Inverse Prognostic Relationships of ^{18}F -FDG PET/CT Metabolic Parameters in Patients with Distal Bile Duct Cancer Undergoing Curative Surgery

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Abstract

Purpose As there were few previous studies with a small number of subjects, the purpose of this was to evaluate the prognostic significance of ^{18}F -FDG PET/CT in patients with distal bile duct cancer undergoing curative surgery.

Methods The study included 40 patients (M/F = 24:16; age 68.0 ± 8.0 years) who underwent preoperative ^{18}F -FDG PET/CT followed by curative surgical resection. The participant's age, sex, Eastern Cooperative Oncology Group performance-status score, baseline serum CA 19-9 level, stage, pathologic T and N stages, tumor size, tumor grade, tumor growth pattern, R0 resection, and adjuvant therapy were included as clinicopathological variables for predicting overall survival. The PET variables were maximum standardized uptake value (SUV_{max}), average SUV (SUV_{avg}), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) of the tumor. The Kaplan-Meier method and Cox proportional hazards model were used for the survival analysis.

Results A total of 15 of 40 patients (37.5%) died during the follow-up period. In univariate analysis, low SUV_{max} (≤ 2.7 , $p = 0.0005$) and low SUV_{avg} (≤ 2.6 , $p = 0.0034$) were significant predictors of poor overall survival. In multivariate analyses, only low SUV_{max} (HR = 6.7016, 95% CI 1.9961–22.4993, $p = 0.0047$) was an independent prognostic factor associated with poor overall survival.

Conclusion The SUV_{max} of the primary tumor measured by ^{18}F -FDG PET/CT was an independent significant prognostic factor for overall survival in patients with distal bile duct cancer. However, different results from a previous study warrant further large sample-sized study.

Keywords Cholangiocarcinoma · Distal bile duct cancer · ^{18}F -FDG · PET · Prognosis

Introduction

Cholangiocarcinomas are rare malignant tumors for which the 5-year survival rate has not improved and remained at about 10% over the previous two decades [1]. Cholangiocarcinomas

can be classified into three subgroups based on anatomical location: intrahepatic, perihilar, and distal bile duct cancer [2]. These categories are associated with clinical manifestations and suggest a preferred treatment and prognosis. Distal bile duct cancer is reported to account for 40% of cholangiocarcinomas [1]. Distal bile duct cancer is the second most frequent subtype of cholangiocarcinoma [3]. Surgical resection of the primary tumor remains as the only curative treatment for bile duct cancer. However, most patients with cholangiocarcinomas are diagnosed at an advanced stage with distant metastases or local invasion, which is unresectable. To identify patients who may benefit from surgery and to predict the prognosis, an extensive staging workup is required. Imaging studies include delayed contrast computed tomography (CT), magnetic resonance imaging (MRI), cholangiography, and ^{18}F -FDG PET/CT [4, 5].

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Several prognostic factors, such as preoperative elevated carbohydrate antigen (CA) 19-9 level, positive resection margin, advanced T stage, and lymph node metastasis, were reported to be independent and significant prognostic indicators associated with poorer outcomes for resectable distal bile duct cancer [6]. However, CA 19-9 is not specific to bile duct cancer and is not generally used as a prognostic or a diagnostic tool in clinical practice. Because other prognostic factors are not applicable to patients with unresectable bile duct cancer, a reliable non-invasive prognostic marker is needed.

Positron emission tomography (PET) using ^{18}F -fluoro-2-deoxy-D-glucose (^{18}F -FDG) is a useful tool for predicting prognosis in many kinds of malignancies [7–10]. In addition, several studies have reported that metabolic parameters derived from ^{18}F -FDG PET/CT might be useful for predicting prognosis in biliary tract malignancies [11–14]. These studies, however, included patients with various types of hepatobiliary cancers, such as intrahepatic cholangiocarcinoma or gall bladder cancer. To our knowledge, only one study included patients with distal bile duct cancer. Therefore, the purpose of this study was to evaluate the prognostic significance of ^{18}F -FDG PET/CT in patients with distal bile duct cancer undergoing curative surgery.

