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ORIGINAL ARTICLE

Prognostic value of ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography in patients with combined hepatocellular-cholangiocarcinoma

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Abstract

Purpose The prognostic value of pretreatment ^{18}F-fluorodeoxyglucose positron emission tomography with computed tomography (FDG PET/CT) was assessed in patients with combined hepatocellular-cholangiocarcinoma (cHCC-CC).

Methods A total of 46 patients with cHCC-CC who underwent FDG PET/CT before treatment were retrospectively analysed. Tumour FDG avidity was measured in terms of the tumour-to-normal liver standardized uptake value ratio (TLR) of the primary tumour on FDG PET/CT. The prognostic significance of TLR using the median value of 3.4 as the cut-off value and other clinical variables was assessed using Cox proportional hazards regression models. Differences in progression-free survival (PFS) and overall survival (OS) in relation to TLR were examined by the Kaplan-Meier method.

Results During a median follow-up period of 29 months, 29 patients (63.0%) showed tumour recurrence or progression, and 25 patients (54.4%) died from cancer. Higher TLRs (>3.4) were associated with larger tumour size ($p = 0.007$) and higher tumour stage ($p = 0.030$). In a univariable analysis, TLR, tumour stage and CEA were significant prognostic predictors. In a multivariable analysis, TLR was an independent predictor of PFS (HR 5.19, 95% CI 1.80–15.01; $p = 0.002$) and OS (HR 3.95, 95% CI 1.27–12.24; $p = 0.017$). Patients with a higher TLR showed significantly worse PFS (2-year survival rate 17.8% vs. 62.9%; $p = 0.001$) and OS (2-year survival rate, 39.1% vs. 77.3%; $p = 0.001$) than those with a lower TLR.

Conclusion Pretreatment TLR of the primary tumour measured on FDG PET/CT is an independent predictor of survival in patients with cHCC-CC.

Keywords FDG PET/CT · Combined hepatocellular-cholangiocarcinoma · Standardized uptake value · Prognosis

Introduction

Combined hepatocellular-cholangiocarcinoma (cHCC-CC) is an uncommon type of primary hepatic malignancy. The reported incidence of this tumour varies between 0.4% and 4.7% [1, 2]. The disease was first described in 1949 [3] and the World Health Organization (WHO) defined it as the intimate intermingling of hepatocellular carcinoma (HCC) and cholangiocarcinoma (CC) in 2010 [4–6]. Some researchers have suggested that cHCC-CC may be derived from hepatic progenitor cells with the potential to differentiate into both hepatocytic and cholangiocytic lineages. cHCC-CC clearly represents a distinct subtype of primary liver carcinoma [6, 7].

Although little is known about the prognosis of cHCC-CC due to the relative rarity of this tumour type, a few studies have demonstrated that it tends to present with more aggressive behaviour and has a poorer prognosis than either HCC or CC. Overall cHCC-CC has a significantly poorer outcome than HCC and CC even after attempted curative resection [2, 8, 9]. Various prognostic factors including tumour size, tumour stage and lymph node involvement have been investigated in different studies but remain controversial [10–13].

It is well known that ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) is useful for evaluating patients with HCC or CC. Moreover, FDG uptake in the primary tumour has been shown

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to provide prognostic information beyond that offered by tumour stage [14–20]. Because of the rarity and resultant small sample size, no study has investigated the prognostic value of FDG PET/CT in patients with cHCC-CC. The aim of this retrospective cohort study was to evaluate the role of tumour FDG avidity on PET/CT in predicting the prognosis in patients with cHCC-CC.

Materials and methods

Study population

We retrospectively reviewed patients who underwent FDG PET/CT for newly diagnosed primary liver carcinoma at our institution between January 2006 and August 2018. From among these patients, 46 with cHCC-CC pathologically confirmed by either surgical resection ($n = 35$) or core biopsy ($n = 11$) were included in this study. All specimens were examined by experienced pathologists using immunohistochemical stains, and the pathological diagnosis was in accordance with 2010 WHO classification. Clinical information was retrospectively obtained from our hospital information system. Pretreatment laboratory data including serum tumour markers and serological examinations were performed within 1 week of the baseline PET/CT examination. To evaluate the severity of liver disease, patients were scored according to the Child-Pugh scoring system, which includes total bilirubin, albumin, prothrombin time, ascites and hepatic encephalopathy. The Model for End-Stage Liver Disease (MELD) score was also calculated using serum creatinine, total bilirubin, and the international normalized ratio (INR) of prothrombin time [21].

The largest tumour diameter measured on contrast-enhanced CT or MR images was used as a surrogate for tumour size. Tumours were clinically restaged using the eighth edition of the American Joint Committee on Cancer (AJCC) TNM staging system based on clinical history, PET/CT findings, and diagnostic CT and MR images.

This retrospective observational study was approved by our Institutional Review Board and the requirement to obtain written informed consent was waived.

