Nucl Med Mol Imaging (2017) 51:69–78
DOI 10.1007/s13139-016-0440-y

ORIGINAL ARTICLE

ISSN (print) 1869-3482
ISSN (online) 1869-3474

The Role of F-18 FDG PET/CT in Intrahepatic Cholangiocarcinoma

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Received: 18 April 2016 / Revised: 20 June 2016 / Accepted: 14 July 2016 / Published online: 6 August 2016

Abstract
Purpose The aim of this study was to evaluate the diagnostic and prognostic role of metabolic parameters of FDG PET/CT in patients with intrahepatic cholangiocarcinoma (ICC).
Methods From December 2008 to December 2013, 76 FDG PET/CT scans performed for initial staging of ICC in a single institution (57 male and 19 female; mean age 68 ± 9 years) were retrospectively reviewed. Patients with history of other known malignancy were excluded. Detection rates of regional lymph node and distant metastasis by FDG PET/CT were analyzed in comparison with conventional imaging modalities such as CT or MRI. Metabolic parameters including maximum, peak and mean standardized uptake values (SUVmax, SUVpeak, SUVmean), metabolic tumor volume (MTV), total lesion glycolysis (TLG), glucose corrected SUV (SUVgluc), and glucose corrected TLG (TLGgluc) were measured for the primary tumor. Cut-off values for the metabolic parameters were calculated by ROC curve analysis, and used to dichotomize the patient groups. The overall survival time (OS) was calculated and compared using the Cox proportional hazard regression analysis.
Results The median duration of follow-up period was 5.4 months (interquartile range: 1.45~15.45). FDG PET/CT showed higher sensitivity than conventional imaging modalities in detection of regional node involvement (74.5 % vs. 61.8 %, $p = 0.013$). In six patients, distant metastasis was identified only by FDG PET/CT. The mean SUVmax, SUVpeak, SUVmean, MTV, and TLG for the primary tumor were 8.2 ± 3.1, 6.8 ± 2.5, 4.0 ± 0.8, 192.7 ± 360.5 cm^3, and 823.7 ± 1615.4, respectively. Patients with higher (≥7.3, HR: 4.280, $p = 0.001$), higher SUVpeak (≥6.5, HR: 2.333, $p = 0.020$), higher SUVmean (≥3.9, HR: 2.799, $p = 0.004$), higher SUVgluc (≥8.1, HR: 2.648, $p = 0.012$), and higher TLGgluc (≥431.6, HR: 2.186, $p = 0.030$) showed significantly shorter survival time. By multivariate study, operability was an independent prognostic factor for longer survival (HR: 4.113, $p = 0.005$).
Conclusion FDG PET/CT is an important diagnostic imaging tool in the nodal staging and detection of distant metastasis in ICC patients. Metabolic parameters may have a significant role as prognostic factors in patients with ICC.

Keywords Cholangiocarcinoma · Intrahepatic Cholangiocarcinoma · Positron-Emission Tomography · Prognosis · SUVmax

Introduction

Cholangiocarcinoma is the second most common primary hepatic cancer, following hepatocellular carcinoma, and it accounts for 3 % of all gastrointestinal cancers [1]. The majority of cholangiocarcinomas are extrahepatic types. About 60-70 % of tumors arise at the bifurcation site of the hepatic ducts and they are called Klatskin tumors, and 20-30 % of tumors arise in the distal common bile duct. The remaining 5-10 % of cholangiocarcionomas arise in intrahepatic ducts of the liver, and are classified as intrahepatic cholangiocarcinoma (ICC).

There is geographic and ethnic variation among incidence rates of ICC, and Asians are twice as affected by the disease than whites and blacks [2]. Even though the incidence of ICC is relatively low, the global age-adjusted mortality rate of ICC has increased for decades [3–6]. Most of ICC patients (90 %)

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die within two years after initial diagnosis [2]. The reasons for high mortality rate include late clinical presentation, difficulty for early diagnosis, concomitant fatal complications, and lack of effective nonsurgical therapy for the advanced stages. Fewer than one-third of cholangiocarcinoma patients have resectable tumor at initial diagnosis. Besides, even for the resectable stages, 5-year survival rate is reported as low as 22 to 44 % [7].

Known factors related to overall survival for patients with ICC include tumor size, number of tumor, positivity for lymph node metastasis, and vascular invasion [8]. Distant metastasis including peritoneal seeding is known to be contraindication to surgical resection, which is unfortunately present in about 10-20 % of the patients at first clinical presentation. Thus, detection of the locoregional lymph node or distant metastasis is crucial in deciding surgical candidates, and guide therapy to avoid redundant surgery.

