

Decision of Surgical Indication of Pancreatic Intraductal Papillary Mucinous Neoplasm by 18F-Fluorodeoxyglucose Positron Emission Tomography with Computed Tomography

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ABSTRACT

Background: Surgery for intraductal papillary mucinous neoplasm (IPMN) is indicated according to the international consensus guidelines (ICG), but ICG frequently overestimates invasive cancer. Utility of 18F-Fluorodeoxyglucose positron emission tomography with computed tomography (FDG-PET/CT) to differentiate invasive carcinoma (i-IPMC) from dysplasia is not well recognized.

Methods: Patients who underwent pancreatectomy for pathologically confirmed IPMN at our institution between 2008 and 2022 were evaluated. For the comparison the patients who received FDG-PET/CT followed by surgical resection for pathologically confirmed PDAC were selected. Which of ICG criteria or the maximum standard uptake values (SUV) at 60 minutes, 120 minutes after FDG injection, or the rate of their change denoted as SUV1, SUV2, or Δ SUV [(SUV2-SUV1)/SUV1 $\times$ 100] predicted i-IPMC better was evaluated.

Results: Totally 120 patients underwent pancreatectomy following preoperative evaluation with FDG-PET/CT. The number of patients with low grade dysplasia, high grade dysplasia, i-IPMC, and PDAC was 11, 8, 52, and 49 patients, respectively. Among 71 patients with IPMN, any of the findings comprising high risk stigmata of ICG were recognized in 64%, 63%, and 60% of those with low, high grade dysplasia, and i-IPMC, respectively ($P=1.000$). Multivariate analyses including either of SUV1, SUV2, or Δ SUV showed that these indices (SUV1, odds ratio =37.5; SUV2, odds ratio =23.5; Δ SUV, odds ratio =290.3) but not the factors composing ICG criteria were independent predictor of i-IPMC.

Conclusion: FDG-PET/CT can diagnose malignancy more accurately than ICG and routine application as preoperative evaluation is recommended.

Key words: pancreatic IPMN, PET-CT, diagnoses and examination

Abbreviations:

IPMN: intraductal papillary mucinous neoplasm;
ICG: international consensus guidelines;
FDG-PET/CT: 18F-Fluorodeoxyglucose positron emission tomography with computed tomography;
PDAC: pancreatic ductal adenocarcinoma;
LGD: low-grade dysplasia;
HGD: high-grade dysplasia;
i-IPMC: invasive carcinoma;
HRS: high-risk stigmata;
WF: worrisome features;
SUV: standardized uptake value;
RFS: recurrence-free survival;
OS: overall survival;
AUC: area under the curve.

INTRODUCTION

Intraductal papillary mucinous neoplasm (IPMN) is a pancreatic cyst disease characterized by a wide spectrum of dysplastic changes. According to the 2019 World Health Organization (WHO) classification, IPMN is classified into lesions with low- and high-grade dysplasia and associated invasive carcinoma (1). Morphologically, it is classified into main pancreatic and branch duct types based

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on tumor location. Most cases of branch duct-type IPMN are benign, and the annual incidence of pancreatic cancer is reported to be 1.4-6.9% (2-5). The main pancreatic duct type is usually indicated for surgical resection upon diagnosis because of the high incidence of malignancy; however, invasive carcinoma is pathologically confirmed in 11-81% of patients who undergo surgical resection (6-11). The international consensus Fukuoka Guidelines (ICG) for the management of IPMNs of the pancreas recommend that comprehensive evaluation using imaging modalities such as computed tomography (CT), magnetic resonance imaging (MRI), or endoscopic ultrasonography (EUS) should be utilized to determine surgical indications. They propose a mural nodule ≥ 5 mm or dilated main pancreatic duct ≥ 10 mm as high-risk stigmata (HRS) indicating surgical resection (12). However, a recent study suggested an overestimation of malignancy by the ICG criteria, reporting that 19% of patients received unnecessary resection (13). Since IPMN is encountered more likely in elderly population, and pancreatic resection can result in lethal postoperative morbidity and/or long-term complications such as pancreatic exocrine insufficiency or diabetes mellitus (DM), more accurate preoperative differentiation of invasive carcinoma from dysplasia is expected. In addition, we occasionally encounter the patients with preoperative diagnosis of pancreatic ductal adenocarcinoma (PDAC) based on the imaging studies followed by pathologic diagnosis of IPMN. In such cases, ICG criteria cannot be applied.