Acquisition of FDG PET/CT imaging

All patients fasted for at least 6 h and had a blood glucose level <150 mg at the time of PET/CT. Whole-body PET and CT images were acquired 60 min after injection of 5.0 MBq/kg FDG without administration of intravenous or oral contrast agent on a Discovery LS or a Discovery STE PET/CT scanner (GE Healthcare) in 11 and 35 patients, respectively. Continuous spiral CT was performed with an eight-slice helical CT scan (140 keV, 40–120 mA; Discovery LS) or a 16-slice helical CT scan (140 keV, 30–170 mA; Discovery STE). An emission scan was then obtained from head to thigh for 4 min per frame in 2-D mode (Discovery LS) or 2.5 min per frame in 3-D mode (Discovery STE). PET images were reconstructed using the CT scan for attenuation correction using the ordered-subsets expectation maximization (OSEM) algorithm with 28 subsets and two iterations (matrix 128 × 128, voxel size 4.3 × 4.3 × 3.9 mm; Discovery LS) or the OSEM algorithm with 20 subsets and two iterations (matrix 128 × 128, voxel size 3.9 × 3.9 × 3.3 mm; Discovery STE).

Analysis of FDG PET/CT imaging

All images were reviewed by two board-certified nuclear medicine physicians using commercially available imaging software (MIM 6.4; MIM Software Inc., Cleveland, OH, USA). For semiquantitative analysis, the maximum standardized uptake value (SUVmax) of the primary tumour was measured using a spherical volume of interest (VOI) over the primary tumour volume. In non-FDG-avid tumours, the location and extent of the primary tumour on PET/CT images was determined by correlation with contrast-enhanced CT or MR images. In patients with multiple cHCC-CC lesions, only the image showing the highest SUVmax was included in the analysis. The mean SUV (SUVmean) of normal liver was obtained by taking the average of three VOIs (1 cm in diameter) placed at a location where cHCC-CC was not detected on liver CT or MRI. Precautions were taken when placing the VOIs to avoid beam-hardening artefacts, focal changes in fatty liver or fatty sparing, major vessels, bile ducts and the liver surface margin. The tumour-to-normal liver SUV ratio (TLR) was calculated using the following expression: TLR = SUVmax of tumour/SUVmean of normal liver. Discrepancies between readers were resolved by consensus.

Statistical analysis

Primary endpoints were progression-free survival (PFS) and overall survival (OS). Survival time was defined as the time from initial treatment to the date of detected disease progression (for PFS) or death (for OS) or to the date of the last follow-up visit. Disease progression was defined as a 20% increases in size of known cHCC-CC lesions from baseline or the presence of newly developed metastases on follow-up imaging according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

Variables for a univariable survival analysis included age at diagnosis, sex, tumour size, TNM stage, tumour markers, MELD score and TLR. TLR was categorized using the median value as low (≤3.4) or high (>3.4). Tumour size was divided on the basis of the previously proven prognostic indicator of 5 cm into ≤5 cm or >5 cm [22]. Significant variables in the univariable analysis, sex, age, TLR, TNM stage and tumour size were included in a multivariable survival analysis. A

multivariable Cox proportional hazards model was used to assess the potential independent effects of prognostic variables after adjusting for other risk factors.

Differences in clinical characteristics between the two TLR groups were tested using the chi-squared test (categorical variables) or the Mann-Whitney *U* test (continuous variables). Survival curves were estimated using the Kaplan-Meier method, and differences between groups were compared using the log-rank test. All statistical tests were two-sided with the significance level set at 0.05, and were performed with SPSS 23.0 (IBM Corp., Armonk, NY, USA) and MedCalc 15.5 (MedCalc, Mariakerke, Belgium).

Results

Patient clinical characteristics

Patient clinical characteristics are summarized in Table 1. The patients comprised 32 men and 14 women with a mean age of 60.0 ± 9.1 years (range 35 to 76 years). Of these 46 patients, 32 (69.6%) had hepatitis virus infection, and 43 (93.5%) had a Child-Pugh classification A.

According to the AJCC staging system for primary liver carcinoma, 30 patients (65.2%) had stage I/II disease, 2 (4.3%) had stage III disease, and 14 (30.5%) had stage IV disease. The 32 patients with stage I–III disease and 3 patients with stage IVA disease underwent surgical resection of the primary tumour. The remaining 11 patients with stage IVA or IVB disease were treated with other treatments including chemotherapy, radiotherapy and transarterial chemoembolization according to the oncologist's decision.

cHCC-CC tumours demonstrate independent biphenotypic differentiation. Of the 46 tumours, 34 (73.9%) were graded according to the Edmondson and Steiner system for the HCC component [23], and 30 (65.2%) were histologically diagnosed as adenocarcinoma graded as well differentiated to poorly differentiated for the CC component. Detailed information on tumour differentiation could not be obtained for the other tumours.