Materials and Methods

Study Subjects

This retrospective study included a total of 46 adult patients who were pathologically proven to have distal bile duct cancer and who underwent preoperative ^{18}F -FDG PET/CT scan between January 2008 and December 2014, followed by curative surgical resection. Distal cholangiocarcinomas were defined as tumors that arise between the junction of the cystic duct-bile duct and the ampulla of Vater. Among these patients, six were excluded from further analysis due to previous history of another malignancy ($n = 2$), high blood glucose level more than 200 mg/dL before ^{18}F -FDG injection ($n = 1$) or different PET scanner model using different protocols ($n = 3$). After exclusions, a total of 40 patients were finally enrolled in this study.

The initial work-up included serum CA 19-9 test. For initial image testing, delayed-contrast multidetector-row computed tomography (MDCT) scan and/or contrast-enhanced magnetic resonance imaging (MRI) scan/MRCP were performed. Additionally, endoscopic ultrasound (EUS) and/or endoscopic retrograde cholangiopancreatography (ERCP) and/or percutaneous transhepatic biliary drainage (PTBD) with tissue sampling was performed before surgery for diagnosis and/or biliary decompression. All patients were staged based on pathology according to the 2010 American Joint Committee on Cancer staging manual, seventh edition.

This retrospective observational study was approved by our institutional review board with an exemption of written consent from study subjects.

^{18}F -FDG PET/CT Imaging

All patients fasted for at least 6 h before the ^{18}F -FDG PET/CT study. After blood glucose levels were measured, the subjects were injected with 5.0 MBq/kg of ^{18}F -FDG. Imaging was performed 60 min later on a Discovery STe PET/CT scanner (GE Healthcare; $n = 40$ patients) without intravenous or oral contrast agent. Whole-body CT was performed with a continuous spiral technique with a 16-slice helical CT (140 keV; 30–170 mA; section width 3.75 mm). After the CT scan, an emission scan was obtained from the basal skull to thigh for 2.5 min per frame in 3-D mode with reconstruction of attenuation-corrected PET images ($3.9 \times 3.9 \times 3.3$ mm) using a 3-D ordered-subset expectation maximization algorithm (20 subsets, 2 iterations). Standard uptake value (SUV) was derived by adjusting for injected dose and patient body weight.

Image Analysis

All ^{18}F -FDG PET/CT images were reviewed and analyzed on a workstation (GE Advantage Workstation 4.4) with volume viewer software, which provides an automatically delineated volume of interest (VOI) using an isocontour threshold method based on the SUV. The ^{18}F -FDG PET/CT images were interpreted by two experienced nuclear medicine physicians.

To determine the tumor segmentation threshold SUV, a VOI of 5×5 voxels was manually drawn in the right hepatic lobe at the level of the hepatic hilum on a transverse PET image, ensuring that VOIs were restricted to areas of physiologic activity. The average standardized uptake value (SUV_{avg}) plus 2 standard deviations of the liver VOI were used as a threshold SUV to determine the tumor boundary in each patient. Using this threshold SUV, a VOI was placed over the primary tumor detected on ^{18}F -FDG PET/CT on simultaneously displayed axial, coronal, and sagittal images (Fig. 1). The software automatically calculated the maximum SUV (SUV_{max}), SUV_{avg} , and metabolic tumor volume (MTV) of the primary tumor. Total lesion glycolysis (TLG) of the primary tumor was determined as a product of SUV_{avg} multiplied by MTV. If the primary tumor was indistinguishable from the background due to low ^{18}F -FDG uptake, the location of the primary tumor was determined by contrast-enhanced CT and/or MRI, where the SUV_{avg} , MTV, and TLG of the primary tumor were considered the lowest arbitrary values among patients as dummy variables for survival analysis ($n = 3$). The dummy values were established as 1.0, 0.01 cm^3 , and 0.01 cm^3 , respectively [15].

Fig. 1 Representative transverse (a), coronal (b), and sagittal (c) ^{18}F -FDG PET/CT images for tumor segmentation from a patient with distal bile duct cancer

Clinical Follow-up

All patients underwent surgical resection with curative intent. Postoperative adjuvant chemotherapy was administered to patients according to tumor stage or medical condition. The routine follow-up program consisted of physical examinations and laboratory tests, including assays for carcinoembryonic antigen (CEA) and CA 19-9 levels. The laboratory tests were performed once every 3 months for the first 2 years and then biannually for the next 3 years. Abdominopelvic computed tomography (CT) was included as part of the routine follow-up protocol.