Recently, 18F-Fluorodeoxyglucose positron emission tomography with computed tomography (FDG-PET/CT) has been increasingly used for the purpose of tumor staging or differentiation of malignant tumors from non-malignant tumors in various tumors (14-16). In pancreatic ductal adenocarcinoma, FDG-PET/CT is useful for assessing the response to chemotherapy or chemoradiotherapy (17). Several studies have reported the utility of FDG-PET/CT in differentiating invasive carcinoma from dysplasia in IPMN (18). However, it is controversial whether FDG-PET/CT has superior diagnostic performance compared to ICG. We previously reported that the rate of change in the maximum standardized uptake value at 60 min (SUV1) and 120 min (SUV2) using FDG-PET/CT (Δ SUV) was a predictor of postoperative recurrence in breast and pancreatic cancers (19,20). It is also reported that FDG accumulation increases in the delayed phase of malignancy and that Δ SUV can differentiate malignancy from inflammation (21). This study aimed to evaluate the ability of PET/CT to differentiate invasive carcinoma from dysplasia compared to the ICG criteria.

MATERIAL AND METHOD

Patients

This study was approved by the Institutional Review Board of the National Defense Medical College (#4610). Patients who underwent pancreatectomy for IPMN at the National Defense Medical College Hospital between January 2008 and April 2022 were retrospectively evaluated. Only patients with pathologically confirmed IPMN were selected. Each patient was histologically diagnosed with either adenoma with low-grade dysplasia (LGD), adenoma with high-grade dysplasia (HGD), or invasive carcinoma (i-IPMC). For the comparison, the patients preoperatively evaluated with PET/CT followed by the surgical resection for pathologically confirmed pancreatic ductal adenocarcinoma (PDAC) during the same period were also selected.

Collected data

The following clinical and pathologic data were collected for the analyses: patients' age, sex, history of diabetes, surgical procedures, and pathologic diagnosis based on the WHO classification. Tumor stage as pancreatic cancer was defined according to the 7th edition of the UICC staging system (22). Diabetes comorbidity was defined as a preoperative HbA1c level $\geq 6.5\%$. Preoperative findings indicating high-risk stigmata (HRS) and worrisome features (WF), according to the 2017 edition of ICG, were evaluated using preoperative imaging studies, including CT, MRI, and/or EUS, and blood examinations.

Evaluation of PET/CT

SUVmax at 60 and 120 min after FDG injection were denoted as SUV1 and SUV2, respectively. The Δ SUV was calculated using the following formula: $(\text{SUV2}-\text{SUV1})/\text{SUV1} \times 100$ (19). Cut-off values were determined by a receiver operating characteristic (ROC) curve analysis in relation to the pathological diagnosis of i-IPMC.

Comparison of FDG-PET/CT findings and ICG criteria

Which of the FDG-PET/CT findings represented as SUV1, SUV2, or Δ SUV or factors comprising HRS or WF in the ICG criteria more accurately predicted i-IPMC among patients with a preoperative diagnosis of IPMN were evaluated.

Statistics

Continuous data were expressed as medians and ranges and compared using the Mann-Whitney U test. Categorical data were compared using Pearson's χ^2 or Fisher's exact test, as appropriate. Univariate analyses were performed using logistic regression models. Survival curves were made by the Kaplan-Meier method and compared by log-rank test. All data were analyzed using the statistical software package JMP Pro, version 15.2 (SAS Institute, Japan). Differences were considered statistically significant at a P-value < 0.05.