Higher FDG uptake was associated with higher tumour stage, lymph node metastasis and poorer tumour differentiation of the CC component ($p = 0.030$, $p = 0.057$ and $p = 0.032$, respectively; chi-squared test). Higher FDG uptake was also significantly associated with larger tumour size ($p = 0.007$, Mann-Whitney *U* test). The severity of liver disease measured in terms of the total bilirubin level, INR, albumin level, Child-Pugh score and MELD score was not significantly different between the two groups. No significant differences in serum tumour markers including alpha fetoprotein (AFP), carbohydrate antigen 19-9 (CA19-9), prothrombin induced by vitamin K absence or antagonist-II (PIVKA-II) and carcinoembryonic antigen (CEA) were identified between the groups. There were no significant differences in any other clinical variables.

Prognostic factors for PFS and OS

During a median follow-up period of 29 months, 29 patients (63.0%) showed tumour recurrence or progression, and 25 patients (54.4%) died from cancer. In the univariable Cox regression analysis, TLR and TNM stage were significant predictors of PFS and OS (Table 2). CEA was investigated in 39 of 46 patients, and it was also a significant predictor of PFS and OS in the univariable analysis. Histological differentiation was not a significant variable for predicting PFS and OS (Table 2). In the multivariable Cox regression analysis, a higher TLR (>3.4) was significantly associated with a poorer PFS (hazard ratio, HR, 5.19, 95% CI 1.80–15.01; $p = 0.002$) and OS (HR 3.95, 95% CI 1.27–12.24; $p = 0.017$) after adjusting for age, sex, TNM stage and tumour size (Table 3). TNM stage was a significant independent predictor of OS (HR 3.40, 95% CI 1.03–11.29; $p = 0.045$), but not of PFS (HR 2.43, 95% CI 0.83–7.08; $p = 0.104$).

In an additional multivariable survival analysis in the subgroup of 39 cHCC-CC patients with CEA, a higher TLR (>3.4) was also a significant independent predictor of a poorer PFS (HR 5.15, 95% CI 1.60–16.51; $p = 0.006$) and OS (HR 4.56, 95% CI 1.35–15.41; $p = 0.015$). However, CEA was not a significant independent predictor of PFS or OS (Table 4).

A Kaplan-Meier analysis of patients stratified by TLR demonstrated a worse PFS in those with a higher TLR (>3.4) than in those with a lower TLR (≤3.4; 2-year survival rate 17.8% vs. 62.9%; median survival time 7.2 vs. 43.0 months; $p = 0.001$; Fig. 1a). Also, patients with a higher TLR (>3.4) had a poorer OS than those with a lower TLR (≤3.4; 2-year survival rate 39.1% vs. 77.3%; median survival time 17.6 vs. 52.3 months; $p = 0.001$; Fig. 1b).

Discussion

FDG uptake measured as SUVmax is known to provide prognostic information in various cancers [24–28]. Although many studies have also shown the potential prognostic value of FDG uptake in patients with HCC or CC [14–20], data are not yet available to determine the prognosis in patients with cHCC-CC due to the relative rarity of this diagnosis. In the present retrospective cohort study in patients with cHCC-CC, TLR was a significant independent predictor of both PFS and OS. In the multivariable survival analysis, TLR was an independent predictor of survival in patients with cHCC-CC. Patients with a TLR >3.4 showed a fivefold increase in the risk of disease progression and a fourfold increase in the risk of death after adjusting for other clinical variables.

Table 1 Patient clinical characteristics

	All patients($n = 46$)	TLR ≤3.4($n = 23$)	TLR >3.4($n = 23$)	p value
Age (years)	59 (54–68)	61 (54.5–69.8)	58.0 (53.3–63.8)	0.328
Male sex	32 (69.6%)	15 (65.2%)	17 (73.9%)	0.526
Viral hepatitis aetiology	32 (69.6%)	15 (65.2%)	14 (60.9%)	0.763
TNM stage				
I/II	30 (65.2%)	19 (82.6%)	11 (47.8%)	0.030
III	2 (4.3%)	0 (0.0%)	2 (8.7%)	
IVA	11 (23.9%)	2 (8.7%)	9 (39.1%)	
IVB	3 (6.5%)	2 (8.7%)	1 (4.3%)	
Edmondson-Steiner grade (HCC component)				
I/II	29 (85.3%)	14 (77.8%)	15 (93.8%)	0.196
III/IV	5 (14.7%)	4 (22.2%)	1 (6.2%)	
Tumour differentiation (CC component)				
Well or moderate	11 (36.7%)	8 (57.1%)	3 (18.8%)	0.032
Poor	19 (63.3%)	6 (42.9%)	13 (81.2%)	
Serum tumour markers				
AFP (ng/ml)	8.5 (3.6–224.0)	10 (4.6–175.4)	6.9 (3.4–49.9)	0.956
CA19-9 (U/ml)	13.6 (8.1–37.0)	18.5 (7.9–57.5)	11.7 (9.0–26.2)	0.780
PIVKA2 (mAU/ml)	30 (23.0–72.0)	27.5 (22.0–38.0)	38 (25.3–546.8)	0.064
CEA (ng/ml)	1.6 (1.0–2.4)	1.6 (1.3–2.0)	1.5 (0.9–1.1)	0.876
Total bilirubin (mg/dl)	0.8 (0.5–1.1)	1 (0.6–1.3)	0.7(0.5–1.0)	0.198
Creatinine (mg/dl)	0.8 (0.7–0.9)	0.91 (0.73–0.96)	0.76 (0.71–0.85)	0.077
INR	1.05 (0.98–1.14)	1.07 (0.94–1.14)	1.05 (0.99–1.14)	1.000
Albumin (g/dl)	4.3 (3.9–4.6)	4.2 (3.9–4.6)	4.3 (3.9–4.7)	0.435
MELD score	7 (7.0–9.0)	7.0 (7.0–9.0)	7 (7.0–8.8)	0.559
Child-Pugh score A	43 (93.5%)	20	23	0.076
Tumour size (cm)		3.5 (2.6–5.5)	6.8 (5.0–9.8)	0.007
SUVmax	7.2 (5.0–11.3)	5.0 (4.0–6.2)	11.3 (8.8–13.7)	<0.001
Distant metastasis	3 (6.5%)	2 (8.7%)	1 (4.3%)	0.555
LN metastasis	14 (30.4%)	4 (17.4%)	10 (43.5%)	0.057
Treatment				
Resection	35 (76.1%)	19 (82.6%)	16 (69.6%)	0.305
Other	11 (23.9%)	4 (17.4%)	7 (30.4%)	

