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Impact of Metabolic Parameters of ^{18}F-Fluorodeoxyglucose Positron-emission Tomography After Hepatic Resection in Patients With Intrahepatic Cholangiocarcinoma

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Abstract. *Background: The aim of this study was to identify the prognostic impact of metabolic parameters of ^{18}F-fluorodeoxyglucose (FDG) positron-emission tomography (PET) in patients with intrahepatic cholangiocarcinoma (IHCC) undergoing hepatic resection. Patients and Methods: Twenty-four patients with IHCC who underwent surgical resection were enrolled and ^{18}F-FDG PET parameters maximum standardized uptake value (SUVmax), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) were measured, as well as overall and recurrence-free survival. Results: High TLG was significantly associated with large tumor size and high carbohydrate antigen 19-9 level. Patients with high SUVmax, high MTV or high TLG had a significantly worse prognosis regarding both overall and recurrence-free survival than those with low SUVmax, low MTV and low TLG, respectively. Multivariate Cox proportional hazards analysis identified that high TLG significantly influenced both overall and recurrence-free survival. Conclusion: Preoperative assessment of TLG by ^{18}F-FDG PET might be a useful prognostic predictor after hepatic resection in patients with IHCC.*

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Key Words: Intrahepatic cholangiocarcinoma, metabolic tumor volume, total lesion glycolysis, lymph node metastasis, prognosis.

Intrahepatic cholangiocarcinoma (IHCC) is primary liver cancer arising in the intrahepatic bile ducts, which accounts for 5-10% of primary liver cancers and is the second most frequent form of primary hepatic malignancies in adults after hepatocellular carcinoma (1, 2). Radical surgical resection is the only effective curative treatment, but the survival rates for patients with IHCC remain unfavorable, although advances in diagnostic and surgical approaches to IHCC have been achieved. There are many preoperative prognostic factors in IHCC (3-6). Lymph node metastasis is reportedly the most significant predictor of poor outcome in IHCC, but extended lymphadenectomy does not improve survival (3, 5, 6). Additionally, preoperative diagnosis of lymph node metastasis is still difficult despite the use of computed tomographic (CT) or positron-emission tomographic (PET) scan. Lymphatic invasion or vascular invasion were reported to be prognostic factors, but these are postoperative factors. R0 resection was also reported to be an independent predictor of long-term survival. Surgical resection is still the most effective treatment in the modern era.

^{18}F-Fluorodeoxyglucose (FDG) PET has been used in the diagnostic imaging of many cancer types such as lung, pancreatic, and metastatic liver cancer. Recent meta-analyses showed that various FDG PET parameters including maximum standardized uptake value (SUVmax), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) were prognostic factors in multiple types of malignancies (7-9). But information on the prognostic value of FDG-PET in IHCC is limited. Therefore, the aim of this study was to identify preoperative predictors of prognosis in patients with IHCC undergoing hepatic resection, and examine the impact of metabolic parameter of ^{18}F-FDG-PET/CT in those patients.

