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ORIGINAL SCIENTIFIC REPORT

Reappraisal of Prognostic Impact of Tumor SUVmax by ^{18}F-FDG-PET/CT in Intrahepatic Cholangiocarcinoma

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Abstract

Background We previously reported that tumor standardized uptake value (SUVmax) by ^{18}F-fluorodeoxyglucose-positron emission tomography/computed tomography (PET/CT) was a potential predictor in patients undergoing surgery for intrahepatic cholangiocarcinoma (ICC). However, the prognostic value of SUVmax in the era of multidisciplinary strategy has remained unclear. The aim of this study was to reappraise the prognostic value of tumor SUVmax in patients undergoing surgery for ICC.

Methods Data from 82 consecutive ICC patients, who underwent ^{18}F-FDG-PET/CT and subsequent surgery between 2006 and 2017, were retrieved from a prospectively maintained institutional database. Adjuvant strategy was administrated during this study period in our center.

Results Tumor SUVmax was associated with tumor size (p = 0.002) and tumor number (p = 0.005), but not associated with T and N stage classified by American Joint Committee on Cancer-classification system, and other tumor factors. According to the tumor SUVmax cut-off values of 8.0 based on the minimum p value approach, actuarial 5-year overall survival (OS) rates in patients undergoing upfront surgery for ICC were significantly stratified at 54.7% versus 26.0% (low vs. high tumor SUVmax group, p = 0.008). The actuarial 3-year disease-free survival (DFS) rates were also significantly stratified at 41.0% versus 18.3% ($p < 0.001$). Multivariate Cox regression analyses revealed that tumor SUVmax retained its significance on OS (p = 0.039) as well as DFS ($p < 0.001$).

Conclusion Even in the era of multidisciplinary strategy, high tumor SUVmax still represents poor prognosis in patients undergoing surgery for ICC. These patients, therefore, would probably be required more effective strategies.

Introduction

Intrahepatic cholangiocarcinoma (ICC) is the second most common primary liver cancer after hepatocellular carcinoma (HCC) with dismal prognosis [1, 2]. Surgery is considered the only curative treatment for ICC patients, yet the recurrence rate after the surgery is 50–60%, and the 5-year overall survival rate after surgery is still 15–40% [2, 3]. While several investigators have identified prognostic factors (i.e., lymph node metastasis, or multiple tumor [2–5]), many reported prognostic factors were the ones available after surgery. If we could identify high-risk patients before surgery, it may help clinicians in adopting

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more effective therapy. However, data on such predictors in ICC patients are currently limited as compared to other gastrointestinal malignancies.

^{18}F-fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) is able to visualize tumor glucose metabolism and has been used for the diagnosis and staging of various malignancies. Further, the maximum standardized uptake value (SUVmax), which represents tumor ^{18}F-FDG avidity, has been shown to be useful for predicting the prognosis of several malignant diseases, including hepatobiliary tumors [6–8]. Especially in ICC, we initially reported that patients with high tumor SUVmax showed poor disease-free survival (DFS) ($n = 27$) [6], suggesting its possibility as a preoperative indicator.

Recently, the prognosis of ICC after surgery seemed to be improved due to the multidisciplinary strategy such as postoperative adjuvant therapy or aggressive treatment for recurrences [5, 9, 10]. Unfortunately, the impact of tumor SUVmax in our initial report was evaluated in the era when there was no postoperative adjuvant strategy. Therefore, the actual prognostic value of tumor SUVmax in the era of multidisciplinary strategy was still unclear. The purpose of this study is to reappraise whether tumor SUVmax measured by ^{18}F-FDG-PET imaging can predict long-term outcomes of patients undergoing surgery for ICC.

Patients and methods

Patients

We reviewed a prospectively maintained database of consecutive patients, who underwent curative-intent surgery for mass-forming ICC (with or without periductal infiltration) at the Department of Surgery, Kyoto University, between January 2006 and December 2017, since adjuvant strategy was clearly administrated during this study period [5]. ICC is defined as a tumor, whose center of the mass is judged to be located in the second or more distal branch of the intrahepatic bile duct [11]. This study used an independent cohort from our previous report [6]. Inclusion criteria were: (1) patients with pathologically proven ICC diagnosed by at least two experienced pathologists and (2) patients who underwent ^{18}F-FDG-PET study before surgery. Exclusion criteria were patients with apparent distant metastases detected on CT, magnetic resonance imaging, or ^{18}F-FDG-PET/CT.