RESULTS

Patients background

Totally 97 patients underwent surgical resection for pathologically confirmed IPMN during the study period. Twenty-six patients without preoperative evaluation by FDG-PET/CT were excluded. The remaining 71 patients were selected for the analyses in this study. The number of patients who underwent surgical resection for pathologically confirmed PDAC during the study period was 203 patients. Among them 49 patients (24%) who underwent FDG-PET/CT were selected. Surgical procedures and pathologic stages of the patients with low or high grade dysplasia, i-IPMC and PDAC were summarized in *table 1*. Postoperative recurrence-free survival (RFS) and overall survival (OS) curves of these three groups of

Table 1 - Characteristics of the whole patients

Pathologic diagnosis		LGD/HGD	i-IPMC	PDAC	P
number of patients		19	52	49	
Age (yr)		73 (63-79)	73 (55-87)	71 (50-86)	0.296
Sex, Male/Female		10/9	33/19	30/19	0.700
Surgical procedure	DP	7	6	18	0.525
	PD	10	34	30	
	TP	2	2	1	
pT	is	19	0	0	<0.001
	1	0	5	5	
	2	0	5	33	
	3	0	36	9	
	4	0	6	2	
pN	0	19	17	39	<0.001
	1	0	35	10	
pM	0	19	51	48	1.000
	1	0	1	1	
pStage	0	19	0	0	<0.001
	IA	0	4	3	
	IB	0	3	4	
	IIA	0	10	3	
	IIB	0	28	36	
	III	0	6	2	
	IV	0	1	1	

patients are shown in *fig. 1*. Both RFS and OS the i-IPMC group were significantly worse than those of dysplasia group, whereas they were comparable with those of PDAC group.

ICG criteria vs. histologic diagnosis

Table 2 shows the comparison of the frequency that each finding of HRS or WF was recognized between the

