Preoperative ^{18}F-FDG PET-CT Maximum Standardized Uptake Value Predicts Recurrence of Biliary Tract Cancer

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Abstract. *^{18}F-Fluorodeoxyglucose positron-emission with computed tomography (^{18}F-FDG PET-CT) is an imaging technique based on the increased uptake of glucose characteristically seen in malignant lesions. The preoperative maximum standardized uptake value (SUV_{max}) of PET-CT has been identified as a powerful significant prognostic factor for predicting recurrence in malignant tumors. Therefore, the aim of this study was to determine whether ^{18}F-FDG PET-CT has a prognostic significance in patients with biliary tract cancer after surgical resection. From April 2006 to February 2013, 64 patients who underwent curative resection for biliary tract cancer were reviewed retrospectively. Clinical diagnoses of patients were: intrahepatic cholangio-carcinoma (n=6), hilar cholangiocarcinoma (n=6), extrahepatic cholangio-carcinoma (n=22), gall bladder cancer (n=14) and ampullar cancer (n=16). The mean preoperative SUV_{max} value was 5.1±4.7. The mean follow-up duration was 27 months. Recurrence-free survival at 1, 2 and 5 years were 75.9%, 63.3% and 47.1%. In the univariate analysis, N stage, poor tumor differentiation, the presence of lymphatic invasion and high SUV_{max} (>5.0) were significant risk factors for recurrence. The multivariate analysis showed a high preoperative SUV_{max} (>5.0) to be an independent risk factor for tumor recurrence (p=0.008). In conclusion, preoperative SUV_{max} of the primary tumor was significantly associated with recurrence in patients with biliary tract cancer.*

Biliary tract cancer, which includes intrahepatic cholangiocarcinoma, hilar cholangiocarcinoma, gallbladder carcinoma, extrahepatic cholangiocarcinoma, and ampullar cancer, is a heterogenous group of tumors that arise from biliary duct epithelium.

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Many articles have described the benefits of surgery for biliary tract cancer, resulting in a 5-year survival of up to 50% (1, 2). Nevertheless, tumor recurrence after curative resection remains a major problem. Approximately 60% of patients develop recurrence of their disease after curative resection of biliary tract cancer (3). Therefore, it is necessary to find predictive factors relevant to tumor recurrence to improve the survival outcomes.

Recently, ^{18}F-fluorodeoxyglucose positron-emission with computed tomography (^{18}F-FDG PET-CT) has been used for the diagnosis and staging of various types of cancers. In addition, ^{18}F-FDG PET-CT evaluates the proliferative activity and malignant potential of tumors which influence the prognosis of patients (4-6). Some reports demonstrated that the preoperative maximum standardized uptake value (SUV_{max}) of ^{18}F-FDG PET-CT was a powerful significant prognostic factor in various malignancies (7-9). However, the SUV_{max} of biliary tract cancer in regard to tumor recurrence is less well-defined.

Therefore, the aim of the present study was to determine whether ^{18}F-FDG PET-CT has a prognostic significance in patients with biliary tract cancer after surgical resection.

Patients and Methods

Patients. From April 2006 to February 2013, 78 patients underwent curative resection for biliary tract cancer at the Kyunghee University Hospital, Korea. Among them, 64 patients who underwent curative resection and preoperative ^{18}F-FDG PET-CT were reviewed retrospectively.

^{18}F-FDG PET-CT study. All patients fasted for at least 6 h before ^{18}F-FDG PET-CT. The blood glucose level was checked before ^{18}F-FDG administration and the patient was rescheduled if the blood glucose level exceeded 130 mg/dl. A range of 370-555 MBq of ^{18}F-FDG were injected intravenously. Scanning began 60 min after voiding. No intravenous contrast agent was used for the CT scans. Imaging and data acquisition were performed on a dual-slice Philips Gemini System (Philips Medical Systems, Amsterdam, the Netherlands). A total of 8-10 bed positions were available, and the acquisition time per bed position was 3 min. All patients were examined in the supine position with their arms raised. The

Table I. *Demographic and clinical characteristics of the study population.*

Variable	N
Age (mean±SD), years	61.3±10.7
Gender	
Male	42 (65.6%)
Female	22 (34.4%)
Final diagnosis	6 (9.4%)
Intrahepatic cholangiocarcinoma	6 (9.4%)
Hilar cholangiocarcinoma	
Extrahepatic cholangiocarcinoma	22 (34.3%)
Gall bladder cancer	14 (21.9%)
Ampullar cancer	16 (25.0%)
T Stage	
1	6 (9.4%)
2	37 (57.8%)
3	21 (32.8%)
N Stage	
0	51 (79.7%)
1	13 (20.3%)
Mean CA19-9 (U/ml)	762.6±2333.9
Mean SUV_{max}	5.1±4.7
Treatment	
Hepatectomy	10 (15.6%)
Bile duct resection	4 (6.2%)
Pancreatoduodenectomy	36 (56.3%)
Extended cholecystectomy	14 (21.9%)

SD: Standard deviation, CA: carbohydrate antigen, SUV_{max}: maximum standardized uptake value.