In malignancy of biliary origin, it is well known that F-18 fludeoxyglucose PET/CT has a major influence on clinical decision-making by detecting occult metastasis or characterizing indeterminate lesion [9–13]. However, limited data is available on the role of PET/CT in patients with ICC when compared to conventional image studies (CIS) such as abdominal computed tomography (CT) [14] or magnetic resonance imaging (MRI) [15]. And little is known about the prognostic value of FDG PET parameters. This study aimed to evaluate the diagnostic role of PET/CT in ICC patients in comparison to CIS for nodal and distant metastasis. In addition, we evaluated the relationship between metabolic parameters of the primary tumor and overall survival in patients with ICC.

Material and Methods

Patient Population

The medical records of primary ICC patients from a single institution between December 2008 and December 2013 were retrospectively reviewed. Inclusion criteria were: primary intrahepatic cholangiocarcinoma patient, availability of pretreatment PET/CT and availability of further follow-up. Exclusion criteria were: history of prior malignancy, extrahepatic cholangiocarcinoma, intrahepatic neuroendocrine carcinoma, and no initial PET/CT. For analysis of diagnostic performance of PET/CT, patients were included only if they underwent abdominal CT or MRI within 2 weeks from the PET/CT exam. For lymph node status comparison between PET/CT and CIS, patients without pathologic result or without sufficient follow-up at least one year were all excluded. The initial TNM stage was based on intrahepatic bile duct staging of the 7th edition of American Joint Committee on Cancer (AJCC) staging guidelines. Institutional review board of this hospital approved our study, and informed consent was waived due to retrospective study design.

F-18 FDG PET/CT Scan

At least 6 hours of fasting was kept in all patients before the PET/CT exam. The injected ^{18}F-FDG was approximately 0.14 mCi/Kg, and images were obtained after 60 minutes. No intravenous contrast was administered. Combined PET/CT inline systems, either Biograph Duo or Biograph True Point (Siemens Medical Solutions, Knoxville, TN) were used in our study. The acquisition time was about 2~3 min per bed position. CT images were acquired from orbitomeatal line to upper thigh (120 kVp, 80 mAs, 5 mm slice thickness; 130 kVp, 80 mA, 5 mm slice thickness), followed by PET scan over the same body region. CT images were used for attenuation correction. Images were reconstructed using an iterative reconstruction algorithm, called ordered subset expectation maximization (OSEM). The axial spatial resolution was 4.5 mm or 6.5 mm at the center of the field of view.

Image Interpretation and Data Analysis

All PET/CT images were assessed with automatic rigid transformation software (Mirada XD3, Mirada Medical, Oxford, UK) by consensus of two experienced nuclear medicine physicians. From the PET/CT images, lymph nodes were classified as either positive or negative for metastasis by visual assessment. FDG uptake in the lymph node that is greater than background activity was considered positive. In CIS, metastatic lymph nodes were defined as nodes that are larger than 10.0 mm in size or showing delayed enhancement pattern with or without central necrosis. Histopathology confirmation or a combination of clinical and imaging follow-up was taken as reference standard for lymph node metastasis. Distant metastasis status was evaluated on FDG PET/CT also by visual assessment, comparing against the background activity, and the sites of metastatic tumor were recorded for each patient. Confirmation of distant metastasis was made either by biopsy or further image follow-up.

Semiquantitative analysis was made from the primary tumor by manually drawing a spherical volume of interest (VOI). Metabolic parameters such as maximum standardized uptake value (SUVmax), peak standardized uptake value (SUVpeak), and mean standardized uptake value (SUVmean) were recorded for the primary tumor. Metabolic tumor volume (MTV) was computed by using threshold SUV of 2.5 with the automated software. Total lesion glycolysis (TLG), which is defined as MTV multiplied by the SUVmean, was also computed using the threshold SUV of 2.5. SUVmax corrected by the blood glucose level (SUVgluc = SUVmax x blood glucose level/100) was measured for primary tumor in order to cancel out the perturbing

factor of increased blood glucose level. Correction by the glucose level was also performed in TLG and recorded for the primary tumor as well (TLGgluc = TLG x blood glucose level/100).

Statistical Analysis

Sensitivity and specificity were calculated for detection of metastatic lymph nodes. Diagnostic performance of each imaging modality was compared using the McNemar test. Case-based analysis was made for distant metastasis.

To evaluate the prognostic value of PET/CT exam, confirmed disease-related death was counted for survival analysis. The optimal cut-off values were calculated by receiver operating characteristics (ROC) curves using Youden index, and were used to dichotomize the patients. Overall survival time (OS) was defined as the time from initial PET/CT imaging to the date of death from any cause or the date of last clinical follow-up. Survival curves were analyzed for each parameter using the Kaplan-Meier method. Univariate and multivariate analyses were made using Cox proportional hazards model. Multivariate analysis was performed with variables that showed statistical significance in the univariate analysis. A p-value of <0.05 was considered statistically significant. Statistical Package for Social Science (SPSS) software (version 19.0) and MedCalc (version 16.1) were used for statistical analysis.