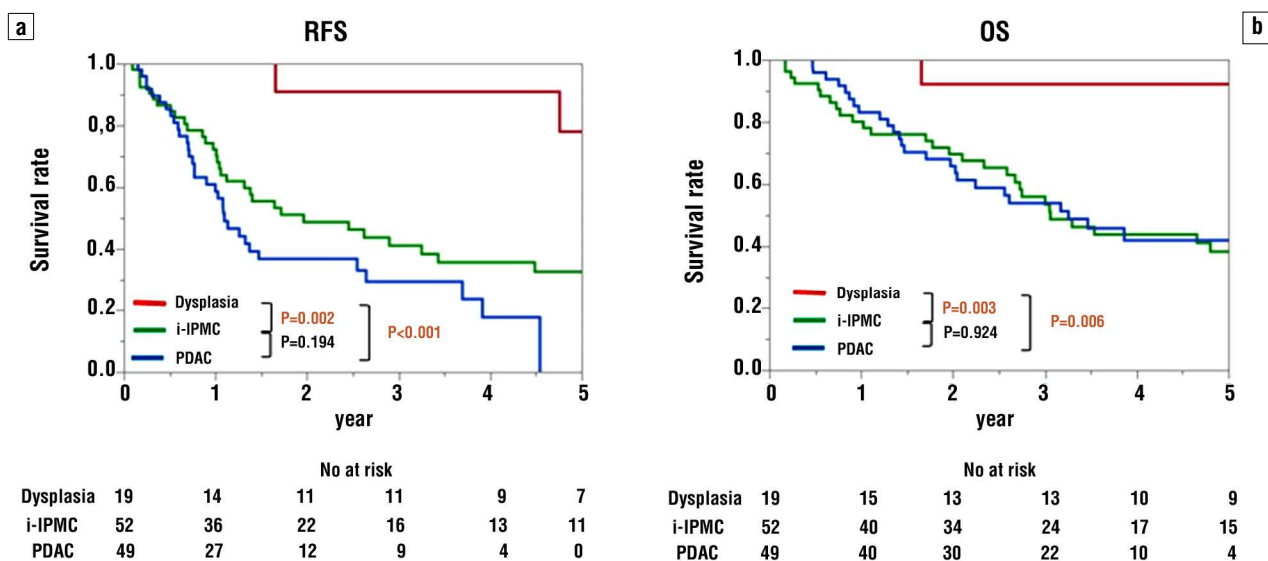


Figure 1 - Postoperative recurrence-free (a) and overall (b) survival curves of the patients with the pancreatic resection of intraductal papillary mucinous neoplasm (IPMN) followed by the pathologic diagnosis of dysplasia and invasive carcinoma (i-IPMC), and those with pathologic diagnosis of PDAC

Table 2 - Number of patients meeting the factors that compose of ICG criteria in preoperative imaging studies

	LGD (n=11)	HGD (n=8)	i-IPMC (n=52)	P-value
High risk stigmata (HRS), n(%)				
MPD $\geq$ 10 mm	3 (27%)	2 (25%)	15 (29%)	1.000
Enhancing mural nodule (MN) $\geq$ 5 mm	5 (45%)	5 (63%)	12 (23%)	0.056
Obstructive jaundice	0	0	13 (25%)	0.074
Any of the above	7 (64%)	5 (63%)	31 (60%)	1.000
Worrisome features (WF), n(%)				
Cyst $\geq$ 3 cm	5 (45%)	4 (50%)	8 (15%)	0.014
Enhancing MN $<$ 5 mm	0	0	2 (4%)	1.000
Thickened/enhanced cyst walls	4 (36%)	5 (63%)	13 (25%)	0.091
MPD size 5-9 mm	5 (45%)	5 (63%)	22 (42%)	0.583
Abrupt MPD caliber change with atrophy of distal pancreas	2 (18%)	1 (13%)	24 (46%)	0.068
Lymphadenopathy	0	0	4 (8%)	1.000
Increased CA19-9	2 (18%)	2 (25%)	32 (62%)	0.010
Cyst growth rate $\geq$ 5 mm/2 year	0	0	0	-
Any of the above	10 (91%)	7 (88%)	49 (94%)	0.405

three groups of patients with LGD, HGD, and i-IPMC. There was no significant difference in the presence of any factor suggesting HRS. Moreover, there was no significant difference in the proportion of patients with any of the findings comprising HRS (LGD, 7 patients (64%); HGD, 5 patients (63%), i-IPMC, 31 patients (60%); $P=1.000$). As for the factors indicating WF, there were significant differences in cyst diameter $\geq$ 3 cm ($P=0.014$), serum CA19-9 levels ($P=0.010$). Here, large cyst diameter was more frequently seen in the patients with dysplasia. The proportion of patients with any findings comprising WF was also comparable (LGD, 10 patients (91%); HGD, 7 patients (88%), i-IPMC, 49 patients (94%); $P=0.405$). The sensitivity, specificity, and accuracy of HRS based on the ICG criteria to predict i-IPMC were 74%, 37%, and 38%, respectively.

SUV and histologic diagnosis

Among 120 patients who underwent FDG-PET/CT, 37 had DM. There was no significant difference in SUV1, SUV2, or Δ SUV between patients with and without DM in any of dysplasia, i-IPMC, or PDAC group. Among 71 IPMN patients, the median SUV1 in patients with LGD/HGD, and i-IPMC was 0 (range, 0-14.3) and 4.7 (range, 0-22.1), respectively ($P=0.002$) (fig. 2a). That of SUV2 was 0 (range, 0-17.5) and 5.8 (range, 0-32.3) ($P=0.001$), respectively, and that of Δ SUV was 0 (range, -16.1-51.0), and 23.1 (range, -10.5-57.9), respectively (fig. 2 b,c). Ten patients (53%) with LGD/HGD and seven (13%) with i-IPMC showed no FDG accumulation. The median SUV1, SUV2, and Δ SUV of the patients with PDAC were 5.3 (range, 1.7-12.1), 6.8 (range, 1.9-18.0), and 25.4 (range, -13.9-65.0), respectively. SUV1 ($P=0.774$), SUV2 ($P=0.841$), and Δ SUV ($P=0.823$) was

