Usefulness of Preoperative ^{18}F -FDG-PET in Detecting Invasive Intraductal Papillary Neoplasm of the Bile Duct

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Abstract. *Background/Aim:* Preoperative identification of the invasive component remains challenging in intraductal papillary neoplasm of the bile duct (IPNB). We evaluated the ability of preoperative ^{18}F -fluorodeoxyglucose positron emission tomography (^{18}F -FDG-PET) to differentiate between non-invasive IPNB, invasive IPNB, and papillary cholangiocarcinoma (CCA). *Patients and Methods:* The maximum standardized uptake values (SUV_{max}) of 11 patients with IPNB (6 non-invasive and 5 invasive) and 20 with papillary CCA who underwent pre-surgical ^{18}F -FDG-PET were assessed. The SUV_{max} cut-off that predicts an invasive component was determined using receiver operating characteristic (ROC) curve analysis. *Results:* The SUV_{max} in patients with invasive IPNB and papillary CCA were significantly higher than in patients with non-invasive IPNB ($p=0.035$ and 0.0025 , respectively). ROC curve analysis revealed an optimal SUV_{max} cut-off of 4.5, which had 94.5% accuracy, 76.0% sensitivity, and 100% specificity. *Conclusion:* Our data suggest that the preoperative ^{18}F -FDG-PET SUV_{max} can differentiate non-invasive IPNB from invasive IPNB and papillary CCA.

Cholangiocarcinoma (CCA) is a rare, but highly lethal malignancy; surgical resection is the only curative approach. Intraductal growth-type CCA is less frequent and carries a more favourable prognosis following resection than other subtypes (1-3). Recently, several intraductal neoplasms of the bile duct that are pre-invasive and present as a precursor lesion of CCA have been identified, including intraductal

papillary neoplasm of the bile duct (IPNB). IPNB is characterized by a predominantly papillary growth pattern with fine fibrovascular cores in dilated bile ducts (4, 5). Previous studies have shown that non-invasive IPNB has a favourable prognosis (6, 7). However, the preoperative identification of invasive IPNB components is challenging. Therefore, surgical resection remains the mainstay of management of IPNB.

Preoperative imaging plays a crucial role not only in the diagnosis of IPNB, but also in devising the surgical strategy. Preoperative identification of the intraductal mass has recently improved with advances in imaging (8). Although computed tomography (CT) and magnetic resonance imaging (MRI) are frequently used to investigate biliary tumours, preoperative identification of the invasive component of IPNB using these modalities remains challenging (9). We reported that ^{18}F -fluorodeoxyglucose positron emission tomography (^{18}F -FDG-PET), which is less invasive, is useful for the management of biliary tract cancers (10, 11). To our knowledge, there are no published reports on identifying invasive component in IPNB using preoperative ^{18}F -FDG-PET.

Cholangiocarcinoma with intraductal papillary growth and IPNB can be confused with each other, as they share many common features and appear to be overlapping pathological entities. Cholangioscopy can confirm the histology and assess the extent of the tumor; however, pathologic diagnosis by preoperative biopsy does not necessarily ascertain the degree of atypia and this varies among IPNBs. Therefore, the aim of this study was to assess the usefulness of preoperative ^{18}F -FDG-PET in differentiating between non-invasive IPNB, invasive IPNB, and papillary CCA.

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Key Words: Intraductal papillary neoplasm of the bile duct, papillary cholangiocarcinoma, ^{18}F -FDG-PET, SUV_{max} .

Patients and Methods

Patients. This is a retrospective review of patients with biliary tumours that showed predominantly intraductal papillary growth who underwent ^{18}F -FDG-PET preoperatively at the Kyoto University Hospital (Kyoto, Japan) between 2002 and 2017. The inclusion criteria were (1) a diagnosis of IPNB or papillary CCA pathologically

confirmed by experienced pathologists, and (2) undergoing resection with curative-intent within 2 weeks after undergoing ^{18}F -FDG-PET. IPNBs (including invasive and non-invasive lesions) and papillary CCA were defined as described previously (12, 13). Briefly, IPNBs were provisionally defined as papillary neoplasms confined to the epithelium without stromal invasion, or those consisting of a neoplastic epithelium and thin fibrovascular stalks with an overall uniform papillary architecture throughout the tumour. Papillary CCAs were invasive tumours that grossly showed predominant intraductal growth and histologically comprised mainly papillary or papillotubular adenocarcinomas with more complex papillary structures. The tumours were also classified into 4 types as described previously: pancreaticobiliary, intestinal, gastric, and oncocytic (12). Patients with no available ^{18}F -FDG-PET data or those with histologically different diseases were excluded. The clinicopathological characteristics and survival data of these patients were extracted from a prospectively maintained institutional database with follow-up data updated on September 1, 2017. The study protocol was approved by the ethical committee of the Graduate School of Medicine, Kyoto University (G1019). Written informed consent was obtained from the participants, and we announced that they were able to opt out at any time by contacting the hospital or via our website.