The clinicopathological data, surgical outcomes and survival data of these patients were extracted from the database. The blood data at the time of admission were evaluated, whereas in cases with jaundice, those after biliary drainage and/or the confirmation of patients having no signs of infection were evaluated. In patients who underwent neoadjuvant chemotherapy, data of ^{18}F-FDG-PET/CT and blood data before neoadjuvant chemotherapy were used for analyses. Primary tumor characteristics and resection margins were confirmed on the basis of final historical findings. The tumor characteristics were also classified as T and N stage in accordance with the American Joint Committee on Cancer (AJCC)-classification system, 8th edition [12]. In this study, we defined T2–T4 as an advanced stage because multiple tumor has shown the significant adverse effect on survival and this factor was included in T2 or more advanced stage [2–5]. However, T1 stage is the solitary tumor with no vascular invasion. Operative mortality was defined as death within 90 days of surgery, and morbidity was evaluated according to the Clavien–Dindo classification system [13]. The follow-up data were updated in November 2018.

The protocol of this study was approved by the ethical committee of the Graduate School of Medicine, Kyoto University. A written consent was obtained from all the participants.

^{18}F-FDG-PET study and image analysis

All ^{18}F-FDG-PET imaging procedures were performed as previously described [6–8]. In this study, we used three PET or PET/CT scanners (Advance, Discovery ST Elite, and Discovery IQ, GE Healthcare, Waukesha, WI). Minimally, two nuclear medicine physicians interpreted the PET images using all the available clinical information and correlative conventional imaging for anatomic guidance. For semiquantitative analysis of ^{18}F-FDG uptake, regions of interest (ROIs) were manually defined on transaxial tomograms. The ROI was drawn on the basis of images from abdominal CT scans in patients who have not shown significantly high uptake. The maximum standardized uptake value (SUV) was calculated for quantitative analysis of tumor ^{18}F-FDG uptake as follows: SUV = C (kBq/ml)/ID (kBq)/body weight (kg), where C is the tissue activity concentration measured by PET, while ID is the injected dose.

Surgical procedures and treatment strategy

The tumor location, extension and patients' liver function, facilitated to determinate the types of operative procedures [3, 5, 14]. Routine lymphadenectomy around the hepatoduodenal ligament, posterior to the pancreas and the common hepatic artery, and sampling of para-aortic lymph nodes were performed. Lymphadenectomy was omitted in the selected cases considering the patient's age and hepatic functional reserve. Biliary reconstruction was considered when tumors involved hepatic hilum. Vascular resection and/or reconstruction was considered if necessary. During the study period, gemcitabine and/or tegafur–gimeracil–oteracil potassium was basically used as postoperative adjuvant chemotherapy for tumors in II–IV stages, classified according to the 7th and 8th edition of AJCC [5, 12]. After surgery, the patients were followed up every 1–3 months at the outpatient department of our institution or primary care doctor. CT was routinely performed once every 3–6 months. If there are suspicious signs of recurrence, multiple image-based modalities were used for documenting the appearance of new lesion(s) [15]. Treatments after recurrence were discussed during the multidisciplinary team conference.

Statistical analysis

Categorical variables were analyzed with Chi-square test or Fisher exact test, while continuous variables were analyzed using the Mann–Whitney U test. Correlation between the continuous variables was evaluated by Spearman's correlation test. (Value was expressed as ρ.) Survival analyses were performed excluding patients who underwent preoperative chemotherapy and those who experienced surgery-related death within 90 days. Overall survival (OS) was calculated from the date of operation until death due to any cause, or the date of the last follow-up. DFS was calculated from the date of the operation until the date of confirmed recurrence, or any cause of death. Survival curves were estimated using the Kaplan–Meier method, and a comparison was performed with the log-rank test. A cut-off value of tumor SUVmax was determined based on the maximum significant OS differences that were calculated using log-rank test (i.e., the minimum p value approach). Then, the value was rounded off to the nearest integer. The prognostic value of the variables was tested by univariate and multivariate analysis in the Cox regression model. The prognostic factors were identified by univariate and multivariate analysis in the Cox regression model. Factors with $p < 0.05$ in univariate analysis were entered into a backward stepwise multivariate model. (Variables were removed if $p \geq 0.050$.) When collinearity was encountered, a choice was made based on clinical reasoning. All p values were two-sided and value less than 0.050 was considered statistically significant. All statistical computations were performed using JMP Pro 12.1 software (SAS Institute Inc., Cary, NC).