comparable between the patients with i-IPMC and PDAC. ROC curve analyses among the patients with IPMN showed that the best cut-off of SUV1, SUV2, and Δ SUV to predict i-IPMC was 2.46 (area under the curve [AUC], 0.79), 3.22 (AUC, 0.79), and 17.6 (AUC, 0.74), respectively (fig. 3). The sensitivity, specificity, and accuracy of SUV1 $\geq$ 2.46 to predict i-IPMC were 85%, 69%, and 80%, respectively. Those of SUV2 $\geq$ 3.22 and Δ SUV $\geq$ 17.6 to predict i-IPMC patients who were diagnosed IPMN preoperatively were 82%, 68%, and 79%, and 65%, 79% and 69%, respectively (table 3).

Univariate and multivariate analyses for the predictors of invasive carcinoma

Table 3 shows the univariate and multivariate analyses of the predictors of i-IPMC among the IPMN patients. There were significant differences in Enhancing mural nodule ($P=0.023$), Obstructive jaundice ($P=0.015$), cyst diameter ($P=0.010$), abrupt MPD caliber change with atrophy of distal pancreas ($P=0.027$) and increased CA19-9 ($P=0.003$). SUV1 ($P<0.001$; odds ratio =11.9; 95% confidence interval [CI], 3.50-40.61), SUV2 ($P<0.007$; odds ratio =10.1; 95% confidence interval [CI], 3.03-33.8), and Δ SUV ($P=0.001$; odds ratio =6.9; 95% CI, 1.98-23.8) were also statistically significant. Multivariate analyses was performed including the above the first five factors and each of SUV1, SUV2, and Δ SUV, which revealed that SUV1 or SUV2 or Δ SUV was independent predictive factors.

DISCUSSION

The present study showed that FDG-PET/CT was superior to ICG as a predictor of i-IPMC among patients