The data are presented as number (proportion) of patients or median (interquartile range)

HCC hepatocellular carcinoma, *CC* cholangiocarcinoma, *TLR* tumour-to-normal liver standardized uptake value ratio, *AFP* alpha fetoprotein, *CA19-9* carbohydrate antigen 19-9, *PIVKA2* prothrombin induced by vitamin K absence or antagonist-II, *CEA* carcinoembryonic antigen, *INR* international normalized ratio, *MELD* Model for End-Stage Liver Disease, *SUVmax* maximum standard uptake value, *LN* lymph node

Since the initial description of cHCC-CC in 1949, several studies have been performed on the prognosis and prognostic indicators of this tumour. Although complete surgical resection currently remains the only chance of cure, most of the literature suggests that this disease has a poor prognosis even after curative resection [10, 13]. Vascular and lymph node invasion and the presence of satellite metastases have been suggested as significant predictors of a poor outcome after resection of cHCC-CC [10, 29–31]. However, such pathological information is limited to specimens from patients who present with operable disease. In contrast, tumour size and TNM stage are considered poor prognostic factors regardless of the operable status. For these factors, the univariable prognostic analysis in our study demonstrated that tumour stage according to the presence of metastasis was also associated with a poor prognosis. However, tumour size using a cut-off value of 5 cm, the criteria distinguishing between T2 (stage II) and T3 (stage III), was not a significant prognostic factor. Indeed, although previous studies have consistently shown that advanced tumour stages is a poor prognostic factor in cHCC-CC, the significance of tumour size remains controversial [10, 22, 29].

Tumour FDG avidity was added as a new potential imaging biomarker for PFS and OS in patients with cHCC-CC

Table 2 Univariable survival analysis in 46 patients with cHCC–CC

Clinical variable	Progression-free survival			Overall survival		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age (1 year increase)	1.02	0.97–1.06	0.450	1.03	0.98–1.09	0.180
Sex, male vs. female	1.18	0.52–2.69	0.690	1.25	0.50–3.18	0.633
AFP (ng/mL, continuous $\log_{10}$ scale)	0.87	0.64–1.17	0.351	0.80	0.57–1.13	0.204
CA19-9 (U/ml, continuous $\log_{10}$ scale)	1.45	0.62–3.39	0.395	2.04	0.68–6.17	0.207
PIVKA2 (mAU/ml, continuous $\log_{10}$ scale)	1.29	0.79–2.09	0.307	1.66	0.91–3.01	0.097
CEA (ng/ml, continuous $\log_{10}$ scale)	2.28	1.09–4.76	0.029	3.11	1.33–7.29	0.009
MELD score (1 point increase)	0.94	0.77–1.15	0.545	1.01	0.83–1.22	0.922
TNM stage (I–III vs. IV)	3.38	1.51–7.59	0.003	3.93	1.64–9.40	0.002
Edmondson-Steiner grade (I/II vs. III/IV)	0.23	0.03–1.70	0.149	0.37	0.05–2.81	0.339
Tumour differentiation (well/moderate vs. poor)	1.43	0.51–3.98	0.498	1.28	0.40–4.08	0.673
TLR (>3.4, categorical)	3.85	1.73–8.57	0.001	3.41	1.44–8.10	0.005
Tumour size (>5 cm, categorical)	1.38	0.66–2.88	0.387	1.42	0.63–3.20	0.398