^{18}F -FDG-PET studies. ^{18}F -FDG-PET studies were performed using a PET/CT scanner (Advance or Discovery ST Elite or Discovery IQ; GE Healthcare, Milwaukee, WI, USA). Patients fasted for at least 4 hours before undergoing ^{18}F -FDG-PET. The plasma glucose level was checked before the injection of ^{18}F -FDG. Data acquisition commenced approximately 60 min after intravenous administration of ^{18}F -FDG. The injected dose was 259-407 MBq (approximately 10 mCi) for the Advance scanner or approximately 3.7 MBq/kg body weight (0.1 mCi) for the Discovery ST Elite and Discovery IQ scanner. Emission data were acquired in a two-dimensional (2D) mode for 3 min per bed with the Advance scanner, or in a 3D mode for 2-3 min per bed with the Discovery ST Elite and Discovery IQ scanner. For transmission scanning, data acquisition was performed for 1 min per bed with the Advance scanner. In PET/CT scanning with the Discovery ST Elite and Discovery IQ scanner, CT data were used for attenuation correction. For the Advance scanners, images were reconstructed using the ordered-subsets expectation-maximization (OSEM) algorithm, and the VUE Point Plus 3D OSEM algorithm was used for image reconstruction when using the Discovery ST Elite and Discovery IQ scanner. For quantitative analysis, at least 2 board-certified radiologists/nuclear medicine physicians assessed ^{18}F -FDG accumulation on a workstation by calculating the standardized uptake value (SUV) in the regions of interest (ROIs) placed over the suspected lesions using all available clinical information and correlative conventional imaging for anatomic guidance. The SUV was calculated for the quantitative analysis of the tumours' ^{18}F -FDG uptake as follows: $\text{SUV} = \text{C (kBq/mL)} / \text{injected dose (kBq)} / \text{body weight (kg)}$, where C is the tissue activity concentration measured by PET. The maximum SUV (SUV_{max}) for the focal area of uptake, defined as the highest SUV in the pixel within the ROIs, was measured and recorded.

Statistical analysis. Continuous values are expressed as median (range) and were compared using the Wilcoxon signed ranks test. Categorical variables were compared using Fisher's exact test. Overall survival (OS) was calculated from the date of surgery to the date of death or last follow-up. Recurrence-free survival (RFS) was

calculated using the date of death or recurrence as the terminal event using the Kaplan-Meier method, and was analysed using the log-rank test. The SUV_{max} cut-off that predicts tumour invasion was determined using receiver operating characteristic (ROC) curve analysis. The optimal SUV_{max} cut-off, sensitivity, and specificity were determined using the Youden index. All analyses were 2-sided, and differences were considered significant when $p < 0.05$. All statistical analyses were performed using the JMP statistical software package (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics. There were 377 patients with primary biliary neoplasms who underwent surgical resection during the study period. Forty patients had biliary tumours that showed predominantly intraductal papillary growth, 9 of whom did not undergo preoperative ^{18}F -FDG-PET; the remaining 31 patients were included in this study. Eleven tumours were classified as IPNBs and 20 as papillary CCAs. The clinical characteristics of the patients are shown in Table I; none of the patients received any treatment before surgery, and all underwent curative surgical resection. The median follow-up time after surgery was 69 months (range=4-171 months). The 1-, 3-, and 5-year OS rates were 89.7%, 72.8%, and 62.7%, respectively. Patients with non-invasive IPNB had no recurrence after surgery, and only 1 patient with invasive IPNB experienced intrahepatic recurrence and underwent repeat curative resection. There were no significant differences in recurrence rates between each group (Figure 1A). However, a significant difference was found in survival between patients with IPNBs and those with papillary CCA. Patients with papillary CCA exhibited poorer OS than those with IPNBs (5-year OS, 47.0% vs. 100%, respectively, $p=0.020$, Figure 1B). No significant differences in clinical factors between the 3 groups were found; tumour locations, tumour sizes, and vascular invasion patterns were also comparable. However, there were significant differences in the depth of tumour invasion, lymph node metastasis, and histological subtype between IPNBs and papillary CCA ($p=0.047$, 0.028, and 0.011, respectively).