Results

Patient Characteristics

A total of 76 ICC patients were enrolled in our study. The study group was composed of 57 male (75.0 %) and 19 female (25.0 %) with mean age of 68.0 ± 9 (range 48-90 years). All patients included in this study were diagnosed with adenocarcinoma, including nine TNM stage I (11.8 %), four stage II (5.2 %), three stage III (3.9 %), and 60 stage IV (78.9 %). Mean primary tumor size was 6.4 ± 3.3. Primary tumors of 23 patients were Tis or T1, while those of 53 patients were T2, T3 or T4. According to pathologic reports, moderately differentiated primary tumors were most common (59/76, 77.6 %). Morphologic types of the primary tumors were 71 mass-forming type (93.4 %), four intraductal growing type (5.3 %) and one periductal infiltrating type (1.3 %), respectively. Positive cases for lymph node metastasis at initial diagnosis were 50 (65.8 %) and negative cases for lymph node metastasis were 26 (34.2 %). For mean laboratory values were as follows: carbohydrate antigen 19-9 (CA 19-9) level, 5056.1 ± 20499.0 U/ml (range: 1.9~131000.0); total bilirubin, 1.6± 2.6 (0.3~13.2); aspartate aminotransferase (AST), 50.9 ± 35.0 U/L (12.0~190.0); alanine aminotransferase (ALT), 55.3 ± 61.7 U/L (9.0~341.0); and blood glucose level, 114.4 ± 23.5 (83.0~195.0).

Table 1 Characteristics of the patients (n = 76)

Characteristic	Value
Total number	76
Male	57 (75.0 %)
Female	19 (25.0 %)
Age, year	68 ± 9 (range: 48-90)
Primary tumor	
Size	6.4 ± 3.3
< 5 cm	23 (30.3 %)
≥ 5 cm	53 (69.7 %)
T stage	
Tis or T1	23 (30.3 %)
T2 ~ T4	53 (69.7 %)
Tumor differentiation	
Well differentiated	1 (1.3 %)
Moderately differentiated	59 (77.6 %)
Poorly differentiated	12 (15.8 %)
Unknown	4 (5.3 %)
Morphologic type	
Mass forming	71 (93.4 %)
Intraductal growing	4 (5.3 %)
Periductal infiltrating	1 (1.3 %)
Lymph node status	
Positive for metastasis	50 (65.8 %)
Negative for metastasis	26 (34.2 %)
Clinical TNM stage	
I	9 (11.8 %)
II	4 (5.2 %)
III	3 (3.9 %)
IV	60 (78.9 %)
Lab data	
CA 19-9, U/mL (range)	5056.1 ± 20499.0 (1.9 ~ 131000.0)
Total bilirubin, mg/dL (range)	1.6 ± 2.6 (0.3 ~ 13.2)
AST/ALT U/L (range)	50.9 ± 35.0 (12.0 ~ 190.0) / 55.3 ± 61.7 (9.0 ~ 341.0)
Blood glucose level	114.4 ± 23.5 (range: 83.0 ~ 195.0)
Treatment	
Surgical	10 (13.1 %)
Chemotherapy	23 (30.3 %)
Surgery + adjuvant chemotherapy	17 (22.4 %)
No therapy	26 (34.2 %)
Prognosis	
Disease related death	32 (42.1 %)
Censored	44 (57.9 %)

Of all 76 patients, 27 had surgery, and 40 patients were treated by chemotherapy; 17 patients were treated by both

Table 2 Case-based diagnostic accuracy of PET/CT and CIS for detection of lymph node metastasis

		PET/CT		CIS[a]		Total	*p* value
		Positive	Negative	Positive	Negative		
LN metastasis	Positive	41	14	31	24	55	
	Negative	1	9	0	10	10	
Sensitivity (%)		74.5		61.8			0.013*
Specificity (%)		90.0		100			1.000
Accuracy (%)		76.9		63.1			N/A[b]

[a] CIS (Conventional imaging studies)

[b] Not applicable

* Statistically significant

surgery and adjuvant chemotherapy. No identifiable therapy was performed in 26 patients. The median duration of follow-up period was 5.4 months (interquartile range: 1.45~15.45). Thirty two patients showed disease related death during the study period, and data of the other 44 patients were interpreted as censored. The median overall survival time was 14.0 months. Details about patient characteristics are summarized in Table 1.

Comparison of the lymph node staging by PET/CT and CIS was available in 65 patients, because 11 patients did not have pathologic results or sufficient follow-up of at least one year. Prognosis was evaluated in all 76 enrolled patients.

Lymph Node and Distant Metastasis

All included patients (n = 65) were evaluated by CIS such as enhanced abdominal CT from lung base to pelvis or abdominal MRI within 2 weeks of PET/CT study. CIS did not include chest CT which was not available in all included patients.