When recurrence or disease progression was suspected during follow-up, ^{18}F -FDG PET/CT, whole body bone scan, other CT scans such as chest CT, and/or histological diagnosis were performed based on the physician's discretion. Overall survival (OS) was measured from the date of curative surgery to the date of death from any cause. Progression-free survival (PFS) was measured from the date of curative surgery to the date of first recurrence of disease. Patients who survived until the date of the last clinical follow-up were censored.

Statistical Analysis

The clinicopathological variables for survival analysis were age, sex, baseline serum CA 19-9 level, cancer stage, pathologic T stage, pathologic N stage, pathological tumor size, pathological tumor grade, tumor growth type (papillary vs. flat- or nodular-infiltrating), resection margin, and performance of adjuvant therapy. The PET variables were SUV_{max} , SUV_{avg} , MTV, and TLG of the primary tumor. For survival analysis, due to the small number of subjects,

continuous variables of SUV_{max} , SUV_{avg} , MTV, and TLG of the primary tumor and pathologic tumor size and baseline serum CA 19-9 levels were dichotomized based on the cutoff values determined by receiver operation characteristic (ROC) curve analysis. Ordinal variables with values ≥ 3 were also dichotomized according to optimized cutoff points.

Kaplan-Meier analysis using a log-rank test was performed for univariate survival analysis. The only significant variables on univariate analysis ($p < 0.1$) were entered into a stepwise multivariate analysis that used a multivariable Cox proportional hazard stepwise regression model to assess their predictive power.

MedCalc version 18.5 for Windows (MedCalc Software bvba) was used for the statistical analyses. A p value less than 0.05 was considered statistically significant. Continuous variables are expressed as a mean $\pm$ standard deviation, unless otherwise noted.

Results

Patient Characteristics

Patient clinicopathological and PET characteristics are presented in Table 1. Of the 40 patients, 24 (60%) were male, and the mean age was 68.0 years (range 53–80 years). Preoperative CA 19-9 level was measured by radioimmunoassay ($n = 33$) or by chemiluminescent immunoassay ($n = 7$). Preoperative biliary drainage was performed in 37 patients (92.5%), including endoscopic nasobiliary bile drainage ($n = 17$), endoscopic retrograde bile drainage (ERBD, $n = 8$), percutaneous transhepatic bile drainage only ($n = 11$), and

Table 1 Clinicopathological and PET characteristics ($n = 40$)

		Value (range or %)
Mean age, years (range)		68.0 (53–80)
Sex (male)	Male	24 (60.0%)
Event (death)		15 (37.5%)
Mean follow-up duration, month (range)		63.3 (0.5–95.8)
ECOG performance-status score	0	32 (80.0%)
	1	5 (12.5%)
	2	2 (5.0%)
	3	1 (2.5%)
Pathologic tumor stage	IA	1 (2.5%)
	IB	4 (10.0%)
	IIA	15 (37.5%)
	IIB	19 (47.5%)
	III	1 (2.5%)
T stage	T1	2 (5.0%)
	T2	10 (25.0%)
	T3	27 (67.5%)
	T4	1 (2.5%)
N stage	N0	21 (52.5%)
	N1	19 (47.5%)
Extent of resection	R0	30 (75.0%)
	R1	6 (15.0%)
	R2	4 (10.0%)
Histologic grade	G1	3 (7.5%)
	G2	24 (60.0%)
	G3	12 (30.0%)
	G4	1 (2.5%)
Tumor growth type	PP	10 (25.0%)
	FN	30 (75.0%)
Adjuvant CCRT	No	34 (79.1%)
	Yes	9 (20.9%)
Operative procedure	PPPD	32 (80.0%)
	Segmental resection of bile duct	8 (20.0%)
Tumor size (cm)		2.8 ± 1.1
CA 19-9 (U/ml)		467.2 ± 2353.9
SUV _{max}		4.3 ± 2.0
SUV _{avg} ^a		3.0 ± 0.8
MTV (cm ³) ^a		3.7 ± 7.8
TLG (cm ³) ^a		13.0 ± 28.9