Association between ^{18}F -FDG accumulation and histopathological type. As shown in Figure 2, there was no significant difference in SUV_{max} between invasive IPNB and papillary CCA ($p=0.918$). However, the SUV_{max} in patients with invasive IPNB was significantly higher than in those with non-invasive IPNB (median, 4.5 and 2.4, respectively, $p=0.035$). Moreover, there was a significant difference in SUV_{max} between non-invasive IPNB and papillary CCA (medians, 2.4 and 6.2, respectively, $p=0.0025$).

Ability of SUV_{max} to predict tumour invasion. We performed ROC curve analysis to determine the optimal SUV_{max} cut-

Table I. Comparative analysis of clinicopathological findings between non-invasive IPNB, invasive IPNB, and papillary CCA.

Variables	Non-invasive IPNB n=6	Invasive IPNB n=5	Papillary CCA n=20	p-Value
Clinical factors				
Gender				
Male, n (%)	5 (83.3)	2 (33.3)	12 (60.0)	NS
Age (years)				
Median (range)	68 (54-81)	77 (64-82)	69 (52-84)	NS
CEA (ng/mL)				
Median (range)	1.4 (0.6-3.9)	1.8 (1.0-4.7)	2.6 (0.2-11.4)	NS
CA19-9 (IU/mL)				
Median (range)	24.6 (1.0-79.4)	18.7 (8.1-22.0)	24.0 (1.0-411.5)	NS
Surgical procedure, n (%)				
Right hepatectomy	1 (16.7)	0	2 (10.0)	NS
Left hepatectomy	3 (50.0)	3 (60.0)	4 (20.0)	
Extended right	0	0	2 (10.0)	
Extended left	0	0	2 (10.0)	
Pancreato-duodenectomy	2 (33.3)	2 (40.0)	9 (45.0)	
Other	0	0	1 (5.0)	
Max size of dilated bile duct median (range), (mm)	12 (10-14)	12 (3.5-50)	10 (4.0-53)	NS
Mucobilia				
Present, n (%)	0	1 (20.0)	3 (15.0)	NS
Pathological factor				
Tumour location, n (%)				
Hilar	2 (33.3)	1 (20.0)	3 (15.0)	NS
Intrahepatic	2 (33.3)	2 (40.0)	7 (35.0)	
Distal	2 (33.3)	2 (40.0)	10 (50.0)	
Tumour size (mm)				
Median (range)	22.5 (5.0-54.0)	28.0 (24.0-36.0)	25.0 (5.0-65.0)	NS
Vascular invasion				
Present, n (%)	0	0	3 (15.0)	NS
Bile duct invasion, n (%)				
Within epithelial	0	4 (80.0)	10 (50.0)	*†
With duct wall invasion	0	1 (20.0)	10 (50.0)	
Lymph node metastasis				
Present, n (%)	0	0	8 (40.0)	†
Histological subtype, n (%)				
Pancreaticobiliary	2 (33.3)	3 (60.0)	17 (85.0)	*†
Intestinal	0	0	1 (5.0)	
Gastric	3 (50.0)	1 (20.0)	0	
Oncocytic	1 (16.7)	1 (20.0)	1 (5.0)	
Unknown	0	0	1 (5.0)	

CA 19-9: Carbohydrate antigen 19-9; CEA: carcinoembryonic antigen; IPNB: intraductal papillary neoplasm of bile duct; CCA: cholangiocarcinoma; NS: not significant. * $p < 0.05$ between non-invasive IPNB and papillary CCA. † $p < 0.05$ between IPNBs and papillary CCA.

off that best predicts tumour invasion (Figure 3); the optimal cut-off value was 4.5 (area under the curve=0.913; 95% confidence interval=0.728-0.977). The accuracy, sensitivity, specificity, positive predictive value, and negative predictive value for this cut-off were 94.5, 76.0, 100, 100, and 50%, respectively. This cut-off value was unable to distinguish papillary CCA from invasive IPNB, however, tumours with an SUV_{max} greater than the 4.5 cut-off value were shown to have invasive potentials.