cHCC-CC combined hepatocellular-cholangiocarcinoma, *AFP* alpha fetoprotein, *CA19-9* carbohydrate antigen 19-9, *PIVKA2* prothrombin induced by vitamin K absence or antagonist-II, *CEA* carcinoembryonic antigen, *MELD* Model for End-Stage Liver Disease, *TLR* tumour-to-normal liver standardized uptake value ratio, *HR* hazard ratio, *CI* confidence interval

consistent with other primary liver carcinomas. Many previous studies have demonstrated that tumour FDG avidity measured as the highest SUVmax in the whole tumour lesion is a prognostic biomarker. Although SUVmax is a well-known imaging parameter in FDG PET imaging, there is an external validation issue due to interinstrumental variability. SUV measurement is affected by several technical factors such as imaging protocol, reconstruction settings, partial volume effect, normalization factors, and plasma glucose level [32–35]. Therefore, semiquantitative analysis of primary tumours was performed using the TLR to reduce interinstrumental variability and to strengthen the generalizability of our research findings.

The diagnostic accuracy of FDG PET/CT for evaluation of HCC is limited due to variable FDG uptake in this tumour. However, because the variable FDG uptake in HCC is closely related to molecular features of aggressive biological properties, it is a very useful marker to predict prognosis. In the present study, FDG uptake was an independent predictor of survival in cHCC-CC. In a recent study, Jung et al. found that AJCC tumour stage in cHCC-CC was the only independent risk factor for both tumour recurrence and patient survival [36]. In our study, FDG uptake was a significant independent predictor of survival in patients with cHCC-CC after adjusting for TNM stage, which may indicate that FDG uptake by cHCC-CC is highly associated with tumour aggressiveness [37–39].

In previous studies including TLR as the prognostic factor in HCC, the optimal cut-off value for predicting survival events ranged from 2.0 to 3.1 [14, 16, 17]. Although this optimal threshold approach shows the best prognostic performance, it may cause overestimation of statistical significance as mentioned in the reports of previous studies [40]. In our patients, TLR 3.1 was the optimal cut-off value for predicting

Table 3 Multivariable survival analysis in 46 patients with cHCC-CC

Clinical variables	Progression-free survival			Overall survival		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age (1 year increase)	1.03	0.99–1.08	0.115	1.03	0.99–1.08	0.179
Sex, male vs. female	0.85	0.32–2.22	0.743	0.66	0.22–1.98	0.460
TNM stage (I–III vs. IV)	2.43	0.83–7.08	0.104	3.40	1.03–11.29	0.045
TLR (>3.4, categorical)	5.19	1.80–15.01	0.002	3.95	1.27–12.24	0.017
Tumour size (>5 cm, categorical)	0.37	0.13–1.05	0.063	0.35	0.11–1.16	0.087

cHCC-CC combined hepatocellular-cholangiocarcinoma, *TLR* tumour-to-normal liver standardized uptake value ratio, *HR* hazard ratio, *CI* confidence interval

Table 4 Multivariable survival analysis in the subgroup of 39 cHCC-CC patients with CEA

Clinical variable	Progression-free survival			Overall survival		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age (1 year increase)	1.03	0.98–1.09	0.254	1.06	1.00–1.13	0.058
Sex, male vs. female	0.86	0.26–2.80	0.802	0.84	0.24–2.91	0.784
TNM stage (I–III vs. IV)	2.11	0.38–11.72	0.390	1.72	0.28–10.40	0.555
TLR (>3.4, categorical)	5.15	1.60–16.51	0.006	4.56	1.35–15.41	0.015
CEA (ng/ml, continuous $\log_{10}$ scale)	1.65	0.67–4.09	0.278	2.12	0.78–5.70	0.137
Tumour size (>5 cm, categorical)	0.34	0.09–1.40	0.136	0.54	0.13–2.26	0.399

cHCC-CC combined hepatocellular-cholangiocarcinoma, *TLR* tumour-to-normal liver standardized uptake value ratio, *CEA* carcinoembryonic antigen, *HR* hazard ratio, *CI* confidence interval

disease progression and death. However, the median value of 3.4 was chosen as the TLR cut-off value to avoid bias for hypothesis testing.

Although serum AFP as a tumour marker of HCC and CA19-9 as a tumour marker of CC have been widely used in the diagnosis of primary liver carcinoma, their prognostic value remains unclear [41–43]. In contrast, recent studies have shown that elevated CEA is highly associated with a poor prognosis in HCC [44] and CC [45, 46]. To our knowledge, there are no studies that have investigated the prognostic value of CEA in patients with cHCC-CC. In our univariable survival analysis, CEA was a significant predictor of PFS and OS. However, in the multivariable survival analysis using exclusively the 39 patients with all significant parameters, CEA was not a significant independent predictor of survival after adjusting for TLR and other clinical variables. Further studies are warranted to clarify whether CEA is useful for predicting survival in these patients. Underlying liver function is not associated with prognostic value, unlike in HCC. However, this result is uncertain because most of our subjects (93.5%) had favourable liver function (Child-Pugh score A). Further studies are needed to investigate whether the severity of underlying liver disease has prognostic value in this cohort.