Table 1 Patient demographics of 82 ICC patients

Variables	n = 82
Preoperative factors	
Age, median (range), years	69.5 (32–84)
Gender, male, n (%)	46 (56.1%)
HBV (+), n (%)	4 (4.9%)
HCV (+), n (%)	12 (14.6%)
Tumor SUVmax	6.15 (2.3–22.1)
CA19-9 levels, median (range), IU/ml	34.95 (0–3055)
CEA, median (range), ng/ml	2.9 (0–116.6)
Neoadjuvant chemotherapy, n (%)	4 (4.9%)
Postoperative factors	
AJCC T stage, n (%)	
T1	25 (30.5%)
T2–T4	57 (69.5%)
Tumor size, median (range), cm	3.75 (1.0–14.0)
Microvascular invasion, n (%)	47 (57.3%)
Multiple tumor, n (%)	20 (24.4%)
Major biliary invasion, n (%)	13 (15.9%)
AJCC N stage, n (%)	
N0	48 (58.5%)
Nx	12 (14.6%)
N1	22 (26.8%)
Para-aortic lymph node metastasis, n (%)	4 (4.9%)
Poorly differentiation, n (%)	12 (14.6%)
R0 resection, n (%)	70 (85.4%)
Treatment factors	
Major hepatectomy, ≥3 segments, n (%)	61 (74.4%)
Biliary reconstruction, n (%)	20 (24.4%)
Vascular resection, n (%)	12 (14.6%)
Postoperative adjuvant chemotherapy, n (%)	46 (56.1%)
Gemcitabine	31 (37.8%)
S-1	12 (14.6%)
Gemcitabine + S-1	3 (3.7%)
Surgical outcomes	
Morbidity, n (%)	
None	52 (63.4%)
Class I/II	14 (17.1%)
Class III/VI	14 (17.1%)
Mortality, n (%)	2 (2.4%)

ICC intrahepatic cholangiocarcinoma, *SUVmax* maximum standardized uptake value, *HBV* hepatitis B virus; *HCV* hepatitis C virus, *CA19-9* carbohydrate antigen 19-9, *CEA* carcinoembryonic antigen, *AJCC* American Joint Committee on Cancer, *R0 resection* no macroscopic and microscopic tumor remaining