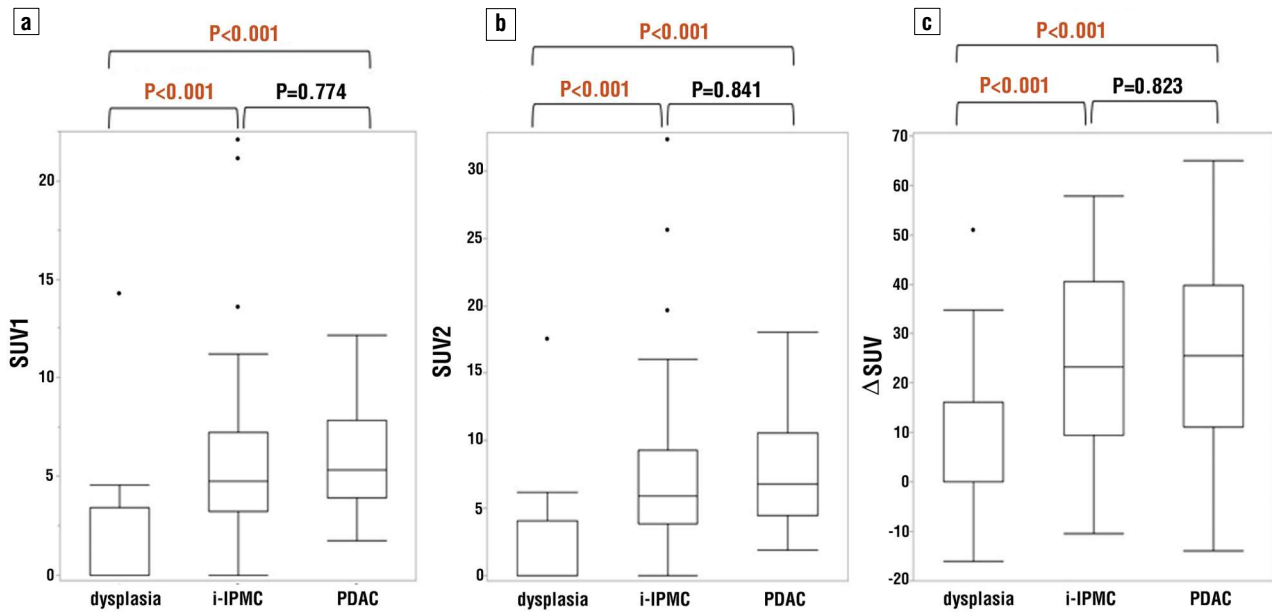


Figure 2 - Correlation between the histologic types and standard uptake value 1 (SUV1) (a), SUV2 (b), and Δ SUV (c). There was a significant difference between dysplasia (LGD/HGD) and invasive carcinoma (i-IPMC) in SUV1, SUV2, and Δ SUV ($p < 0.001$; Kruskal Wallis test)

with a preoperative diagnosis of IPMN. Particularly, higher specificity of Δ SUV to predict i-IPMC than HRS in ICG criteria suggested that FDG-PET/CT was useful to reduce the risk of unnecessary surgery. This aspect should be concerned since IPMNs are commonly diagnosed in elderly patient. Postoperative prognosis was significantly different between the patients with i-IPMC and dysplasia with the latter extremely low risk of recurrence postoperatively, while the former group showed comparable OS with those with PDAC.

Whether HGD should be an indication for resection remains controversial. Our series included only 8

patients; during the median postoperative follow-up of 64 months (range, 7-86), tumor recurrence occurred in only one patient in the remnant pancreas, which was resected, and only one patient died of pneumonia 6 months after surgery. There are reports that patients with HGD have a lower recurrence rate and better prognosis after resection than those with i-IPMC (23, 24). In this study, we included the patients with HGD and LGD into dysplasia group because FDG accumulation and postoperative prognosis was both similar (results were not shown).

According to the international consensus, the

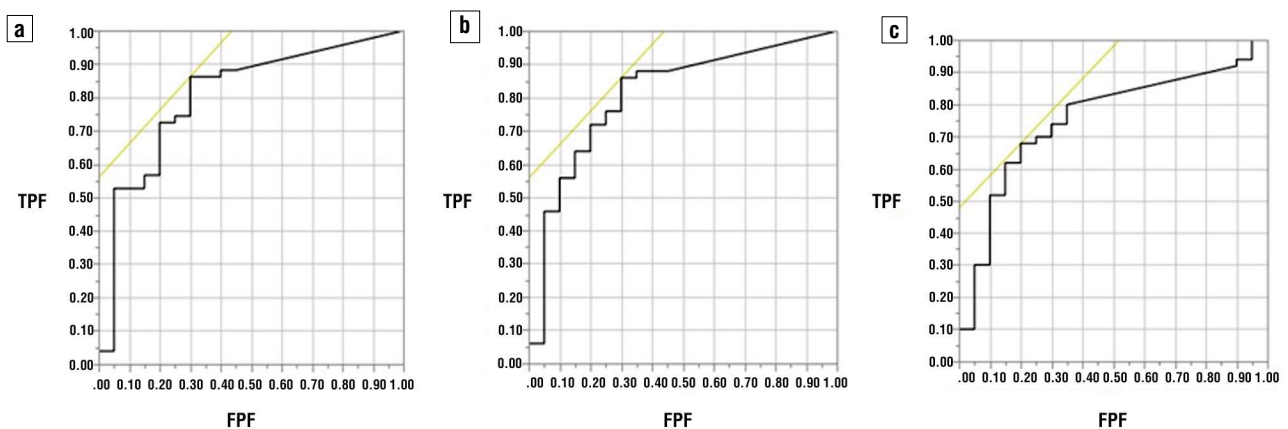


Figure 3 - Receiver operating characteristic (ROC) curves showing the degree of standard uptake value 1 (SUV1) (a), SUV2 (b), and Δ SUV (c) to predict invasive carcinoma (i-IPMC). The best cut-off of SUV1, SUV2, and Δ SUV to predict i-IPMC was 2.46 (area under the curve [AUC], 0.79), 3.22 (AUC, 0.79), and 17.6 (AUC, 0.74), respectively