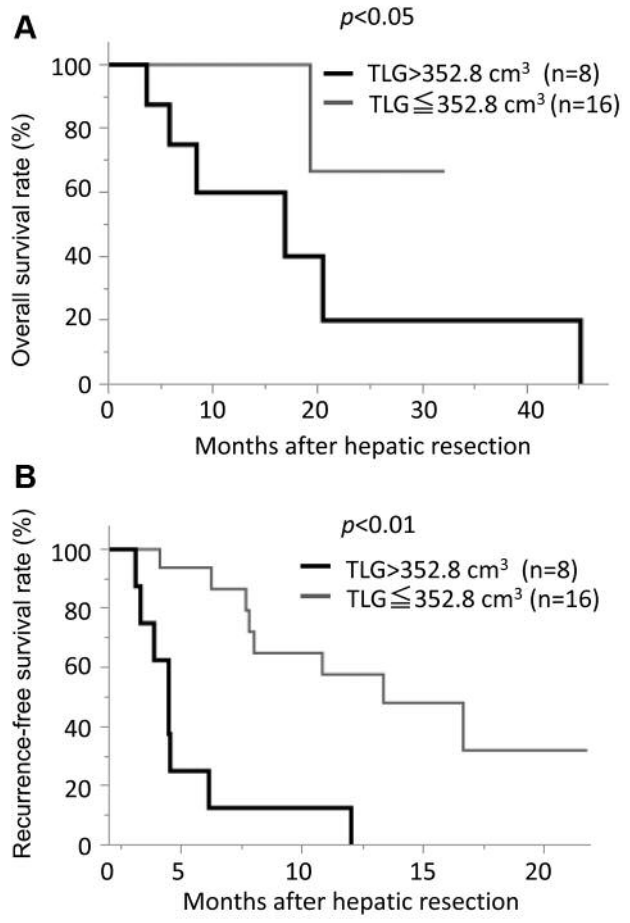

Figure 1. *Overall (A) and recurrence-free (B) survival curves after hepatic resection in patients with intrahepatic cholangiocarcinoma according to TLG (total lesion glycolysis). These curves show that patients with TLG>352.8 cm³ had a significantly poorer prognosis.*

Table I. *Comparison of the clinicopathological factors in patients undergoing hepatic resection for intrahepatic cholangiocarcinoma according to total lesion glycolysis. Continuous data are expressed as mean±standard deviation.*

Variable	TLG≤ 352.8 cm³ (n=16)	TLG> 352.8 cm³ (n=8)	*p*-Value
Age, years	74.3±7.2	69.5±11.9	0.22
Male/female, n	11/5	5/3	0.76
HBV or HCV, n (%)	4 (25.0%)	3 (37.5%)	0.77
Albumin, g/dl	3.9±0.4	3.7±0.5	0.08
Total bilirubin, mg/dl	0.9±0.2	0.8±0.3	0.88
WBC, n/μl	5668±1278	7275 ±3215	0.10
NeutrophiIs, n/μl	3796±1151	3745±1893	0.46
Lymphocytes, n/μl	1471±565	1528±411	0.80
NLR	2.92±1.25	2.48±1.22	0.42
Platelet count, 104/μl	20.3±7.7	27.3±14.3	0.12
ICGR15, %	9.9±4.1	10.3±4.2	0.85
Liver status: nl/ch/lc, n	9/7/0	2/5/1	0.10
Tumor size, cm	5.1±7.2	7.7±10.2	0.03
Stage, n: I/II/III/IV	1/0/9/6	0/0/3/5	0.45
Poor differentiation, n (%)	6 (37.5%)	3 (37.5%)	0.99
Microvascular invasion, n (%)	14 (87.5%)	8 (100%)	0.52
Lymph node metastasis, n (%)	5 (31.2%)	5 (62.5%)	0.20
CEA, ng/ml	9.3±20.6	49.4±97.2	0.12
CA19-9, U/ml	642±1642	2807±4544	0.04
Lobectomy or more, n (%)	9 (56.3%)	6 (75.0%)	0.66
Lymph node dissection, n (%)	8 (50.0%)	6 (75.0%)	0.39
Biliary reconstruction, n (%)	4 (25.0%)	4 (50.0%)	0.36
R0, n (%)	13 (81.2%)	5 (62.5%)	0.36
Operative time, min	438±160	495±133	0.39
Estimated blood loss, g	599±637	1751±1977	0.92
Blood transfusion, n (%)	1 (6.3%)	3 (37.5%)	0.09
Postoperative complications, n (%)	1 (6.3%)	1 (12.5%)	0.89
Hospital stay, days	17.7±8.9	17.8±4.9	0.50

CEA: Carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9; NLR: neutrophil-lymphocyte ratio; nl/ch/lc: normal liver/chronic hepatitis/liver cirrhosis; HBV: hepatitis B antigen; HCV: hepatitis C antibody; ICGR15: indocyanine green dye retention test at 15 min; SUVmax: maximum standardized uptake value; MTV: metabolic tumor volume; TLG: total lesion glycolysis; stage: TNM stage, defined by the Liver Cancer Study Group of Japan; R0: no residual tumor.