ECOG Eastern Cooperative Oncology Group, PP papillary, FN flat and nodular infiltrating, CA 19-9 aspartate aminotransferase, PPPD pancreaticoduodenectomy, SUV standardized uptake value, MTV metabolic tumor volume, TLG total lesion glycolysis

^a Dummy values of three patients with non-visualized tumors were included

percutaneous transhepatic bile drainage followed by ERBD failure ($n = 1$). The SUV_{max} of the primary tumor was 4.3 ± 2.0 , SUV_{avg} was 3.0 ± 0.8 , MTV was 3.7 ± 7.8 cm³, and TLG was 13.0 ± 28.9 cm³. The tumor sizes of three patients with non-visualized tumors were 1.3 cm, 1.8 cm, and 2.2 cm, respectively.

According to the AJCC cancer staging manual seventh edition, 1 patient was diagnosed as stage IA, 4 were stage IB, 15 were stage IIA, 19 were stage IIB, and 1 was stage III. Based on the macroscopic tumor growth pattern, 10 patients were classified into the papillary (PP) type and 30 patients were classified as flat- and nodular-infiltrating (FN) type.

Table 2 Univariate analysis for predicting overall survival

	No. of patients	HR (95% CI)	P value
Age (year > 71 vs. ≤ 70)	17 vs. 23	1.456 (0.522–4.057)	0.478
Sex (male vs. female)	24 vs. 16	1.385 (0.490–3.915)	0.517
ECOG performance-status score (1–3 vs. 0)	8 vs. 32	0.698 (0.198–2.458)	0.523
Stage (stage III/IV vs. stage I/II)	20 vs. 20	1.161 (0.422–3.195)	0.764
Pathologic stage (stage 2b/3 vs. stage 1a/1b/2a)	20 vs. 20	1.161 (0.422–3.195)	0.764
Pathologic T stage (stage 3/4 vs. stage 1/2)	28 vs. 12	1.117 (0.366–3.412)	0.846
Pathologic N stage (N1 vs. N0)	19 vs. 21	1.016 (0.369–2.799)	0.975
R state (R1/R2 vs. R0)	10 vs. 30	1.548 (0.429–5.589)	0.554
Tumor grade (G3/G4 vs. G1/G2)	13 vs. 27	0.812 (0.291–2.268)	0.648
Tumor growth type (FN vs. PP)	30 vs. 10	0.909 (0.297–2.788)	0.855
Adjuvant therapy (yes vs. no)	9 vs. 31	NA	0.050
Tumor size (long diameter > 2.3 cm vs. ≤ 2.3 cm)	25 vs. 15	1.917 (0.644–5.709)	0.182
Baseline CA 19-9 (> 16.79 U/ml vs. ≤ 16.79 U/ml)	31 vs. 9	0.295 (0.082–1.056)	0.195
Operative procedure (segmental resection vs. PPPD)	8 vs. 32	0.952 (0.264–3.439)	0.938
Tumor SUV _{max} (> 2.7 vs. ≤ 2.7)	33 vs. 7	5.283 (0.873–31.987)	< 0.001
Tumor SUV _{avg} (> 2.6 vs. ≤ 2.6)	34 vs. 6	4.586 (0.659–31.896)	0.003
Tumor MTV (> 0.6 cm ³ vs. ≤ 0.6 cm ³)	23 vs. 17	2.532 (0.889–7.214)	0.061
Tumor TLG (> 2.0 cm ³ vs. ≤ 2.0 cm ³)	23 vs. 17	2.532 (0.889–7.214)	0.061

ECOG Eastern Cooperative Oncology Group, FN flat- and nodular infiltrating, PP papillary, CA 19-9 aspartate aminotransferase, PPPD pancreaticoduodenectomy, SUV standardized uptake value, MTV metabolic tumor volume, TLG total lesion glycolysis, HR hazard ratio, CI confidence interval, NA not applicable

Radical pancreaticoduodenectomy was performed in 32 patients. In the remaining eight patients, segmental resection of the common bile duct and cholecystectomy was performed as curative intent. Nine patients received adjuvant concurrent chemoradiation therapy. Because of their advanced age and poor general condition, adjuvant therapy was not performed in 5 of 10 patients with positive pathological resection margin.