Discussion

In this study, we assessed ¹⁸F-FDG accumulation in 31 patients with biliary tumours that showed predominantly intraductal papillary growth. Notably, we found that the SUV_{max} in patients with invasive IPNB and papillary CCA were significantly higher than that in patients with non-invasive IPNB. Our data suggest that the preoperative ¹⁸F-FDG-PET SUV_{max} can predict the invasive potential of IPNBs in patients with these tumours.

Figure 1. Post-surgical overall and recurrence-free survival of patients according to histopathological findings. The Kaplan–Meier method was used to determine patient survival, while the log-rank test was used to compare survival between patients according to the histopathological type of the neoplasm. (A) Non-invasive IPNB vs. tumours with invasive component (invasive IPNB and papillary CCA), * $p=0.116$. (B) IPNBs (invasive and non-invasive) vs. papillary CCA, ** $p=0.020$. IPNB: Intraductal papillary neoplasm of bile duct; CCA: cholangiocarcinoma.

Figure 2. The association between the SUV_{max} and histopathological type. The box-and-whisker plot show the range and 25th percentile/median/75th percentile, assessed using the Wilcoxon signed ranks test between 2 groups. IPNB: Intraductal papillary neoplasm of bile duct; CCA: cholangiocarcinoma; SUV_{max} : maximum standardized uptake value.

Figure 3. Receiver operating characteristic curve of the maximum standard uptake value for predicting tumour invasion, showing the optimal cut-off value to be 4.5 (area under the curve=0.913; 95% confidence interval=0.728-0.977; accuracy, 94.5%; sensitivity, 76.0%; and specificity, 100%).

Although IPNB is listed in the 2010 World Health Organization classification of bile duct tumours, this new entity encompasses both benign and malignant histopathological stages. In our series, patients with IPNBs had more favourable prognoses than those with papillary CCA, which was consistent with previous studies (12, 14, 15). Because IPNBs share similar morphological, clinicopathological, and biological features with intraductal papillary mucinous neoplasms (IPMNs) of the pancreas, IPNB is considered the biliary counterpart of pancreatic IPMN (6, 16-18). Similar to IPNB, IPMN presents at various histopathological stages ranging from benign to malignant; patients with benign IPMN can be observed without surgery, while the postoperative prognosis of patients with invasive IPMN is poor and similar to that of patients with pancreatic ductal adenocarcinoma (19-21). Therefore, the preoperative differentiation between benign and malignant IPMN is important to be determined in order to provide the patients with appropriate treatments. Tomimaru *et al.* reported that the SUV_{max} in patients with malignant IPMN was significantly higher than in patients with benign IPMN (22). Moreover, previous studies showed that ¹⁸F-FDG-PET can estimate the malignant potential of tumours (23-26); similarly, our study shows that the SUV_{max} values of IPNB with invasive component are significantly higher than those of non-invasive tumours.

The common radiologic findings for IPNB are an intraductal mass and bile duct dilatation. Although these findings can be recognized by CT and MRI, the sensitivity of detection using these modalities is reported to be in the range of 41.2-97% (9, 27, 28). Despite recent advances in imaging technologies, the diagnosis of an invasive component in biliary tumours remains challenging, and a tendency to overestimate invasion to the surrounding organs and vessels has been reported (28). In our study, we proposed an optimal SUV_{max} cut-off (4.5) for predicting the existence of an invasive component; its accuracy, sensitivity, and specificity were 94.5, 76.0, and 100%, respectively. Hence, this value's diagnostic capability was considered relatively high for predicting an invasive characteristic. Our findings may therefore be useful for both providing better solutions for non-surgical candidates and improving therapeutic outcomes in surgical candidates.

A limitation of our study was its retrospective, single-centre design; this led to unavoidable selection bias. This study cohort was also small (31 patients), which is a general weakness in studies of uncommon diseases. Further prospective studies with larger patient cohorts and longer clinical follow-up periods are required to validate our findings. Furthermore, the possibility of a partial volume effect should be considered, as this influences the precision of the SUV_{max} because the intraductal masses in IPNBs are generally small.

In summary, preoperative metabolic activity measured by ¹⁸F-FDG-PET was significantly associated with an invasive characteristic in biliary tumours with predominantly intraductal papillary growth. The SUV_{max} obtained using ¹⁸F-FDG-PET may provide useful information regarding the features of these tumours and may allow for individualization of patient care.

Conflicts of Interest

The Authors declare no potential conflict of interests.

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Received April 7, 2018

Revised April 26, 2018

Accepted April 27, 2018