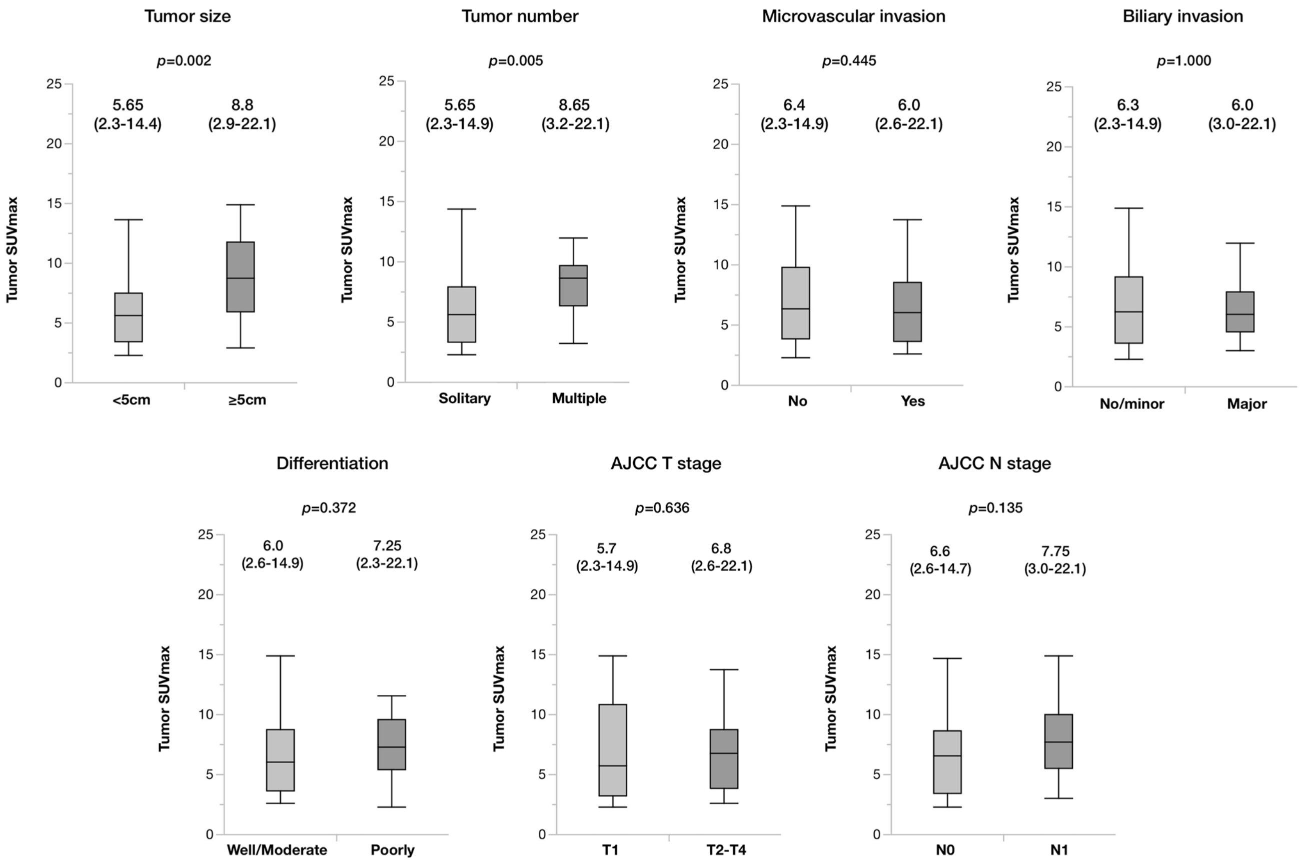

Fig. 1 Box-and-whisker plot of tumor SUVmax in ICC patients according to postoperative tumor characteristics. *SUVmax* maximum standardized uptake value, *ICC* intrahepatic cholangiocarcinoma, *AJCC* American Joint Committee on Cancer

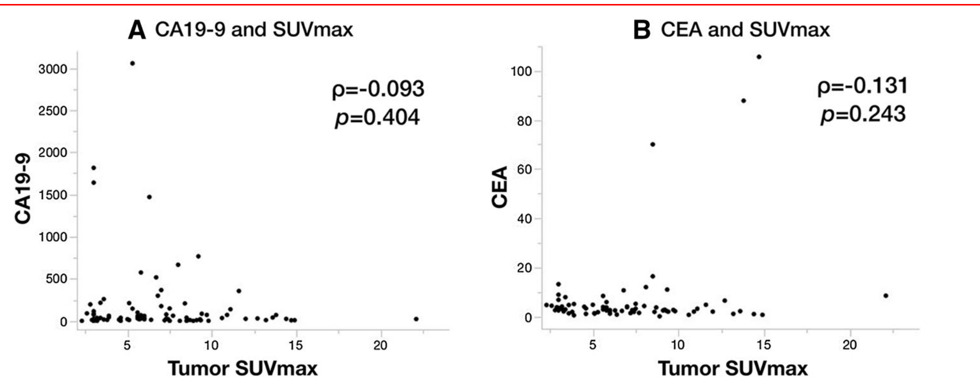

Fig. 2 Correlations between tumor SUVmax and tumor markers in ICC patients. *SUVmax* maximum standardized uptake value, *ICC* intrahepatic cholangiocarcinoma, *CA19-9* carbohydrate antigen 19-9, *CEA* carcinoembryonic antigen

Results

Patient demographics

During the study periods, 109 patients with pathologically proven ICC underwent curative-intent resection. Of these, 82 patients (75.2%) underwent ^{18}F-FDG-PET/CT and subsequent surgery, the remaining 27 did not undergo ^{18}F-FDG-PET/CT because of difficulties in surgical schedule adjustments or refusal to consent to the procedure. One patient with recurrent ICC, who underwent initial surgery at other hospital, was included in this study. Table 1 shows the summary of demographic details collected from the 82 surgically treated patients. Postoperative adjuvant chemotherapy was performed on 46 patients (56.1%). Overall morbidity was found to be 36.6% (n = 30), while