Survival Analysis

A total of 15 of the 40 patients (37.5%) died during the follow-up period. Two patients died in the hospital because of postoperative bleeding at the 14th and 25th postoperative days.

The 1-, 3-, and 5-year survival rates after curative resection of the distal bile duct cancer were 84.7%, 59.8%, and 29.9%, respectively. The median survival duration was 84.6 months (range 14 days to 95.8 months), and the mean follow-up duration was 63.3 months.

For survival analysis, the best cutoff values to categorize low and high primary tumor SUV_{max}, primary tumor SUV_{avg}, primary tumor MTV, primary tumor TLG, primary tumor size, and preoperative level of serum CA 19-9 were set at 2.7, 2.6, 0.6 cm³, 2.0 cm³, 2.3 cm, and 16.79 U/ml, respectively. In univariate analysis, low SUV_{max} (≤ 2.7, $p = 0.0005$) and low SUV_{avg} (≤ 2.6, $p = 0.0034$) were significant predictors of poor overall survival (Table 2; Fig. 2). In multivariate analysis, only

Fig. 2 Kaplan-Meier analysis of overall survival according to **a** SUV_{max} and **b** SUV_{avg}

a low SUV_{max} (HR = 6.7016, 95% CI 1.9961–22.4993, $p = 0.0047$) was the only significant independent prognostic factor associated with poor overall survival. There was no significant predictor for predicting PFS.

Representative ^{18}F -FDG PET/CT images are shown in Figs. 3 and 4

Discussion

This is a relatively large-scale study that investigated the prognostic value of ^{18}F -FDG PET/CT compared with other clinicopathologic parameters in distal bile duct cancer patients. This study demonstrated that the low SUV_{max} of the primary tumor measured by ^{18}F -FDG PET/CT was an independent significant prognostic factor for overall survival in patients with distal bile duct cancer.

There are a limited number of previous studies that have assessed factors to predict cholangiocarcinoma prognosis based on ^{18}F -FDG PET/CT. Lee et al. reported that SUV_{max} of the primary tumor was an independent and significant prognostic factor for overall survival in bile duct and gallbladder cancer [12]. Park et al. reported that preoperative SUV_{max} of the primary tumor was significantly associated with recurrence in patients with biliary tract cancer [13]. This study assessed with types of hepatobiliary cancers, including intrahepatic, hilar, extrahepatic cholangiocarcinomas, gall bladder cancer, and ampulla of Vater cancer. Many authors have reported widely different sensitivities and specificities of ^{18}F -FDG PET/CT scans according to anatomic location, growth pattern, and histopathologic characteristics [4]. Primary tumor SUV_{max} was significantly different in

patients with bile duct cancer according to the site of the primary tumor. Intrahepatic cholangiocarcinoma and gallbladder cancer showed higher SUV_{max} values than extrahepatic cholangiocarcinoma and ampulla of Vater cancer [16]. Therefore, additional analysis was needed to evaluate the prognostic values of PET parameters in patients with distal bile duct cancer only. One recent study with a small number of subjects ($n = 25$) assessed the prognostic value of ^{18}F -FDG PET/CT in distal bile duct cancer patients who underwent curative surgery [17]. In this study, a high primary tumor TLG value (> 13.0), a high primary tumor MTV value (> 2.8 ml), and a high primary tumor SUV_{max} value (> 4.0) were significant prognostic predictors for poor overall survival on univariate survival analysis. After multivariate analysis, only tumor TLG was a significant prognostic factor.

The results of this study differed from the results of previous studies. Our study showed that a low SUV_{max} was a significant prognostic factor for poorer survival, and there are several possible reasons for these discrepant results. First, although the number of our subjects ($n = 43$) was larger than that of a previous study ($n = 25$), it was still relatively small for a cancer survival analysis study. Therefore, the results may be more likely to be biased by statistical error. Second, the tumor growth pattern (papillary vs. periductal infiltrating) may affect the ^{18}F -FDG uptake and patient survival [4], which was not reported in a previous study [16]. The ^{18}F -FDG uptake of periductal infiltrating cancer can be underestimated due to tumor geometry and partial volume effect. Furthermore, periductal infiltrating type was reported to be associated with the worst prognostic factors in extrahepatic hilar and intrahepatic cholangiocarcinomas [18, 19].