Based on the reference standard, lymph nodes (LNs) of 55 patients were positive for metastasis. LN metastasis was confirmed by pathologic result in 16 patients, and by imaging and clinical follow-up in the other 39 patients. And 41 patients out of these 55 showed positive lymph node uptake on PET/CT while only 31 patients showed positive findings in CIS. Regarding lymph node staging, 50 patients had concordant results on both PET/CT and CIS (PET/CT+ and CIS+: 29 and PET/CT- and CIS-: 21) while 15 patients had discordant results (PET/CT+ but CIS-: 13, PET/CT- but CIS+: 2). The PET/CT showed significantly higher sensitivity of 74.5 % (41/55) in detecting metastatic lymph node when compared to 61.8 % (31/55) of CIS ($p = 0.013$). Specificity in metastatic lymph node diagnosis was 90.0 % (9/10) for PET/CT, and 100 % (10/10) for CIS ($p = 1.000$) (Table 2).

Of 76 patients, 32 had distant metastasis at the time of evaluation. Peritoneal carcinomatosis (9/32, 28.1 %) was the most common form of distant metastasis in this study population. Out of these 32 metastatic cases, six were identified only by PET/CT and their metastatic sites were as follows; supraclavicular lymph node (n = 2), pancreas (n = 1), internal mammary chain (n = 1), lung (n = 1), and bone (n = 1). There was alteration in the therapeutic plan in these six patients. Planned surgery was canceled and converted to systemic chemotherapy in two patients. Palliative operation followed by systemic chemotherapy was performed in two patients. One patient refused further treatment, and one patient received conservative care only. Results for distant metastasis based on lesion and followed treatment are summarized in Table 3.

Prognostic Value

The mean SUVmax, SUVpeak, SUVmean, MTV, TLG, SUVgluc, and TLGgluc for the primary tumor were 8.2 ± 3.1

Table 3 Distant metastatic sites only detected by PET/CT and followed treatment

Patient no.	Sites of distant metastasis	SUVmax of metastatic lesion	Treatment change
4	Left supraclavicular lymph node	4.8	Op. → palliative CTx. and CCRTx.
14	Pancreatic head	5.6	Op. → CTx.
28	Left supraclavicular lymph node	2.3	Patient refused
31	Right internal mammary chain	6.7	Op. → CTx.
	Pericardial fat pad	3.2	
49	Lung	2.2	Op. → palliative CTx.
57	Bone, multiple sites	4.5 (left iliac bone)	Op. → conservative care

Table 4 Metabolic parameters of primary tumor

	Parameters	Mean ± SD[a] (range)	Optimal cutoff value	AUC (95 % CI[b])
Primary tumor (n = 76)	SUVmax	8.2 ± 3.1 (2.1 ~ 16.9)	7.3	0.587 (0.469 ~ 0.697)
	SUVpeak	6.8 ± 2.5 (1.8 ~ 13.8)	6.9	0.587 (0.470 ~ 0.698)
	SUVmean	4.0 ± 0.8 (1.6 ~ 6.2)	3.9	0.641 (0.524 ~ 0.747)
	MTV (cm^3)	192.7 ± 360.5 (0.4 ~ 2495.5)	263.6	0.514 (0.398 ~ 0.629)
	TLG	823.7 ± 1615.4 (1.1 ~ 11479.3)	344.6	0.523 (0.407 ~ 0.638)
	SUVgluc	9.3 ± 3.6 (2.2 ~ 20.9)	8.1	0.584 (0.465 ~ 0.696)
	TLGgluc	912.6 ± 1813.0 (1.3 ~ 12397.6)	431.6	0.528 (0.410 ~ 0.643)

[a] Standard deviation; [b] Confidence interval

(range: 2.1~16.9), 6.8 ± 2.5 (1.8~13.8), 4.0 ± 0.8 (1.6~6.2), 192.7 ± 360.5 cm^3 (0.4~2495.5 cm^3), 823.7 ± 1615.4 (1.1~11479.3), 9.3 ± 3.6 (2.2~20.9), and 912.6 ± 1813.0 (1.3~12397.6), respectively. The optimal cutoff values and Area Under Curve (AUC) are summarized in Table 4. The 76 patients were dichotomized by the cutoff values of each metabolic parameter.

According to the univariate analysis, patients with larger tumor size (≥5.0 cm, hazard ratio [HR]: 2.131, $p = 0.046$), higher T stage (T2-T4 vs Tis/T1, HR: 2.434, $p = 0.044$), lymph node status (positive for metastasis, HR: 2.402, $p = 0.030$), clinical stage (advanced stage of III and IV, HR: 7.000, $p = 0.003$) and operability (non-operable, HR: 3.964, $p < 0.001$) showed significantly shorter OS. For metabolic parameters of primary tumor, higher SUVmax (≥7.3, HR: 4.280, $p = 0.001$), higher SUVpeak (≥6.5, HR: 2.333, $p = 0.020$), higher SUVmean (≥3.9, HR: 2.799, $p = 0.004$), higher SUVgluc (≥8.1, HR: 2.648, $p = 0.012$) and higher TLGgluc (≥431.6, HR: 2.186, $p = 0.030$) showed significantly shorter OS (Fig. 1). Age, sex, histologic grade, morphologic type, MTV, TLG, lab data such as CA 19-9, total bilirubin, and γ-glutamyl transpeptidase (γ-GTP) did not demonstrate statistically significant prognosis. On multivariate analysis, non-operability was a unique independent prognostic factor for shorter survival (HR: 4.113, $p = 0.005$) (Table 5).