The major limitations of this study include its retrospective design and the small number of subjects because of the rarity of this tumour. In addition, the relatively uneven distribution of surgical and other treatment modalities due to uncertainty in management guidelines may have influenced the results. However, we confirmed that there was no difference ($p = 0.305$) in surgical and non-surgical treatments between patients with a low TLR and a high TLR. In this study evaluation of variable pathological factors such as vascular invasion, histological subtypes according to the stem cell features and tumour differentiation could have been incomplete, because such information was not assessed or only available in 76.1% of patients who underwent surgical resection.

Conclusion

Pretreatment TLR measured on FDG PET/CT is an independent predictor of survival in patients with cHCC-CC. Further prospective validation studies in a larger number of subjects are required to confirm the prognostic utility of this potential imaging biomarker.

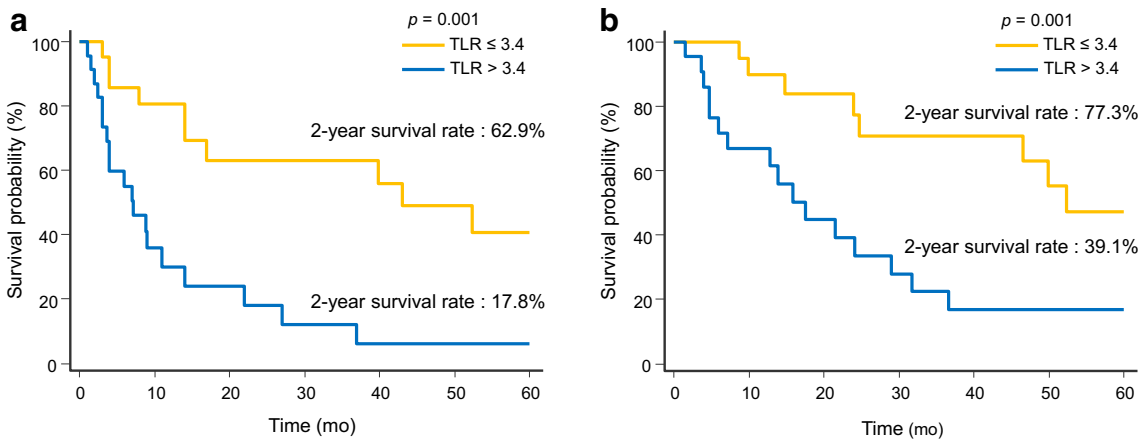

Fig. 1 Kaplan-Meier curves for 46 patients with cHCC-CC. Progression-free survival (**a**) and overall survival (**b**) according to tumour-to-normal liver standardized uptake value ratio (TLR)

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Compliance with ethical standards

Conflicts of interest None.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the principles of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

Informed consent Written informed consent was waived.