Fig. 3 Preoperative transverse PET (a), fused (b) and CT (c) images of ^{18}F -FDG PET/CT, and DWI MR (d) images of a 73-year-old man with distal bile duct cancer showing a high SUV_{max} of 6.3, SUV_{avg} of 3.4, MTV of 5.2 cm^3 , and TLG of 17.8 cm^3 for the primary tumor (white arrow). The patient survived for 48.3 months after curative surgery without disease progression

Fig. 4 Preoperative transverse PET (a), fused (b) and CT (c) images of ^{18}F -FDG PET/CT, and contrast-enhanced CT (d) images of a 70-year-old woman with distal bile duct cancer showing low SUV_{max} of 2.7, SUV_{avg} of 2.5, MTV of 0.2 cm^3 , and TLG of 0.6 cm^3 for the primary tumor (white arrow). The patient died 10.6 months after curative surgery due to peritoneal seeding

Although the prognostic impact of tumor growth type in distal bile duct cancer has not yet been confirmed, significantly lower SUV_{max} , SUV_{avg} , MTV, and TLG were found in the periductal infiltrating group compared with those in the papillary groups ($p = 0.001$, < 0.001 , 0.003 , and 0.003 , respectively). However, there was no significant difference in survival based on tumor growth pattern. Therefore, tumor ^{18}F -FDG uptake may reflect both tumor metabolism and tumor growth patterns, which may result in the lower SUV_{max} , which was associated with worse prognostic factors in our study. It is possible that most patients in a previous study had papillary type cancer [16], which may have contributed to the different results. In addition, in the previous study, 15 patients (60%) had tumor SUV_{max} of greater than 4.0 and the others ($n = 10$, 40%) had less than 4.0 of tumor SUV_{max} . In contrast, the tumor SUV_{max} was less than 4.0 in 26 patients of 40 patients (65%) in our study. In other words, low metabolic tumors were more common in our study than that in previous one. This also supports that the tumor characteristics of enrolled patients might be different from previous study. This might result in different optimal cutoff values in PET parameters between two studies as well. Finally, most subjects underwent the insertion of biliary drainage catheter insertion and antibiotic administration due to active cholangitis. It is known that cholangitis can induce variable degrees of increased ^{18}F -FDG uptake in the biliary tree, which could affect tumor ^{18}F -FDG uptake [20, 21]. Therefore, the tumor ^{18}F -FDG uptake might be overestimated if there is associated inflammatory activity.

In our study, low metabolic tumors were associated with worse prognosis than high metabolic tumors in patients with distal bile duct cancer undergoing curative surgery. Therefore,

it is necessary to perform close clinical follow-up for recurrence in low metabolic tumors. Conflicting results from previous studies warrant further large-scale studies to confirm prognostic values, associated tumor ^{18}F -FDG uptake, and tumor growth pattern in distal bile duct cancer.

There were several limitations to this study. First, the number of cases to evaluate the prognostic value of ^{18}F -FDG PET/CT in the distal bile duct cancer was small. Second, the retrospective design of this single center study could have caused selection bias.

Conclusion

The SUV_{max} of a primary tumor measured by ^{18}F -FDG PET/CT is an independent significant prognostic factor for overall survival in patients with distal bile duct cancer. However, because these results conflict with those reported by previous studies, additional larger-scale studies are warranted.

Compliance with Ethical Standards

Conflict of Interest Hyun Kyung Yi, Yong-Jin Park, Ji Hoon Bae, Jong Kyun Lee, Kwang Hyuk Lee, Seong Ho Choi, Kyung-Han Lee, Byung-Tae Kim, and Joon Young Choi declare that they have no conflicts of interest.

Ethics Statement All procedures performed in studies that involved human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

For this type of study, formal consent was not required.

Informed Consent The institutional review board of our institute approved this retrospective study, and the requirement to obtain informed consent was waived.

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