Table II. *Maximum standardized uptake value (SUV_{max}) according to prognostic parameters.*

Variable	Mean SUV_{max}	*p*-Value
Age		
≤60 years	3.9	0.493
>60 years	3.1	
T Stage		
1	5.6	0.578
2	5.7	
3	4.1	
N Stage		
0	5.2	0.731
1	4.7	
Tumor size		
≤5 cm	4.3	0.000
>5 cm	12.6	
Tumor differentiation		
Well	4.6	0.816
Moderate	5.4	
Poor	4.1	
Lymphatic invasion		
Absent	5.4	0.562
Present	4.4	
Perineural invasion		
Absent	5.6	0.403
Present	4.4	
Vascular invasion		
Absent	5.2	0.791
Present	4.7	

attenuation-corrected PET images, CT images, and co-registered PET-CT images were analyzed simultaneously by a board-certified nuclear medicine physician on a workstation. Tumors were defined as positive FDG uptake if the radioactivity of the tumors was higher than that of the surrounding liver tissue in the visual analysis. Images of each biliary tumor were assessed semiquantitatively by measuring and calculating the SUV_{max} normalized to lean body mass.

Patient follow-up. Patients were examined for tumor recurrence by contrast enhanced CT every 3-6 months and blood test, including tumor markers carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19-9, every 2-3 months after discharge. Recurrence was defined as emergence of radiological findings compatible with biliary tract cancer.

Statistical analysis. Data are presented as the mean±standard deviation. Kaplan–Meier estimates of recurrence-free survival and recurrence were calculated and compared with the log-rank test. Multivariate Cox modeling was performed using variables with a significant difference between groups based on the results of univariate analyses. A *p*-value of less than 0.05 was considered statistically significant.

Results

Patients' characteristics. The study group comprised of 42 men and 22 women, with a mean age of 61.3±10.7 years (Table I). All patients underwent curative surgical resection. The mean follow-up duration was 27 months.

^{18}F-FDG PET-CT and pathological parameters of the primary tumor. Table II shows SUV_{max} in relation to pathological parameters. The mean preoperative SUV_{max} was significantly higher in patients with large tumor size (>5 cm). However, age, T stage, tumor differentiation, lymphatic invasion, perineural invasion and vascular invasion were not associated with preoperative SUV_{max} in this study.

^{18}F-FDG PET-CT and prediction of recurrence. Recurrence-free survival at 1, 2 and 5 years was 75.9%, 63.3% and 47.1% (Figure 1). In the univariate analysis, N stage, poor tumor differentiation, the presence of lymphatic invasion and high SUV_{max} (>5.0) were significant risk factors for

Table III. *Univariate analysis of risk factors for recurrence-free survival.*

Variable	No recurrence (n)	Recurrence (n)	*p*-Value
Age			
≤60 years	19	9	0.209
>60 years	20	16	
Gender			
Male	26	16	0.807
Female	13	9	
T Stage			
1	5	1	0.452
2	23	14	
3	11	10	
N Stage			
0	34	17	0.009
1	5	8	
Tumor size			
≤5 cm	38	22	0.074
>5 cm	1	3	
Tumor differentiation			
Well	9	0	0.019
Moderate	28	19	
Poor	2	6	
Lymphatic invasion			
Absent	34	17	0.010
Present	5	8	
Perineural invasion			
Absent	22	16	0.761
Present	17	9	
Vascular invasion			
Absent	35	22	0.220
Present	4	3	
SUV_{max}			
≤5	21	8	0.006
>5	5	10	

SUV_{max}: Maximum standardized uptake value.