Table 3 - Univariate analysis compared with dysplasia and i-IPMC

Variable		LGD/HGD n=19	i-IPMC n=52	Univariate analysis		Sensitivity	Specificity	PPV	FNR	Accuracy
				P	Odds (95% CI)					
MPD diameter	≥ 10 mm	5 (26%)	15 (29%)	1.000	1.14 (0.35-3.71)	29	74	75	25	41
	<10 mm	14 (74%)	37 (71%)							
Enhancing mural nodule	≥ 5 mm	10 (53%)	12 (23%)	0.023	3.7 (1.22-11.21)	25	47	55	45	30
	< 5 mm	9 (47%)	40 (77%)							
Obstructive jaundice	(+)	0	13 (25%)	0.015	-	5	100	100	-	45
	(-)	19 (100%)	39 (75%)							
Cyst diameter	≥ 3 cm	9 (47%)	8 (15%)	0.010	5.0 (1.53-16.01)	15	53	47	53	25
	< 3 cm	10 (53%)	44 (85%)							
Thickened/enhanced cyst walls	(+)	9 (47%)	13 (25%)	0.087	0.37 (0.12-1.11)	25	53	59	41	32
	(-)	10 (53%)	39 (75%)							
Abrupt MPD caliber change with atrophy of distal pancreas	(+)	3 (16%)	24 (46%)	0.027	4.6 (1.19-17.60)	46	84	89	11	56
	(-)	16 (84%)	28 (54%)							
Lymphadenopathy	(+)	0	4 (7%)	0.568	-	8	100	100	-	32
	(-)	19 (100%)	48 (92%)							
Increased CA19-9	> 37 U/ml	4 (21%)	32 (62%)	0.003	6.0 (1.7-20.7)	62	79	89	11	66
	≤ 37 U/ml	15 (79%)	20 (38%)							
Cyst growth rate	≥ 5 mm/2 year	0	0	-	-	0	100	-	100	27
	< 5 mm/2 year	19 (100%)	52 (100%)							
SUV1	≥ 2.46	6 (32%)	44 (85%)	<0.001	11.9 (3.50-40.61)	85	69	88	12	80
	>2.46	13 (68%)	8 (15%)							
SUV2	≥ 3.22	6 (32%)	42 (82%)	<0.001	10.1 (3.03-33.8)	82	68	88	12	79
	<3.22	13 (68%)	9 (18%)							
ΔSUV	≥17.6	4 (21%)	33 (65%)	0.001	6.9 (1.98-23.8)	65	79	89	11	69
	<17.6	15 (79%)	18 (35%)							

surgical indication for IPMN is determined by HRS and WF based on diagnostic imaging such as CT, MRI, and EUS. Here, the FDG-PET/CT findings were not referred to. In fact the present series included 34 patients with preoperative radiologic diagnosis of PDAC followed by pathologic confirmation of IPMN. All but one of these patients were categorized as i-IPMC, and the another as HGD. In these patients the tumors were not recognized as cystic, and this would be why the large cyst diameter ≥3 cm was conversely more frequent in dysplasia group than in i-IPMC group. Previous analyses of the resected BD-IPMNs suggested that nodule size was a predictor of invasive carcinoma or HGD, with a sensitivity of 73-100% and a specificity of 73-85%. Still, the proposed cut-off values varied from 5 to 10 mm (25-31). Although up to 10% of malignant BD-IPMNs were reported to have no mural nodules, nearly all of these cases were pathologically HGD but not i-IPMC (29,32,33). In the present study, the sensitivity and specificity of existence of enhancing mural nodule ≥ 5 mm to predict i-IPMC were 25 and 47%, respectively. Yamashita et al. has shown the usefulness of contrast-enhanced endoscopic ultrasonography (CE-EUS) to discriminate mural nodules from mucinous clots due to its ability to depict slow flow in the microscopic vessels or parenchymal