Discussion

According to the latest National Comprehensive Cancer Network (NCCN) guideline published in 2015, the treatment plan for intrahepatic cholangiocarcinoma greatly depends on surgical resectability of the primary tumor [14]. The NCCN guideline recommends that initial exploration should evaluate for multifocal hepatic lesions, lymph node metastases, and distant metastasis. Metastasis of lymph node beyond porta hepatis or any single metastasis in liver is considered as distant metastasis, which is contraindication for surgery. Thorough investigation including abdominal CT, MRI, and tumor markers needs to be done for initial work-up in ICC [16].

In our study, overall sensitivity and specificity of PET/CT in node detection were 74.5 % and 90.0 %, respectively. Sensitivity of PET/CT was statistically superior to that of CIS (74.5 % vs 61.8 %, $p = 0.013$). Many other studies reported the importance of accurate lymph node staging, since it is strongly associated with the prognosis of ICC patients [17–20]. However, detection of metastatic lymph node solely by CIS is challenging since positivity depends mostly on the size and shape [21]. Although Kluge et al. reported in 2001 that FDG PET showed low sensitivity of 13 % in evaluation of regional lymph node metastasis for cholangiocarcinoma [22], low diagnostic performance of PET was probably related to lack of anatomic information which now is routinely provided by the fusion of PET with CT. Using PET/CT, Park et al. reported comparable sensitivity (80.0 %) and specificity (92.3 %) with our results, in detection of metastatic regional lymph nodes in peripheral type of ICC [23].

Our result proved the advantage of PET/CT as a whole-body imaging modality in detecting distant metastasis. In our study, six cases of unsuspected distant metastasis were identified only by PET/CT, followed by proper management such as systemic chemotherapy instead of redundant surgical intervention (Fig. 2). Considering the total number of distant metastases cases, therapeutic plan alteration was possible in 18.2 % (6/33) of the patients owing to PET/CT findings. Usefulness of PET/CT in detecting unsuspected distant metastasis was already reported by previous study in both hilar and peripheral type of ICC [24, 25]. Many other studies supported our result that PET/CT at the time of diagnosis is crucial in oncological management in cholangiocarcinoma patients [22, 26–28].

In ICC patients, survival is closely related to curability [29, 30], and our study demonstrated accordant result that operability at the time of diagnosis was an independent prognostic factor for overall survival. Tumor size, T stage, and lymph node metastasis were also proved by our study as significant prognostic factors in overall survival. We additionally