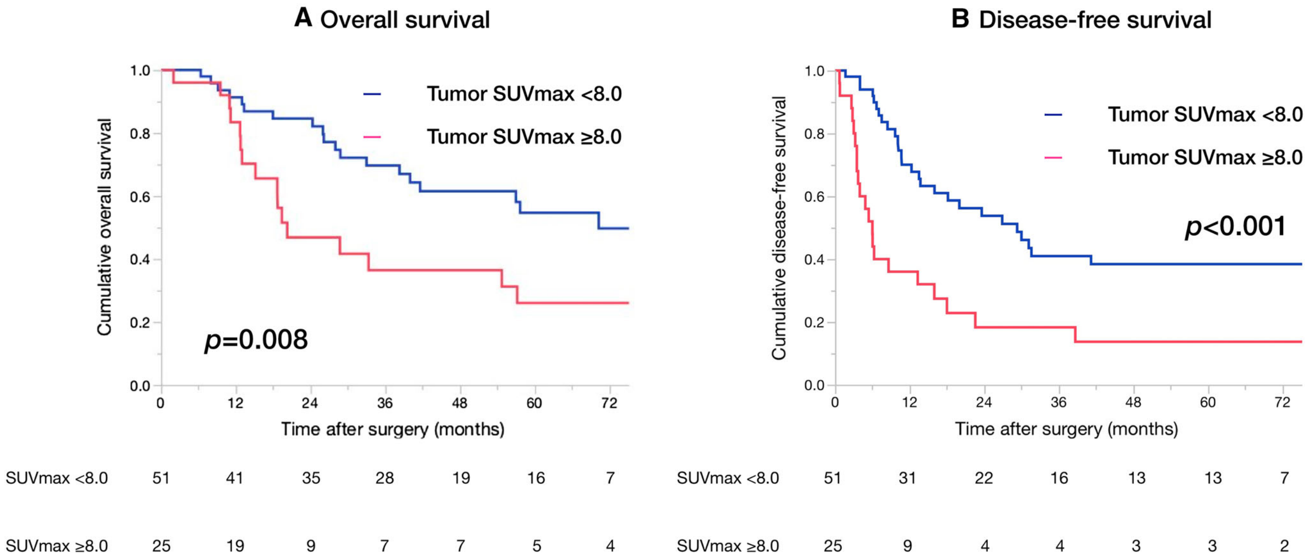

Fig. 3 Overall survival (**a**) and disease-free survival (**b**) of ICC patients after surgery stratified according to the cut-off point of tumor SUVmax at 8.0. *SUVmax* maximum standardized uptake value, *ICC* intrahepatic cholangiocarcinoma

class III/VI morbidity was found to be 17.1% ($n = 14$). Two patients (2.4%) experienced hospital death within 90 days.

Correlations between tumor SUVmax and postoperative tumor factors

The median tumor SUVmax of all 82 patients was found to be 6.15 (range 2.3–22.1). Tumor SUVmax comparison of postoperative tumor factors is shown in Fig. 1. Median tumor SUVmax was higher in large tumor (<5 cm vs. ≥5 cm, $n = 58$ vs. $n = 24$, $p = 0.002$) and multiple tumor (solitary vs. multiple, $n = 62$ vs. $n = 20$, $p = 0.005$). While, median tumor SUVmax did not differ significantly according to the microvascular invasion (no vs. yes, $n = 35$ vs. $n = 47$, $p = 0.445$), biliary invasion (no/minor vs. major, $n = 69$ vs. $n = 13$, $p = 1.000$), tumor differentiation (well/moderate vs. poorly differentiation, $n = 70$ vs. $n = 12$, $p = 0.372$), AJCC T stage (T1 vs. T2–T4, $n = 25$ vs. $n = 57$, $p = 0.636$), and N stage (N0 vs. N1, $n = 48$ vs. $n = 22$, $p = 0.135$).