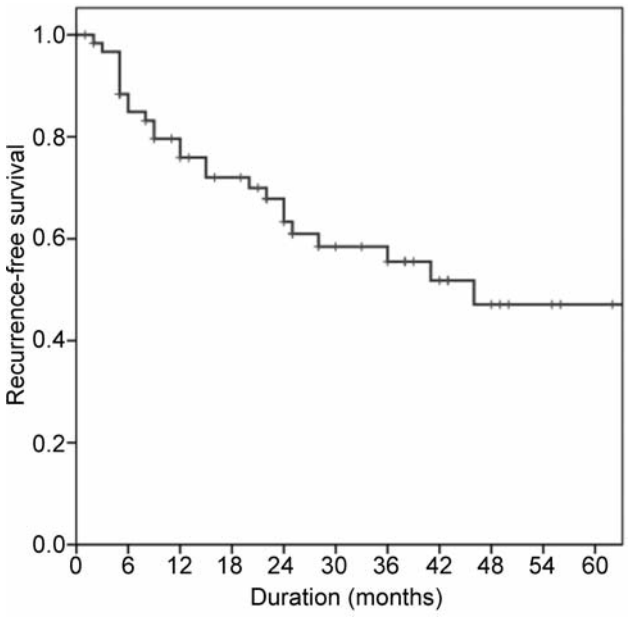

Figure 1. *Recurrence-free survival curve of patients with biliary tract cancer.*

Table IV. *Multivariate analysis of risk factors for recurrence-free survival.*

Variable	Category	Hazard ratio (95% confidence interval)	*p*-Value
SUV_{max}	≤5	Reference	0.008
	>5	4.124 (1.459-11.661)	
Lymphatic invasion	Absent	Reference	0.367
	Present	1.710 (0.533-5.489)	
Tumor differentiation	Well/Moderate	Reference	0.972
	Poor	1.269 (0.338-4.760)	
N Stage	0	Reference	0.992
	1	1.006 (0.324-3.118)	

SUV_{max}: Maximum standardized uptake value.

recurrence (Table III). The multivariate analysis showed high SUV_{max} (>5.0) to be independent risk factors for tumor recurrence (*p*=0.008, hazard ratio=4.124, 95% confidence interval=1.459-11.661) (Table IV).

Discussion

In our study, we investigated the prognostic significance of ^{18}F-FDG PET-CT in patients with biliary tract cancer after surgical resection. We discovered that the mean SUV_{max} was significantly higher in patients with large tumor sizes (>5 cm). Furthermore, SUV_{max} on ^{18}F-FDG PET-CT was an independent risk factor for tumor recurrence at multivariate analysis.

^{18}F-FDG PET-CT is rapidly modifying tumor diagnosis, treatment planning, and monitoring of tumor metastasis and recurrence. Moreover, ^{18}F-FDG uptake on PET-CT is a useful molecular marker in evaluating tumor aggressiveness (10). Harris reported that increased glucose metabolism in cancer cells was associated with oncogene activation, hypoxic conditions and angiogenesis (11). The more aggressive the tumor biology, the more glucose is required for the increased tumor growth and progression. Zhang *et al*. demonstrated that ^{18}F-FDG PET-CT may be used to non-invasively assess biological aggressiveness of non-small cell lung cancer, identifying the surgically-treated patients with poor prognosis who could benefit from additional therapy (12).

In this study, we investigated the relationship between metabolic activity by ^{18}F-FDG PET-CT and tumor aggressiveness. Tumor size was closely associated with high

SUV_{max} on ^{18}F-FDG PET-CT. Furthermore, the preoperative SUV_{max} in the primary tumor on ^{18}F-FDG PET-CT was a significant prognostic factor for predicting recurrence in biliary tract cancer. There is no standard SUV_{max} cut-off value defining the prognosis in patients with bile duct cancer. We used several approaches to determine the best cut-off value of SUV_{max} for predicting recurrence. Multiple statistical analyses using various cut-off values revealed that SUV_{max} of 5.0 was the most significant cut-off value of metabolic activity for recurrence of biliary tract cancer. SUV_{max} was an independent risk factor for recurrence after adjustment of several tumor biology-related factors in the multivariate analysis of this study. More frequent and intensive follow-up or prophylactic adjuvant treatment in patients with high SUV_{max} in ^{18}F-FDG PET-CT may be warranted.

In conclusion, we found that preoperative SUV_{max} of the primary tumor was significantly associated with recurrence in patients with biliary tract cancer and may allow for individualization of patient care. Future studies are warranted to validate our results and define the prognostic effect of ^{18}F-FDG PET-CT on bile duct cancer.

Conflicts of Interest

The Authors indicate that no potential conflicts of interest exist

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