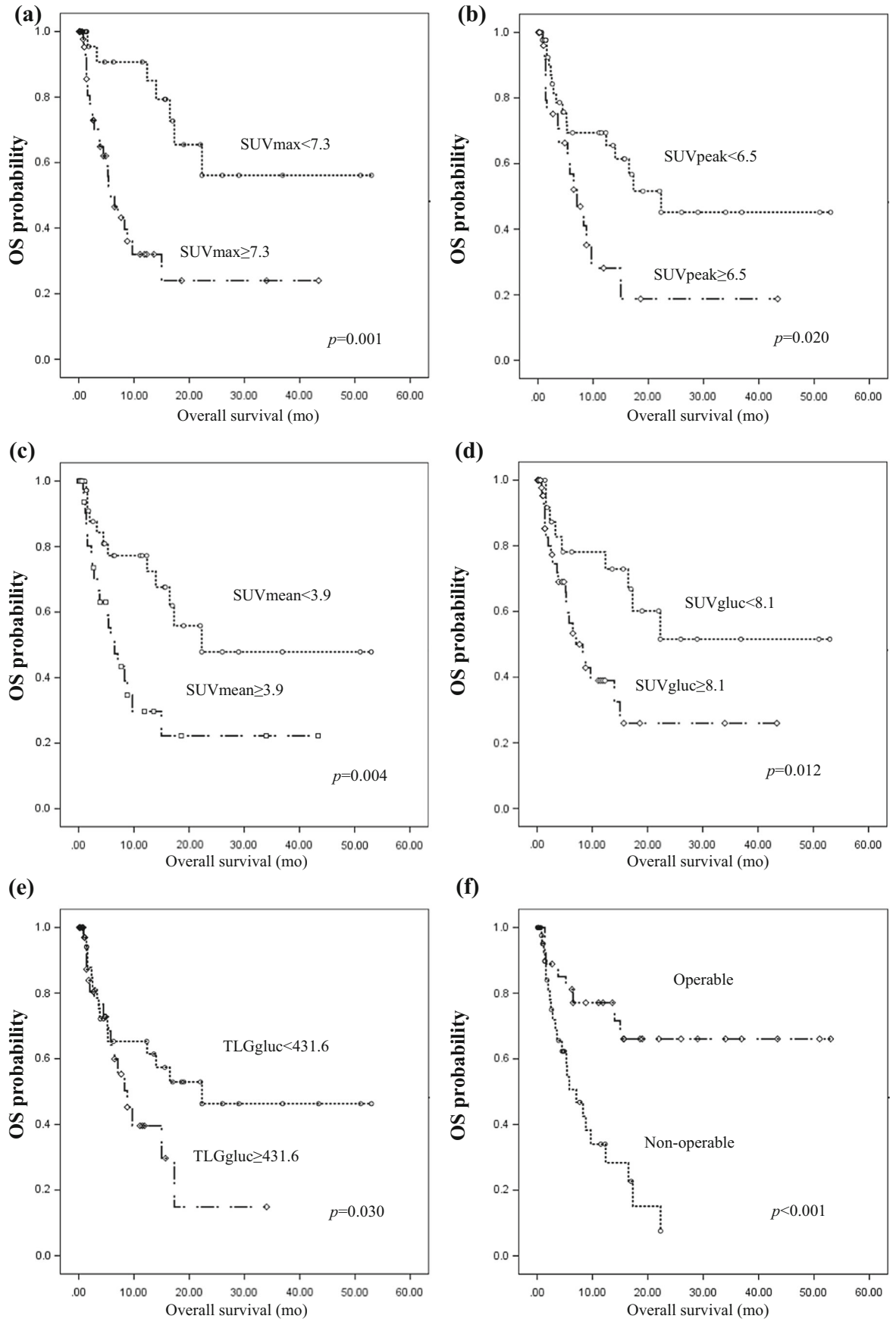

Fig. 1 Kaplan-Meier curves for OS probabilities for (a) SUVmax, (b) SUVpeak, (c) SUVmean, (d) SUVgluc, (e) TLGgluc, and (f) operability

Table 5 Cox proportional hazard regression analysis of factors associated with overall survival of intrahepatic cholangiocarcinoma

Variable		Univariate analysis			Multivariate analysis		
		HR[a]	95 % CI[b]	*p* value	HR	95 % CI	*p* value
Age (yr)	≥67 vs. < 67	1.020	0.498-2.090	0.956			
Sex	male vs. female	1.387	0.653-2.949	0.395			
Primary tumor size (cm)	≥5 vs. < 5	2.131	1.000-4.551	**0.046***	1.215	0.481-3.069	0.681
T stage	Tis/T1 vs. T2-T4	2.434	1.000-5.948	**0.044***	1.335	0.493-3.613	0.570
Histologic grade	WD[c]/MD[d] vs. PD[e]	1.694	0.727-3.947	0.245			
Morphologic type	mass forming vs. non-mass forming[f]	3.294	0.445-24.396	0.243			
Lymph node metastasis	positive vs. negative	2.402	1.063-5.429	**0.030***	1.206	0.456-3.192	0.706
AJCC[g] stage	advanced (III/IV) vs. early (I/II)	7.000	1.641-29.869	**0.003***	2.852	0.436-18.661	0.274
Operability	Non-operable vs. operable	3.964	1.748-8.991	**<0.001***	4.113	1.527-11.079	**0.005***
CA 19-9 (U/mL)	≥36.1 vs. <36.1	1.467	0.722-2.979	0.287			
Total bilirubin, (mg/dL)	≥1.58 vs. <1.58	1.717	0.703-4.198	0.230			
γ-GTP (U/L)	≥85 vs. <85	1.326	0.626-2.810	0.460			
Primary tumor							
SUVmax	≥7.3 vs. <7.3	4.280	1.782-10.280	**0.001***	4.018	0.834-19.358	0.083
SUVpeak	≥6.5 vs. <6.5	2.333	1.145-4.756	**0.020***	1.289	0.309-5.369	0.727
SUVmean	≥3.9 vs. <3.9	2.799	1.348-5.811	**0.004***	1.697	0.419-6.866	0.458
MTV	≥263.6 vs. <263.6	2.131	0.903-5.030	0.077			
TLG	≥344.6 vs. <344.6	1.860	0.915-3.784	0.082			
SUVgluc	≥8.1 vs. <8.1	2.648	1.187-5.904	**0.012**	1.159	0.301-4.472	0.830
TLGgluc	≥431.6 vs. <431.6	2.186	1.062-4.500	**0.030**	1.136	0.404-3.192	1.136

[a] Hazard ratio; [b] Confidence interval;

[c] Well differentiated; [d] Moderately differentiated; [e] Poorly differentiated;

[f] Intraductal growing and periductal infiltrating type;

[g] American Joint Committee on Cancer

* Statistically significant

demonstrated that higher SUVmax, SUVpeak, and SUVmean of primary tumor were significantly correlated with poorer OS. Glucose corrected metabolic parameters such as SUVgluc and TLGgluc of primary tumor were also