Correlations between tumor SUVmax and tumor markers

We next evaluated the relationship between tumor SUVmax with carbohydrate antigen 19-9 (CA 19-9) and carcinoembryonic antigen (CEA), which are commonly measured in ICC patients [2, 4, 13]. Figure 2 shows scatter plots between tumor SUVmax and these tumor markers. No significant correlation was found between tumor SUVmax and CA19-9 (Spearman's $\rho = -0.093$ and $p = 0.404$) and CEA levels ($\rho = -0.131$, and $p = 0.243$).

Survival analysis

While performing survival analyses, six patients were excluded: four patients who underwent neoadjuvant chemotherapy, and two patients who experienced surgery-related death within 90 days. The median follow-up time after surgery was 28.8 (range 2.0–109.2) months. Median OS time and 1-, 3-, and 5-year OS rate were 57.0 months and 88.7%, 58.7%, and 44.7%, respectively. Median DFS time and 1-, 3-, and 5-year DFS rate were 16.0 months and 58.7%, 33.5%, and 30.2%, respectively.

We determined the optimal tumor SUVmax cut-off value to better understand its clinical impacts. While using minimum p value approach, the tumor SUVmax cut-off value dividing patients into two groups (high and low tumor SUVmax group) based on the maximum difference in OS was 8.0. The tumor SUVmax < 8.0 was observed in 51 patients, while tumor SUVmax ≥ 8.0 was observed in 25 patients. Figure 3 shows the Kaplan–Meier curve stratified according to the tumor SUVmax cut-off value of 8.0. (Patients backgrounds are shown in Table 2.) High tumor SUVmax group included younger patients (<65 years, $p = 0.004$), larger tumor (≥5 cm, $p < 0.001$), multiple tumor ($p < 0.001$), and postoperative adjuvant chemotherapy ($p = 0.040$) than low tumor SUVmax group. The median OS time and 3- and 5-year OS rates were

Table 2 Patients characteristics according to high and low tumor SUVmax in 76 ICC patients

	Tumor SUVmax ≥ 8 *n* = 25	Tumor SUVmax < 8 *n* = 51	*p* value
Clinical factors			
Age (years)			
<65	13 (52.0%)	10 (19.6%)	0.004*
≥65	12 (48.0%)	41 (80.4%)	
Gender			
Male	13 (52.0%)	33 (64.7%)	0.287
Female	12 (48.0%)	18 (35.3%)	
HBV[a]			
Negative	24 (96.0%)	48 (94.1%)	1.000
Positive	1 (4.0%)	3 (5.9%)	
HCV			
Negative	20 (80.0%)	44 (86.3%)	0.481
Positive	5 (20.0%)	7 (13.7%)	
Postoperative adjuvant chemotherapy			
Yes	18 (72.0%)	24 (47.1%)	0.040*
No	7 (28.0%)	27 (52.9%)	
Postoperative factors			
AJCC T stage			
T1	7 (28.0%)	17 (33.3%)	0.638
T2–T4	18 (72.0%)	34 (66.7%)	
Tumor size			
<5 cm	11 (44.0%)	43 (84.3%)	<0.001*
≥5 cm	14 (56.0%)	8 (15.7%)	
Tumor number			
Solitary	12 (48.0%)	45 (88.2%)	<0.001*
Multiple	13 (52.0%)	6 (11.8%)	
Microvascular invasion			
No	11 (44.0%)	21 (41.2%)	0.815
Yes	14 (56.0%)	30 (58.8%)	
Biliary invasion[a]			
No/minor	22 (88.0%)	44 (86.3%)	1.000
Major	3 (12.0%)	7 (13.7%)	
Differentiation[a]			
Well/moderate	20 (80.0%)	44 (86.3%)	0.481
Poorly	5 (20.0%)	7 (13.7%)	
AJCC N stage[a]			
N0	15 (60.0%)	31 (60.8%)	0.310
N1	8 (32.0%)	10 (19.6%)	
Nx	2 (8.0%)	10 (19.6%)	
Resection margin[a]			
R0	20 (80.0%)	45 (88.2%)	0.489
R1	5 (20.0%)	6 (11.8%)	

ICC intrahepatic cholangiocarcinoma, *SUVmax* maximum standardized uptake value, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *AJCC* American Joint Committee on Cancer, *R0 resection* no macroscopic or microscopic tumor remaining

*Significant difference ($p < 0.05$)

[a]Fisher's exact test; χ^2 test used for all the other analyses

Table 3 Association between recurrence and tumor SUVmax by ^{18}F-FDG-PET/CT in the 48 recurrent ICC patients