perfusion, which are not usually visualized by Doppler ultrasonography or contrast enhanced CT (38). They also showed in another more recent study of 115 patients with IPMN that the accuracy of CE-EUS to detect mural nodule was 92%, which was higher than 72% by contrast enhanced CT, whereas accuracy of predicting i-IPMC based on the presence of mural nodule was only 52%, which was lower than 59% by contrast enhanced CT (39). We could not evaluate the utility of CE-EUS in this study because this examination was applied only recently in our institution, but this modality is expected to increase the accuracy of differentiating i-IPMC from dysplasia.

Although FDG-PET/CT is unfavorable in terms of radiation exposure from radioisotopes and CT, it is a noninvasive and simple examination compared with endoscopic examinations especially with sampling of pancreatic juice. Several studies have evaluated the utility of FDG-PET/CT in differentiating invasive cancer from IPMN (34-39). The number of patients who underwent FDG-PET/CT and the proportion of patients with i-IPMC in our study were comparable with these studies, which were 29-94 patients and 15-70%, respectively. In previous reports, the sensitivity, specificity, and accuracy of FDG-PET/CT for predicting i-IPMC was

54-100%, 76-100%, and 86-96%, respectively. Regarding the comparison of the ICG criteria and SUV, Pedrazzoli et al (35) reported that the sensitivity and specificity of the ICG criteria for detecting malignancy were 93.2% and 22.2%, respectively, and those of FDG-PET/CT were 83.3% and 100%, respectively. Tomimaru et al (40) reported that the sensitivity, specificity, and accuracy of the presence or absence of mural nodules in differentiating malignant IPMN were 93, 80%, and 86%, respectively. Moreover, those of FDG-PET/CT with a cut-off of 2.5 were 93%, 100%, and 96%, respectively, and patients with SUVmax < 2.5 could be followed up for a median of 24 months without significant radiologic changes in the tumor. These reports and the present study suggest that the sensitivities of FDG-PET/CT and ICG criteria are comparable, but FDG-PET/CT has a higher specificity and can diagnose malignancies more accurately.

Commonly, the SUV at 60 min after FDG administration corresponding to SUV1 in the present study has been used as an indicator of malignancy. However, several reports have suggested the advantages of dual-point evaluation (21,41,42). Saito et al. used a dual-point evaluation and reported the sensitivity, specificity, and accuracy of the index combining SUV1 and retention index that corresponded to Δ SUV was 79%, 92%, and 84%, respectively (43). In our study, the superiority of SUV2 or Δ SUV in comparison with SUV1 could not be demonstrated. SUV2 tends to be higher than SUV1 in malignant tumors but either SUV2 or Δ SUV did not improve diagnostic performance on a dual-point evaluation regardless of the coexistence of diabetes. The small number of patients with dysplasia might be a reason for the negative results, but our results might suggest that a single-point evaluation would be sufficient to differentiate i-IPMC from dysplasia, regardless of the examination time.

This study had some limitations. This was a single-center retrospective analysis of a small number of patients. This might be a cause of underestimation of usefulness of ICG as well as Δ SUV to discriminate i-IPMC. A large cohort study is expected. Second, EUS was not performed in all patients in the present series. However, as we mentioned in the above, EUS or CE-EUS is superior to CT in the detection of mural nodules, which do not necessarily account for invasive cancer. Comparison of EUS and FDG-PET/CT is another concern, but we should notice that significance of the two modalities is different.

In conclusion, FDG-PET/CT showed better diagnostic accuracy than the ICG criteria to differentiate i-IPMC from dysplasia and its routine utilization is recommended.

Conflicts of Interest and Source of Funding

The authors declare no conflicts of interest associated with this manuscript.

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