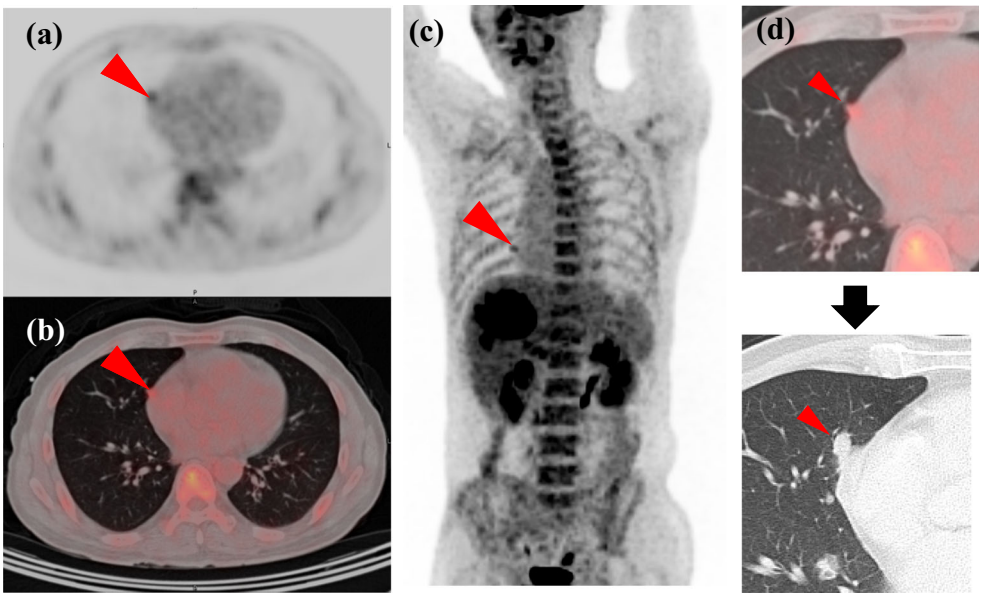

Fig. 2 Initial PET/CT exam of a 51 year-old male with primary ICC in right hepatic lobe. Additional focal FDG uptake (SUVmax: 2.3) is seen in the medial segment of right middle lobe of lung, and the patient is upstaged from stage II to stage IVb. The small FDG-avid lung nodule showed increased size after 2 months on follow-up lung CT, suggesting progression of metastasis. (a) PET, (b) PET/CT fusion, and (c) maximal intensity projection images show a small FDG-avid lung nodule at staging; (d) follow-up CT shows progression of the metastatic nodule