	SUVmax ≥ 8 *n* = 21	SUVmax < 8 *n* = 27	*p* value
Pattern of recurrence			
Intrahepatic recurrence	4 (19.0%)	10 (37.0%)	0.174
Systemic recurrence	17 (81.0%)	17 (63.0%)	
Nodal recurrence	6 (28.6%)	6 (22.2%)	0.614
Main treatment variables			
Systemic chemotherapy	19 (90.5%)	21 (77.8%)	0.765[†]
Surgery	1 (4.8%)	3 (11.1%)	
Radiofrequency ablation	0 (0%)	1 (3.7%)	
Palliative therapy	1 (4.8%)	2 (7.4%)	

ICC intrahepatic cholangiocarcinoma, *^{18}F-FDG-PET* ^{18}F-fluorodeoxyglucose-positron emission tomography/computed tomography

[†]Fisher's exact test; χ^2 test used for all the other analyses

significantly stratified at 70.3 months, and 69.7% and 54.7% versus 20.3 months, and 36.4% and 26.0%, low tumor SUVmax versus high tumor SUVmax group, respectively ($p = 0.008$, Fig. 3a); the median DFS time and 1- and 3-year cumulative recurrence rates were significantly stratified at 29.3 months, and 70.0% and 41.0% versus 6.0 months, and 36.0% and 18.3%, respectively ($p < 0.001$, Fig. 3b). During the follow-up period, 48 patients experienced postoperative recurrence (60.3%); 27 patients (52.9%) in the low tumor SUVmax group, and 21 patients (84.0%) in the high tumor SUVmax group. No significant differences were observed with regard to patterns of disease recurrence and treatment variables (Table 3).

Finally, multivariate analyses were performed to assess whether tumor SUVmax could independently predict OS and DFS without being influenced by postoperative factors. Confounders were selected based on the previous studies [3, 4, 11]. Tumor number, tumor size, major biliary invasion, and adjuvant chemotherapy were excluded from this

Table 4 Univariate and multivariate analyses of prognostic factors in the 76 ICC patients after surgery

	Univariate			Multivariate		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Overall survival						
Age (years)						
≥65 versus <65	0.705	0.365–1.394	0.307	–	–	–
Gender						
Male versus female	0.662	0.338–1.291	0.223	–	–	–
Tumor SUVmax						
≥8.0 versus <8.0	2.376	1.216–4.605	0.012*	2.073	1.039–4.097	0.039*
T stage						
T2–T4 versus T1	2.763	1.271–6.903	0.009*	2.670	1.198–6.796	0.015*
N stage						
N1 versus N0/Nx	3.947	1.994–7.781	<0.001*	3.043	1.508–6.132	0.002*
Differentiation						
Poorly versus well/moderate	1.874	0.753–4.055	0.164	–	–	–
Resection margin						
R1 versus R0	1.494	0.600–3.233	0.363	–	–	–
Disease-free survival						
Age (years)						
≥65 versus <65	0.627	0.354–1.136	0.121	–	–	–
Gender						
Male versus female	0.860	0.486–1.542	0.607	–	–	–
Tumor SUVmax						
≥8.0 versus <8.0	2.781	1.548–4.929	<0.001*	3.171	1.749–5.677	<0.001*
T stage						
T2–T4 versus T1	2.425	1.255–5.155	0.007*	2.814	1.442–6.029	0.002*
N stage						
N1 versus N0/Nx	2.282	1.221–4.143	0.011*	–	–	–
Differentiation						
Poorly versus well/moderate	1.924	0.872–3.807	0.100	–	–	–
Resection margin						
R1 versus R0	1.553	0.703–3.074	0.258	–	–	–

Final model after stepwise Cox proportional hazards analysis

ICC intrahepatic cholangiocarcinoma, *N1* positive for nodal metastasis, *N0* negative for nodal metastasis, *Nx* nodal metastasis status undetermined

*Significantly different ($p < 0.05$)

analysis, because of following reasons: (1) These factors were clinically correlated with T stage as postoperative factors, (2) T stage can be the determinant of adjuvant settings rather than individual factors. The results of univariate and multivariate analysis identifying poor prognostic tumor factors for OS and DFS using the Cox hazard model are shown in Table 4. High tumor SUVmax retained its significant adverse effect on OS and DFS ($p = 0.039$ and $p < 0.001$). The advanced T2–T4 disease was (reference, T1 disease) also identified as an independent predictive factor of poor OS and DFS ($p = 0.015$ and $p = 0.002$), while the N1 disease (reference, N0/Nx disease) was identified as an independent predictive factor of poor OS ($p = 0.002$).