Patients and Methods

Patient characteristics. This study enrolled 24 patients with IHCC who had undergone surgical resection at the Department of Hepatobiliary and Pancreatic Surgery, Graduate School of Medicine, Gunma University, Gunma, Japan, between April 2007 and December 2017. All patients had a confirmed pathological diagnosis of a malignancy arising from the intrahepatic cholangiocarcinoma. Patient demographic and clinical characteristics, including perioperative factors, tumor characteristics and survival were analyzed, and factors predicting overall (OS) and recurrence-free (RFS) survival were evaluated by univariate and multivariate analyses. The study protocol conformed to the ethical guidelines of the 1975 Helsinki Declaration and was approved by our Institutional Review Board (approval number: 2017-237).

^{18}F-FDG/PET imaging. PET imaging was performed within 1 month before hepatic resection using a PET/CT scanner (Discovery STE; GE Healthcare, CA, USA) with a 700 mm field of view at Gunma University Hospital and another PET/CT scanner (Aquideo, PCA-7000B; Toshiba, Tokyo, Japan) at Hidaka Hospital. The patients fasted for at least 6 h before PET imaging. FDG PET/CT image acquisition, reconstruction, and attenuation correction were performed as previously described (10). All ^{18}F-FDG images were interpreted by two experienced nuclear physicians (H.T. and T.Y.). The interpreting physicians were unaware of the patient's clinical history and data. Tracer uptake in the primary tumor was defined as positive if the uptake was higher than that of the normal mediastinum. Discrepant results were resolved by consensus review. For the semiquantitative analysis, functional images for the SUV were produced using attenuation-corrected transaxial images, the injected dose of ^{18}F-FDG, the patient's body weight, and the cross-calibration factor between

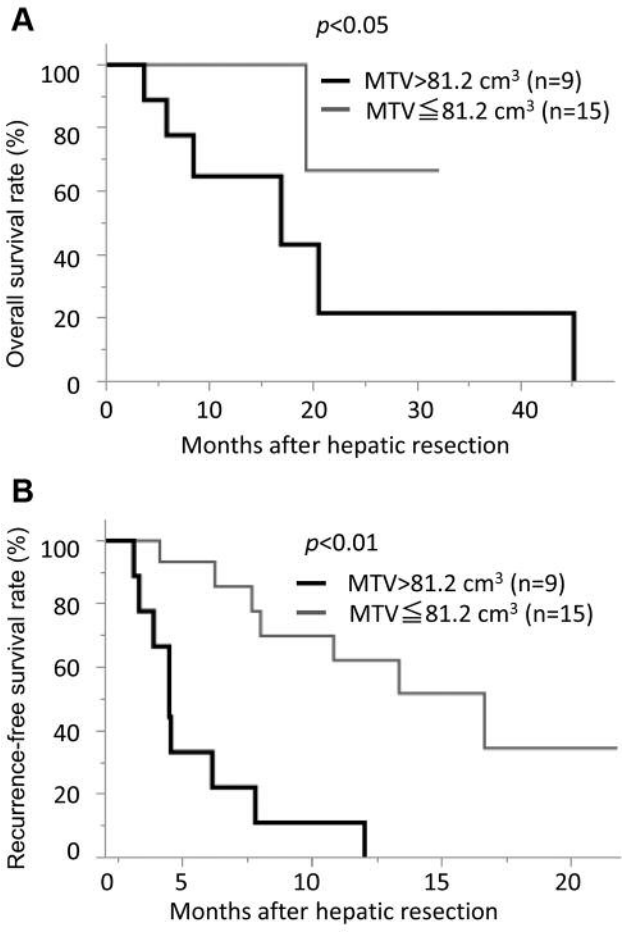

Figure 2. *Overall (A) and recurrence-free (B) survival curves after hepatic resection in patients with intrahepatic cholangiocarcinoma according to MTV (metabolic tumor volume). These curves show that patients with MTV>81.2 cm^3 had a significantly poorer prognosis.*