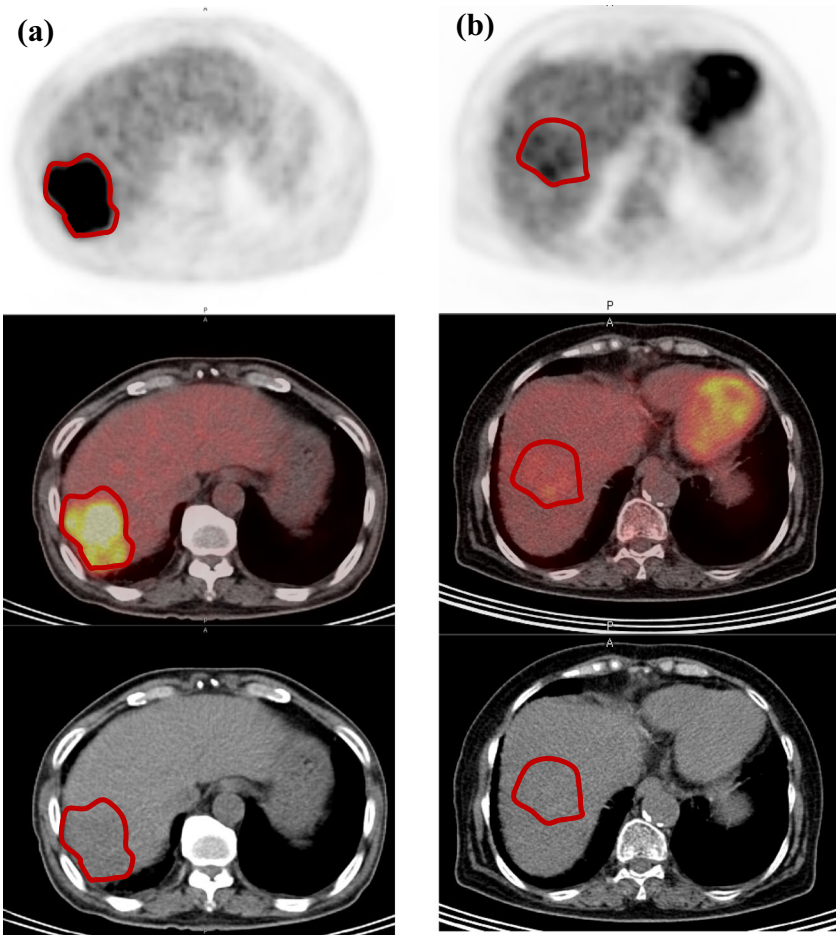

Fig. 3 Different prognosis according to different PET parameters; (a) A 72 year-old male (stage III) with primary tumor of high metabolic parameters (SUVmax: 9.9, SUVmean: 5.0, SUVpeak: 9.1, SUVgluc: 15.7, TLGgluc: 900.7) showed overall survival of 1.6 months; (b) A 83 year-old female of higher stage IV but with primary tumor of low metabolic parameters (SUVmax: 4.1, SUVmean: 2.9, SUVpeak: 3.7, SUVgluc: 4.3, TLGgluc: 142.7) showed longer overall survival of 16.5 months. Red outline is border of tumor margin

significantly correlated with OS (Fig. 3). There were many trials to demonstrate the prognostic roles of PET/CT in biliary cancer [9, 10, 12, 22, 24, 26–28, 31], but few studies looked exclusively at ICC patients. Our study covered 76 ICC patients, which outnumbers other similar studies.

Cho et al. reported that there was no difference in overall survival of ICC patients according to SUVmax, which is contrary to our result [32]. They measured both primary and metastatic lesions that showed increased FDG uptake. We solely measured metabolic parameters of the primary tumor excluding any metastatic lesion, which may affect different survival outcome. Second, different patient population may be attributable for different result. Also, they used cut-off value of 7.5 for SUVmax of ICC which was a lack of statistical significance ($p = 0.695$). This may have led to little association of SUVmax and overall survival in ICC, while significant association was found between SUVmax and OS in other hepatobiliary malignancy.

In our study, histologic grade of the primary tumor showed no correlation with OS, which is probably due to a relatively larger number of moderately differentiated type (77.6 %) than others including well differentiated (1.3 %), poorly differentiated type (15.8 %), and unknown (5.3 %). Similar interpretation would be possible for the morphologic type of the primary tumor since mass forming type (93.4 %) outnumbers other intraductal growing (5.3 %) and periductal infiltrating types (1.3 %). More reliable statistical comparison would be made with similar numbers in each divided group, after securing larger patient population. Laboratory data such as tumor marker (CA 19-9), total bilirubin level, and γ-GTP at the time of diagnosis were not proved to be significant prognostic factors as well which corresponds to previous study result performed in hepatobiliary cancer [32]. However, further study needs to verify laboratory data using time serial methods such as doubling time of tumor marker that may reflect tumor progression.

Although there was growing evidence that PET parameters representing tumor burden, such as MTV and TLG, are closely related to prognosis in head and neck cancer [33] and lung cancer [34], our study of ICC showed no significant correlation between metabolic tumor burden and the overall survival. However, glucose corrected TLG (TLGgluc) was demonstrated as a significant prognostic factor in univariate analysis that implies possible blood glucose effect in SUV measurement. Actually, optimal cut-off values for TLG moved from 344.6 to 431.6 after blood glucose based correction, which might explain different results in survival outcome according to TLG and TLGgluc. Further investigations in larger population or

prospective study needs to be performed to identify suitable cut-off in regards to tumor burden parameters in ICC patients.

There are a few limitations in our study. First, most ICC patients present with advanced status with relatively low operability at the time of diagnosis, and this disproportionate patient population might hinder precise prediction of prognosis. Many patients of advanced stages were transferred to other hospitals or convalescent hospitals and their data were regarded as censored. Out of 49 inoperable ICC patients that accounted for more than half of the advanced status population, 26 denied chemotherapy and followed-up visit. They were expected to expire sooner or later in other hospitals or at their home, but the exact survival data could not be identified. It may serve as bias in statistics. Second, various kinds of chemotherapy regimen were tried even for those who received palliative therapy. Further analysis for each chemotherapy regimen group needs to be performed if larger ICC patient population is warranted. These intrinsic limitations exist because our result is from a single center study with retrospective design. In the future, sharing big data of patients with nationwide hospitals or prospective multicenter study with larger number of patients is required for validation of the full diagnostic and prognostic role of PET/CT in ICC.

Conclusion

PET/CT is useful in nodal staging with higher sensitivity than CIS in intrahepatic cholangiocarcinoma patients. PET/CT is also advantageous in detecting unexpected distant metastasis with an impact on clinical management. SUV parameters of the primary tumor are associated with overall survival, and operability is an independent prognostic factor in ICC patients.

Compliance with Ethical Standards This study was not funded.

Conflict of Interest Yeongjoo Lee, Ie Ryung Yoo, Sun Ha Boo, Hyoungwoo Kim, Hye Lim Park, and Joo Hyun O declare that they have no conflict of interest.

Ethical Statement The study was approved by an institutional review board or equivalent and has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The institutional review board waived the need to obtain informed consent.

Ethical Approvement This article does not contain any studies with human participants or animals performed by any of the authors.

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