References

1. Lee WS, Lee KW, Heo JS, Kim SJ, Choi SH, Kim YI, et al. Comparison of combined hepatocellular and cholangiocarcinoma with hepatocellular carcinoma and intrahepatic cholangiocarcinoma. Surg Today. 2006;36:892–7.
2. Lee JH, Chung GE, Yu SJ, Hwang SY, Kim JS, Kim HY, et al. Long-term prognosis of combined hepatocellular and cholangiocarcinoma after curative resection comparison with hepatocellular carcinoma and cholangiocarcinoma. J Clin Gastroenterol. 2011;45:69–75.
3. Goodman ZD, Ishak KG, Langloss JM, Sesterhenn IA, Rabin L. Combined hepatocellular-cholangiocarcinoma. A histologic and immunohistochemical study. Cancer. 1985;55:124–35.
4. Akiba J, Nakashima O, Hattori S, Tanikawa K, Takenaka M, Nakayama M, et al. Clinicopathologic analysis of combined hepatocellular-cholangiocarcinoma according to the latest WHO classification. Am J Surg Pathol. 2013;37:496–505.
5. Theise ND, Park YN, Nakanuma Y. Combined hepatocellular-cholangiocarcinoma. In: Bosman FT, Carneiro F, Hruban RH, Theise ND, editors. WHO classification of tumours of the digestive system. 4th ed. Lyon: IARC Press; 2010. p. 225–7.
6. Kim H, Park C, Han KH, Choi J, Kim YB, Kim JK, et al. Primary liver carcinoma of intermediate (hepatocyte-cholangiocyte) phenotype. J Hepatol. 2004;40:298–304.
7. Zhang F, Chen XP, Zhang W, Dong HH, Xiang S, Zhang WG, et al. Combined hepatocellular cholangiocarcinoma originating from hepatic progenitor cells: immunohistochemical and double-fluorescence immunostaining evidence. Histopathology. 2008;52:224–32.
8. Kassahun WT, Hauss J. Management of combined hepatocellular and cholangiocarcinoma. Int J Clin Pract. 2008;62:1271–8.
9. Yin X, Zhang BH, Qiu SJ, Ren ZG, Zhou J, Chen XH, et al. Combined hepatocellular carcinoma and cholangiocarcinoma: clinical features, treatment modalities, and prognosis. Ann Surg Oncol. 2012;19:2869–76.
10. Koh KC, Lee H, Choi MS, Lee JH, Paik SW, Yoo BC, et al. Clinicopathologic features and prognosis of combined hepatocellular cholangiocarcinoma. Am J Surg. 2005;189:120–5.
11. Kim KH, Lee SG, Park EH, Hwang S, Ahn CS, Moon DB, et al. Surgical treatments and prognoses of patients with combined hepatocellular carcinoma and cholangiocarcinoma. Ann Surg Oncol. 2009;16:623–9.
12. Taguchi J, Nakashima O, Tanaka M, Hisaka T, Takazawa T, Kojiro M. A clinicopathological study on combined hepatocellular and cholangiocarcinoma. J Gastroenterol Hepatol. 1996;11:758–64.
13. Park SE, Lee SH, Yang JD, Hwang HP, Hwang SE, Yu HC, et al. Clinicopathological characteristics and prognostic factors in combined hepatocellular carcinoma and cholangiocarcinoma. Korean J Hepatobiliary Pancreat Surg. 2013;17:152–6.
14. Na SJ, Oh JK, Hyun SH, Lee JW, Hong IK, Song BI, et al. (18)F-FDG PET/CT can predict survival of advanced hepatocellular carcinoma patients: a multicenter retrospective cohort study. J Nucl Med. 2017;58:730–6.
15. Sun DW, An L, Wei F, Mu L, Shi XJ, Wang CL, et al. Prognostic significance of parameters from pretreatment (18)F-FDG PET in hepatocellular carcinoma: a meta-analysis. Abdom Radiol (NY). 2016;41:33–41.
16. Lee JW, Oh JK, Chung YA, Na SJ, Hyun SH, Hong IK, et al. Prognostic significance of (18)F-FDG uptake in hepatocellular carcinoma treated with transarterial chemoembolization or concurrent chemoradiotherapy: a multicenter retrospective cohort study. J Nucl Med. 2016;57:509–16.
17. Hyun SH, Eo JS, Lee JW, Choi JY, Lee KH, Na SJ, et al. Prognostic value of (18)F-fluorodeoxyglucose positron emission tomography/computed tomography in patients with Barcelona Clinic Liver Cancer stages 0 and A hepatocellular carcinomas: a multicenter retrospective cohort study. Eur J Nucl Med Mol Imaging. 2016;43:1638–45.
18. Jo IY, Son SH, Kim M, Sung SY, Won YK, Kang HJ, et al. Prognostic value of pretreatment (18)F-FDG PET-CT in radiotherapy for patients with hepatocellular carcinoma. Radiat Oncol J. 2015;33:179–87.
19. Ikeno Y, Seo S, Iwaisako K, Yoh T, Nakamoto Y, Fuji H, et al. Preoperative metabolic tumor volume of intrahepatic cholangiocarcinoma measured by (18)F-FDG-PET is associated with the KRAS mutation status and prognosis. J Transl Med. 2018;16:95.
20. Lee Y, Yoo IR, Boo SH, Kim H, Park HL, Hyun OJ. The role of F-18 FDG PET/CT in intrahepatic cholangiocarcinoma. Nucl Med Mol Imaging. 2017;51:69–78.
21. Durand F, Valla D. Assessment of the prognosis of cirrhosis: Child-Pugh versus MELD. J Hepatol. 2005;42(Suppl):S100–7.
22. Bergquist JR, Groeschl RT, Ivanics T, Shubert CR, Habermann EB, Kendrick ML, et al. Mixed hepatocellular and cholangiocarcinoma: a rare tumor with a mix of parent phenotypic characteristics. HPB (Oxford). 2016;18:886–92.
23. Edmondson HA, Steiner PE. Primary carcinoma of the liver: a study of 100 cases among 48,900 necropsies. Cancer. 1954;7:462–503.
24. Piccardo A, Puntoni M, Bertagna F, Treglia G, Foppiani L, Arecco F, et al. (18)F-FDG uptake as a prognostic variable in primary differentiated thyroid cancer incidentally detected by PET/CT: a multicentre study. Eur J Nucl Med Mol Imaging. 2014;41:1482–91.
25. Bastiaannet E, Hoekstra OS, de Jong JR, Brouwers AH, Suurmeijer AJ, Hoekstra HJ. Prognostic value of the standardized uptake value for (18)F-fluorodeoxyglucose in patients with stage IIIB melanoma. Eur J Nucl Med Mol Imaging. 2012;39:1592–8.
26. Zhu D, Wang Y, Wang L, Chen J, Byanju S, Zhang H, et al. Prognostic value of the maximum standardized uptake value of pre-treatment primary lesions in small-cell lung cancer on 18F-FDG PET/CT: a meta-analysis. Acta Radiol. 2018;59:1082–90.
27. Diao W, Tian F, Jia Z. The prognostic value of SUVmax measuring on primary lesion and ALN by (18)F-FDG PET or PET/CT in patients with breast cancer. Eur J Radiol. 2018;105:1–7.
28. Paesmans M, Berghmans T, Dusart M, Garcia C, Hossein-Foucher C, Lafitte JJ, et al. Primary tumor standardized uptake value measured on fluorodeoxyglucose positron emission tomography is of