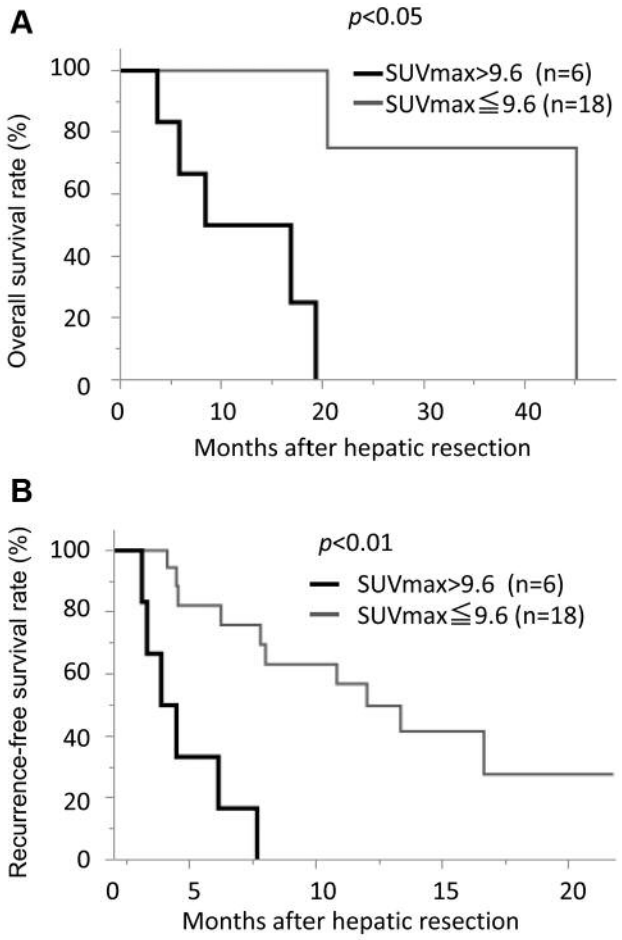

Figure 3. *Overall (A) and recurrence-free (B) survival curves after hepatic resection in patients with intrahepatic cholangiocarcinoma according to maximum standardized uptake value. These curves show that patients with SUVmax>9.6 had a significantly poorer prognosis.*

PET and the dose calibrator. SUV was defined as follows: SUV=radioactive concentration in the region of interest (ROI) [MBq/g]/injected dose (MBq)/patient's body weight (g). The ROI was manually drawn over the primary tumor on the SUV images. When the tumor was larger than 1 cm in diameter or the shape of the tumor was irregular or multifocal, a ROI of approximately 1 cm in diameter was drawn over the area corresponding to the maximal tracer uptake. ROI analysis was conducted by a nuclear physician with the aid of corresponding CT scans. The SUVmax in the ROI was used as a representative value for the assessment of FDG uptake in the lesion. CT scan for the purpose of initial staging was carried out with intravenous contrast medium. CT images were interpreted by the two Board-certified radiologists (T.H. and Y.T.). Syngo.via software (Siemens Medical Solutions, Erlangen, Germany) at the Gunma University Hospital on a workstation to automatically calculate the MTV and TLG. MTVs were defined as the tumor volume inside the tumor boundaries using SUV thresholds that were 60% of the tumor SUVmax. TLGs were calculated by multiplying the mean SUV by the tumor volume inside the tumor boundaries.

Preoperative calculation of the cut-off value of the SUVmax, MTV and TLG. The receiver operating characteristics (ROC) curves of preoperative ^{18}F-FDG/PET parameters were analyzed, and OS was predicted by comparing the area under the ROC curve (AUC). The best cut-off value was 9.6 for SUVmax (sensitivity=71.43%; specificity=99.42%; AUC=0.798), 81.2 for MTV (sensitivity=85.71%; specificity=82.35%; AUC=0.882) and 352.8 for TLG (sensitivity= 85.71%; specificity=81.27%; AUC=0.9076).