Discussion

Preoperative indicators may allow clinicians to estimate prognosis and adopt more effective multidisciplinary therapy. Previously, we reported that high tumor SUVmax by ^{18}F-FDG-PET/CT was associated with poor DFS in patients undergoing surgery for ICC. However, our initial data were reported in the era when there was no adjuvant strategy. To confirm the actual prognostic value of tumor

SUVmax in patients undergoing surgery for ICC, we therefore reappraised its prognostic value. In this setting, the present study highlighted that tumor SUVmax posed a prognostic impact on OS and DFS. Collectively, high tumor SUVmax still represents poor prognosis in patients undergoing surgery for ICC even in the era of multidisciplinary strategy.

Prognostic utility of tumor SUVmax in ICC after surgery has still been limited. The reason for this is the rarity of ICC itself. To the best of our knowledge, this study was the largest sized study which investigated the impact of tumor SUVmax in ICC. We evaluated the relationship between tumor SUVmax and tumor factors and found that tumor number and tumor size were associated with tumor SUVmax. This may be the one reason why tumor SUV max posed a prognostic value. However, multivariate analysis which emphasized T and N stage identified tumor SUVmax as an independent predictor for OS and DFS. We hypothesize that tumor SUVmax may pose a prognostic value reflecting pathological tumor factor and undetermined tumor biology. Besides our data, Jiang et al. [16] demonstrated the significant association between tumor SUVmax, tumor differentiation, and tumor diameter in resected ICC, yet, they did not examine survival analysis. Further, we found that there was no correlation between tumor SUVmax and known prognostic tumor markers. These findings also suggested that the tumor SUVmax can be used as a practical tool predicting the prognosis of patients undergoing surgery for ICC.

This present study proposed a tumor SUVmax cut-off value of 8.0 based on minimum p value approach. As a supportive data, Ma et al. [17] ($n = 32$) proposed the same cut-off value of tumor SUVmax as ours, suggesting reproducibility of our results. Recently we reported that the prognosis of ICC is significantly improved in this decade (i.e., after 2006), possibly due to the adjuvant therapy and advances of treatment after recurrence [5, 9, 10]. Moreover, prospective phase III trial concluded the efficacy of adjuvant chemotherapy for biliary tract cancer [18]. Nevertheless, the prognosis of patients with high tumor SUVmax was still poor. Considering the results that findings at recurrence were similar between the low and high tumor SUVmax groups, focusing on the adjuvant strategy may be rational for the improvement of the outcomes. One candidate of tumor SUVmax use is indication of neoadjuvant therapy. The rational of this hypothesis is that tumor SUVmax can be measured preoperatively as well as objectively unlike the pathological factors. Another candidate is expansion use for postoperative adjuvant chemotherapy (e.g., stronger regimen or expansion of indication criteria), because tumor SUVmax posed independent prognostic value in our series. However, these are still in hypotheses and further study will eventually confirm them.

The main limitation of the present study was its retrospective design, which was conducted in Japanese and single institutional cohort of patients. Certain biases such as the development of modality (e.g., detector arrangement of ^{18}FDG-PET) could not be completely avoided. Secondly, although this study is the largest sized study among the previous reports investigating the prognostic utility of tumor SUVmax for ICC after surgery [6, 16, 17, 19, 20], the statistical approach was still limited. For example, the number of confounders in multivariate analysis was extremely restricted, although the major confounders based on the previous studies [3, 4, 11] were included. Much larger sample sized study allows the prognostic value of tumor SUVmax to be more reliable. Despite these limitations, we believe that this study does provide some significant insights which can help surgeons and clinicians in determining the treatment strategy of patients with ICC.

Conclusion

Even in the era of multidisciplinary strategy, high tumor SUVmax still represents poor prognosis in patients undergoing surgery for ICC. These patients, therefore, would probably require more effective strategies. Further study will eventually confirm our hypothesis.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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