prognostic value for survival in non-small cell lung cancer: update of a systematic review and meta-analysis by the European Lung Cancer Working Party for the International Association for the Study of Lung Cancer Staging Project. J Thorac Oncol. 2010;5:612–9.
29. Yano Y, Yamamoto J, Kosuge T, Sakamoto Y, Yamasaki S, Shimada K, et al. Combined hepatocellular and cholangiocarcinoma: a clinicopathologic study of 26 resected cases. Jpn J Clin Oncol. 2003;33:283–7.
30. Shin CI, Lee JM, Kim SH, Choi JY, Lee JY, Han JK, et al. Recurrence patterns of combined hepatocellular-cholangiocarcinoma on enhanced computed tomography. J Comput Assist Tomogr. 2007;31:109–15.
31. Tang D, Nagano H, Nakamura M, Wada H, Marubashi S, Miyamoto A, et al. Clinical and pathological features of Allen's type C classification of resected combined hepatocellular and cholangiocarcinoma: a comparative study with hepatocellular carcinoma and cholangiocellular carcinoma. J Gastrointest Surg. 2006;10:987–98.
32. Boellaard R, Krak NC, Hoekstra OS, Lammertsma AA. Effects of noise, image resolution, and ROI definition on the accuracy of standard uptake values: a simulation study. J Nucl Med. 2004;45:1519–27.
33. Keyes JW, Jr. SUV: standard uptake or silly useless value? J Nucl Med 1995;36:1836–9.
34. Soret M, Bacharach SL, Buvat I. Partial-volume effect in PET tumor imaging. J Nucl Med. 2007;48:932–45.
35. Westerterp M, Pruim J, Oyen W, Hoekstra O, Paans A, Visser E, et al. Quantification of FDG PET studies using standardised uptake values in multi-centre trials: effects of image reconstruction, resolution and ROI definition parameters. Eur J Nucl Med Mol Imaging. 2007;34:392–404.
36. Jung DH, Hwang S, Hong SM, Chung YK, Song GW, Lee YJ, et al. Post-resection prognosis of combined hepatocellular carcinoma-cholangiocarcinoma according to the 2010 WHO classification. World J Surg. 2017;41:1347–57.
37. Lee JD, Yun M, Lee JM, Choi Y, Choi YH, Kim JS, et al. Analysis of gene expression profiles of hepatocellular carcinomas with regard to 18F-fluorodeoxyglucose uptake pattern on positron emission tomography. Eur J Nucl Med Mol Imaging. 2004;31:1621–30.
38. Ahn KJ, Hwang HS, Park JH, Bang SH, Kang WJ, Yun M, et al. Evaluation of the role of hexokinase type II in cellular proliferation and apoptosis using human hepatocellular carcinoma cell lines. J Nucl Med. 2009;50:1525–32.
39. Lee JD, Yang WI, Park YN, Kim KS, Choi JS, Yun M, et al. Different glucose uptake and glycolytic mechanisms between hepatocellular carcinoma and intrahepatic mass-forming cholangiocarcinoma with increased (18)F-FDG uptake. J Nucl Med. 2005;46:1753–9.
40. Altman DG, Lausen B, Sauerbrei W, Schumacher M. Dangers of using "optimal" cutpoints in the evaluation of prognostic factors. J Natl Cancer Inst. 1994;86:829–35.
41. He P, Tang ZY, Ye SL, Liu BB. Relationship between expression of alpha-fetoprotein messenger RNA and some clinical parameters of human hepatocellular carcinoma. World J Gastroenterol. 1999;5:111–5.
42. Taketa K. Alpha-fetoprotein: reevaluation in hepatology. Hepatology. 1990;12:1420–32.
43. Nehls O, Gregor M, Klump B. Serum and bile markers for cholangiocarcinoma. Semin Liver Dis. 2004;24:139–54.
44. Yoshikawa M, Morine Y, Ikemoto T, Imura S, Higashijima J, Iwahashi S, et al. Elevated preoperative serum CEA level is associated with poor prognosis in patients with hepatocellular carcinoma through the epithelial-mesenchymal transition. Anticancer Res. 2017;37:1169–75.
45. He C, Zhang Y, Song Y, Wang J, Xing K, Lin X, et al. Preoperative CEA levels are supplementary to CA19-9 levels in predicting prognosis in patients with resectable intrahepatic cholangiocarcinoma. J Cancer. 2018;9:3117–28.
46. Loosen SH, Roderburg C, Kauertz KL, Koch A, Vucur M, Schneider AT, et al. CEA but not CA19-9 is an independent prognostic factor in patients undergoing resection of cholangiocarcinoma. Sci Rep. 2017;7:16975.