Surgical procedures. All patients underwent dynamic CT imaging preoperatively. The details of our surgical techniques and patient follow-up methods were reported previously (5). Major hepatectomy with bile duct resection was performed when bile duct invasion was suspected to have affected the first hepatic duct. Partial hepatectomy was performed for peripheral IHCC without bile duct invasion. When we considered it desirable to confirm the surgical margins, the resected specimen was sent for frozen pathology. The right and left lobes of the liver have different routes of lymphatic drainage; therefore, the technique for lymph node dissection was tailored to the

Table II. *Cox proportional hazard model of the association of all clinical characteristics with overall survival using univariate and multivariate analyses.*

	Univariate analysis		Multivariate analysis	
Variable	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Age, years	0.96 (0.91-1.02)	0.23		
Male gender	0.77 (0.28-2.26)	0.61		
HBV or HCV	1.59 (0.22-8.21)	0.60		
Albumin <3.8 g/dl	11.1 (1.76-214.92)	<0.01	4.83 (0.21-23.73)	0.30
Total bilirubin, mg/dl	1.19 (0.04-15.35)	0.90		
ICGR15, %	1.19 (0.89-1.72)	0.24		
Liver cirrhosis	3.19 (0.01-14.15)	0.67		
SUVmax>9.6	4.16 (1.25-26.72)	<0.01	3.93 (2.02-39.43)	<0.01
MTV>81.2 cm^3	7.67 (1.22-147.59)	0.02		
TLG>352.8 cm^3	8.70 (1.37-168.08)	0.01	1.96 (1.43-13.05)	<0.01
Tumor size >5 cm	2.77 (0.49-21.80)	0.25		
CEA >10 ng/ml	5.56 (0.66-46.42)	0.10		
CA19-9 >100 Um/l	9.46 (1.16-195.84)	0.03	3.42 (0.81-5.82)	0.23
Stage IV	1.67 (0.29-9.49)	0.54		
Poor differentiation	0.69 (0.09-3.58)	0.67		
Microvascular invasion	21.56 (019-114.10)	0.34		
Lymph node metastasis	3.19 (0.61-23.35)	0.16	4.16 (0.52-18.99)	0.09
Lobectomy	5.37 (0.79-107.21)	0.08		
Lymph node dissection	2.36 (0.37-45.73)	0.39		
Bile duct reconstruction	1.79 (0.33-9.80)	0.48		
R1/2	2.87 (0.52-15.72)	0.20		
Operative time, min	1.00 (0.99-1.01)	0.56		
Estimated blood loss, g	1.00 (0.99-1.00)	0.99		
Blood transfusion	2.81 (0.49-15.81)	0.21		
Postoperative complications	4.09 (0.39-25.21)	0.19		

CI: Confidence interval; HR: hazard ratio; HBV: hepatitis B antigen; HCV: hepatitis C antibody; lc: liver cirrhosis; ICGR15: indocyanine green dye retention test at 15 min; SUVmax: maximum standardized uptake value; MTV: metabolic tumor volume; TLG: total lesion glycolysis; stage: TNM stage, defined by the Liver Cancer Study Group of Japan; R1/2: residual tumor.

location of the primary tumor. Postoperative surgical complications were recorded according to the Clavien-Dindo classification (11).

Follow-up strategy and recurrence pattern. After discharge, all patients were examined for recurrence by ultrasonography and tumor markers by CT every 3 months. When recurrence was suspected, additional examinations such as MRI or ^{18}F-FDG/PET were performed.

Histopathological examination. All of the resected specimens were cut into serial 5- to 10-μm-thick slices and fixed in 10% formalin. The sections were stained with hematoxylin and eosin. Tumor differentiation, microvascular invasion, intrahepatic metastasis were assessed by the pathologist according to the criteria of the Liver Cancer Study Group of Japan (12). Histologically, all cases were identified as mass-forming type IHCC.

