control group for determining the best surgical method.

In conclusion, the SUV_{max} value obtained from ^{18}F-FDG-PET/CT scan was considered as a reliable risk factor for RFS and OS of HCC patients complicated by mPVTT. Low SUV_{max} could serve as an indicator for selecting suitable candidates with low risk of recurrence for surgical resections and to achieve long-term survivals. More precisely, thrombectomy, which did not increase the risk of tumor recurrence, was appropriate for HCC combined with mPVTT patients with low SUV_{max} values. However, it remained unclear whether surgical resections were suitable for patients with high SUV_{max} values. Thus, more in-depth clinical studies are needed to solve this question. Also, larger cohorts and multicentral studies are needed for further investigation as to whether *en bloc* resection combined with portal vein reconstruction could prevent local tumor thrombus recurrence. Moreover, whether the mechanisms underlying HCC prediction by SUV_{max} were associated with tumor differentiation or proliferation is urgently needing to be addressed.

ACKNOWLEDGEMENTS

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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REFERENCES

1. Ikai I, Yamamoto Y, Yamamoto N, Terajima H, Hatano E, Shimahara Y, et al. Results of hepatic resection for hepatocellular carcinoma invading major portal and/or hepatic veins. Surg Oncol Clin N Am 2003;12:65-75.
2. Llovet JM, Bustamante J, Castells A, Vilana R, Ayuso Mdel C, Sala M, et al. Natural history of untreated nonsurgical hepatocellular carcinoma: rationale for the design and evaluation of therapeutic trials. Hepatology 1999;29:62-7.
3. Villa E, Moles A, Ferretti I, Buttafoco P, Grottola A, Del Buono M, et al. Natural history of inoperable hepatocellular carcinoma: estrogen receptors' status in the tumor is the strongest prognostic factor for survival. Hepatology 2000;32:233-8.
4. Iwao I, Masatoshi K, Shigeki A, Masao O, Masamichi K, Michiie S, et al. Report of

the 18th follow-up survey of primary liver cancer in Japan. Hepatol Res 2010;40:1043-59.
5. Kokudo T, Hasegawa K, Matsuyama Y, Takayama T, Izumi N, Kadoya M, et al. Survival benefit of liver resection for hepatocellular carcinoma associated with portal vein invasion. J Hepatol 2016;65:938-43.
6. Poon RT, Fan ST, Ng IO, Wong J. Prognosis after hepatic resection for stage IVA hepatocellular carcinoma: a need for reclassification. Ann Surg 2003;237:376-83.
7. Ikai I, Hatano E, Hasegawa S, Fujii H, Taura K, Uyama N, et al. Prognostic index for patients with hepatocellular carcinoma combined with tumor thrombosis in the major portal vein. J Am Coll Surg 2006;202:431-8.
8. Ban D, Shimada K, Yamamoto Y, Nara S, Esaki M, Sakamoto Y, et al. Efficacy of a hepatectomy and a tumor thrombectomy for hepatocellular carcinoma with tumor thrombus extending to the main portal vein. J Gastrointest Surg 2009;13:1921-8.
9. Imamura H, Seyama Y, Kokudo N, Maema A, Sugawara Y, Sano K, et al. One thousand fifty-six hepatectomies without mortality in 8 years. Arch Surg 2003;138:1198-206.
10. Kenjo A, Miyata H, Gotoh M, Kitagawa Y, Shimada M, Baba H, et al. Risk stratification of 7,732 hepatectomy cases in 2011 from the National Clinical Database for Japan. J Am Coll Surg 2014;218:412-22.
11. Choi KK, Kim SH, Choi SB, Lim JH, Choi GH, Choi JS, et al. Portal venous invasion: the single most independent risk factor for immediate postoperative recurrence of hepatocellular carcinoma. J Gastroenterol Hepatol 2011;26:1646-51.
12. Torizuka T, Tamaki N, Inokuma T, Magata Y, Yonekura Y, Tanaka A, et al. Value of fluorine-18-FDG-PET to monitor hepatocellular carcinoma after interventional therapy. J Nucl Med 1994;35:1965-9.
13. Hatano E, Ikai I, Higashi T, Teramukai S, Torizuka T, Saga T, et al. Preoperative positron emission tomography with fluorine-18-fluorodeoxyglucose is predictive of prognosis in patients with hepatocellular carcinoma after resection. World J Surg 2006;30:1736-41.
14. Seo S, Hatano E, Higashi T, Hara T, Tada M, Tamaki N, et al. Fluorine-18 fluorodeoxyglucose positron emission tomography predicts tumor differentiation, P-glycoprotein expression, and outcome after resection in hepatocellular carcinoma. Clin Cancer Res 2007;13:427-33.
15. Shiomi S, Nishiguchi S, Ishizu H, Iwata Y, Sasaki N, Tamori A, et al. Usefulness of positron emission tomography with fluorine-18-fluorodeoxyglucose for predicting outcome in patients with hepatocellular carcinoma. Am J Gastroenterol 2001;96:1877-80.
16. Matono R, Yoshiya S, Motomura T, Toshima T, Kayashima H, Masuda T, et al. Factors linked to longterm survival of patients with hepatocellular carcinoma accompanied by tumour thrombus in the major portal vein after surgical resection. HPB (Oxford) 2012;14:247-53.
17. Pawlik TM, Poon RT, Abdalla EK, Ikai I, Nagorney DM, Belghiti J, et al. Hepatectomy for hepatocellular carcinoma with major portal or hepatic vein invasion: results of a multicenter study. Surgery 2005;137:403-10.
18. Kondo K, Chijiiwa K, Kai M, Otani K, Nagaike K, Ohuchida J, et al. Surgical strategy for hepatocellular carcinoma patients with portal vein tumor thrombus based on prognostic factors. J Gastrointest Surg 2009;13:1078-83.
19. Trojan J, Schroeder O, Raedle J, Baum RP, Herrmann G, Jacobi V, et al. Fluorine-18 FDG positron emission tomography for imaging of hepatocellular carcinoma. Am J Gastroenterol 1999;94:3314-9.
20. Khan MA, Combs CS, Brunt EM, Lowe VJ, Wolverson MK, Solomon H, et al. Positron emission tomography scanning in the evaluation of hepatocellular carcinoma. J Hepatol 2000;32:792-7.
21. Kim JM, Kwon CHD, Joh JW, Sinn DH, Choi GS, Paik SW. Prognosis of preoperative positron emission tomography uptake in hepatectomy patients. Ann Surg Treat Res 2018;94:183-9.
22. Inoue Y, Hasegawa K, Ishizawa T, Aoki T, Sano K, Beck Y, et al. Is there any difference in survival according to the portal tumor thrombectomy method in patients with hepatocellular carcinoma? Surgery 2009;145:9-19.
23. Chok KS, Cheung TT, Chan SC, Poon RT, Fan ST, Lo CM. Surgical outcomes in hepatocellular carcinoma patients with portal vein tumor thrombosis. World J Surg 2014;38:490-6.
24. Mano Y, Aishima S, Kubo Y, Tanaka Y, Motomura T, Toshima T, et al. Correlation between biological marker expression and fluorine-18 fluorodeoxyglucose uptake in hepatocellular carcinoma. Am J Clin Pathol 2014;142:391-7.
25. Kitamura K, Hatano E, Higashi T, Narita M, Seo S, Nakamoto Y, et al. Proliferative activity in hepatocellular carcinoma is closely correlated with glucose metabolism but not angiogenesis. J Hepatol 2011;55:846-57.