Statistical analysis. The associations of continuous and categorical variables with the relevant outcome variables were assessed using Student's *t*-test and the chi-square test, respectively. Patient survival was analyzed using the Kaplan–Meier method and groups compared using the log-rank test. Uni- and multivariate analyses were performed using a logistic regression model. To identify prognostic factors, some variables which were found to have independent association in univariate analysis (except MTV) were included in a multivariate Cox proportional model to analyze both OS and RFS because MTV was a confounding factor Lymph node metastasis is reportedly the most significant predictor of poor outcome in IHCC (5, 6), and therefore lymph node metastasis was included in the multivariate analysis. Statistical analyses were performed using JMP software (version 12.2.0; SAS Institute, Cary, NC, USA). Results with a *p*-value of less than 0.05 were considered statistically significant.

Results

The clinicopathological characteristics of the patients according to TLG (>352.8 cm^3 and ≤352.8 cm^3) are shown in Table I. A high TLG was significantly associated with large tumor size and high carbohydrate antigen 19-9 (CA19-9) level. The OS and RFS curves of the patients according to TLG are illustrated in Figure 1. Patients with high TLG had a significantly worse prognosis regarding both OS and RFS than did patients with low TLG. The OS and RFS curves according to MTV and SUVmax are illustrated in Figures 2 and 3, respectively. Patients with high (>81.2 cm^3)

Table III. *Cox proportional hazard model of the association of all clinical characteristics with recurrence-free survival using univariate and multivariate analyses.*

	Univariate analysis		Multivariate analysis	
Variables	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Age, years	0.93 (0.85-1.01)	0.11		
Male gender	3.21 (0.51-61.93)	0.29		
HBV or HCV	1.59 (0.22-8.21)	0.60		
Albumin <3.8 g/dl	2.27 (0.74-6.59)	0.14		
Total bilirubin, mg/dl	4.26 (0.58-26.01)	0.14		
ICGR15, %	1.00 (0.86-1.15)	0.97		
Liver cirrhosis: lc	4.03 (0.21-25.07)	0.27		
SUVmax >9.6	9.12 (2.53-36.63)	0.01	2.97 (0.47-25.02)	0.25
MTV >81.2 cm^3	7.01 (2.32-23.69)	<0.01		
TLG >352.8 cm^3	7.08 (2.33-22.58)	<0.01	5.91 (1.06-36.74)	0.04
Tumor size >5 cm	3.51 (1.19-12.79)	0.02	4.69 (1.07-27.32)	0.04
CEA >10 ng/ml	1.876 (0.41-6.35)	0.37		
CA19-9 >100 Um/l	3.65 (1.15-11.27)	0.03	1.83 (1.06-36.74)	0.36
Stage IV	1.74 (0.63-4.77)	0.28		
Poor differentiation	0.85 (0.29-2.31)	0.76		
Microvascular invasion	1.48 (1.19-2.43)	0.02	1.51 (1.38-2.79)	0.03
Lymph node metastasis	3.27 (1.12-9.75)	0.03	1.11 (0.19-5.05)	0.89
Lobectomy	1.78 (0.64-5.74)	0.27		
Lymph node dissection	2.37 (0.82-6.71)	0.45		
Bile duct reconstruction	1.79 (0.33-9.80)	0.11		
R1/2	2.87 (0.52-15.72)	0.20		
Operative time, min	1.00 (0.99-1.01)	0.12		
Estimated blood loss, g	1.00 (0.99-1.00)	0.11		
Blood transfusion	3.61 (0.90-12.99)	0.07		
Postoperative complications	4.09 (0.10-11.12)	0.64		

CI: Confidence interval; HR: hazard ratio; HBV: hepatitis B antigen; HCV: hepatitis C antibody; lc: liver cirrhosis; ICGR15: indocyanine green dye retention test at 15 min; SUVmax: maximum standardized uptake value; MTV: metabolic tumor volume; TLG: total lesion glycolysis; stage: TNM stage, defined by the Liver Cancer Study Group of Japan; R1/2: residual tumor.

MTV had a significantly worse prognosis regarding both OS and RFS than did patients with low MTV. Moreover, patients with high (>9.6) SUVmax had a significantly worse OS and RFS than did patients with low SUVmax.

The prognostic factors for OS and RFS, according to univariate analyses, are shown in Tables II and III. The significant prognostic factors for OS in univariate analysis were low serum albumin level, high SUVmax, high MTV, high TLG and CA19-9 >100 U/ml. The significant prognostic factors for RFS were high SUVmax, high TLG, high MTV, tumor size >5 cm, lymph node metastasis, CA19-9 >100 U/ml and the presence of microvascular invasion. Multivariate analysis identified two factors of poor prognosis that influenced OS (high SUVmax and high TLG), and three that influenced RFS (high TLG, tumor size >5 cm and microvascular invasion).

Discussion

According to multivariate analysis, in this retrospective study, high TLG was an independent predictor of both OS and RFS after curative hepatic resection in patients with ICC. In this multivariate analysis, high SUVmax was an independent predictor of OS, but not RFS. Consequently, TLG reflects the malignant potential of IHCC much better than SUVmax.

SUVmax in IHCC was reported as independent prognostic factor. Ma *et al*. reported SUVmax of more than 8 reflecd poorer prognosis in patients with TNM stage I and II cholangiocarcinoma (13). Seo *et al*. also reported SUVmax>8.5 as an independent predictor of postoperative recurrence in multivariate analysis (14). SUVmax is a measurement of a single pixel with the highest radiotracer concentration in the region of interest, which means it does not reflect the nature of the whole tumor. MTV represents the active metabolic tumor volume and then TLG was calculated by multiplying the tumor volume by the mean SUV of tumor. Our data show that the group with a high MTV had a larger mean tumor size and higher CA19-9 level. MTV and TLG are reported to have a prognostic significance in many cancer types. Yoo *et al*. reported that TLG was a better prognostic

predictor than SUVmax in patients with gallbladder carcinoma (15). Aditionally, Lee *et al*. reported TLG to be a better prognostic predictor than SUVmax in patients with distal bile duct adenocarcinoma after curative resection (16). There are few reports on MTV and TLG in IHCC. Recently, Ikeno *et al*. reported a high MTV to be associated with KRAS mutation and poor postoperative outcomes in 50 patients with resected IHCC, suggesting that the MTV of IHCC as measured by ^{18}F-FDG-PET may provide useful information for tumor molecular profiles and prognosis (17). Some reports investigated metabolic parameters in patients with IHCC, but one also included biliary tract cancer (18) and the other included non-surgical cases (19).

To date, surgical resection remains the only potentially curative treatment for IHCC, but early recurrence is common even in patients who have undergone curative resection. A better understanding of the preoperative factors associated with poor prognosis in patients with IHCC scheduled for curative resection would inform decisions about the need for additional preoperative treatment of high-risk patients, such as neoadjuvant chemotherapy. The evidence supporting the therapeutic benefits of neo- and adjuvant treatment relies on retrospective series or relatively small prospective studies (20). It is essential to be able to identify patients at risk of recurrence despite complete curative resection of IHCC so that neo- and adjuvant chemotherapy can be more effectively targeted and outcomes can be improved.

Our study had some limitations. The sample was relatively small, which made it difficult to evaluate the outcomes of curative resection; however, few previous studies have examined the role of pre- and postoperative treatment of IHCC after curative resection.

In conclusion, we found that preoperative assessment of TLG by ^{18}F-FDG PET might be a useful prognostic predictor after hepatic resection in patients with IHCC. Those patients with association of high TLG may need additional preoperative chemotherapy.

Conflicts of Interest

The Authors declare no conflicts of interest.

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