

ORIGINAL**Comparing the performance of visual estimation and standard uptake value of F-18 fluorodeoxyglucose positron emission tomography/computed tomography for detecting malignancy in pancreatic tumors other than invasive ductal carcinoma**

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Abstract : Introduction The utility of FDG PET/CT for the detection and evaluation of invasive ductal carcinoma has been widely reported, but a few studies have assessed the utility of FDG PET/CT to detect malignancy in a variety of pancreatic lesions other than invasive ductal carcinoma. **Purpose** To compare the diagnostic performance of visual estimation with the semi-quantitative scores of FDG PET/CT for detecting malignancy in a variety of pancreatic lesions other than invasive ductal carcinoma. **Material and Methods** Images of pathologically proven pancreatic lesions from 32 patients were retrospectively evaluated : 14 benign lesions, 7 borderline (low malignant) lesions, and 11 malignant lesions. The average scores from visual estimation by the two observers were compared to two semi-quantitative analyses of FDG uptake in the lesions, namely the maximum standardized uptake value (SUVmax) and mean standardized uptake value (SUVmean). **Results** Visual analysis value, SUVmax and SUVmean were 0.33 ± 0.21 , 1.8 ± 0.7 and 1.5 ± 0.7 for the benign lesions, 0.70 ± 0.28 , 5.0 ± 2.6 and 3.1 ± 1.7 for the borderline lesions, and 0.73 ± 0.18 , 4.7 ± 2.5 and 3.2 ± 1.6 for the malignant lesions, respectively. Receiver operating characteristic analysis revealed the areas under the curves for detecting non-benign (malignant or borderline) lesions through visual analysis, SUVmax, and SUVmean were 0.914, 0.954, and 0.875, respectively. **Conclusion** For a variety of pancreatic lesions other than invasive ductal carcinoma, visual analysis and semi-quantitative analyses all showed strong diagnostic performance. However, semi-quantitative analysis with SUVmax proved to be the most effective method for detecting non-benign pancreatic lesions. *J. Med. Invest.* 61 : 171-179, February, 2014

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INTRODUCTION

The role of F-18 fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) is expanding in the diagnosis and staging

of many tumors. The utility of FDG PET/CT for the detection and evaluation of invasive ductal carcinoma has been widely reported ; its high sensitivity of more than 90% is equal to or greater than that of CT (1-3). PET/CT is an important tool for staging prior to pancreatic resection for cancer ; its sensitivity and specificity for diagnosing pancreatic cancer in 51 patients was reported to be 91% and 64%, respectively (1). It has also been shown that findings of FDG PET led to modifications in therapeutic management for 34% of patients (4).

There are many kinds of benign or malignant pancreatic lesions other than invasive ductal carcinoma, including, but not limited to, serous cystic neoplasm, intraductal papillary-mucinous neoplasm (IPMN), neuroendocrine tumor (NET), and solid-pseudopapillary neoplasm (SPN). FDG PET shows promise in distinguishing benign from malignant cystic lesions of the pancreas (5, 6), having detected 16 of 17 malignant cysts (94% sensitivity) with 95% specificity (5).

The purpose of this study is to compare the diagnostic performance of visual estimation of FDG PET/CT to two semi-quantitative analyses using standardized uptake values (SUV) for detecting malignancy in a variety of pancreatic lesions other than invasive ductal carcinoma.

METHOD

Data were retrospectively analyzed for 32 consecutive patients (15 men, 17 women ; mean age 63 years, range 28-79 years) with pancreatic lesions who were examined by FDG PET/CT prior to therapy between May 2006 and November 2012. The study protocol was approved by the ethics review board of Tokushima University Hospital. We performed visual and semi-quantitative analyses of the FDG uptake in the lesions.

Visual analysis and semi-quantitative analyses

For the visual analysis, two radiologists well experienced in nuclear medicine evaluated each pancreatic lesion by continuously-distributed test. Each observer used a continuous rating scale of a line marking method to rate his or her confidence level on the paper format independently. At the left end of the line, a confidence level were definitely absent was indicated, whereas at the right end, a confidence level that lesions were definitely malignancy was indicated. Intermediate levels of confidence

were indicated by the different positions on the line between the two ends. The distance between the left end and the marked point was converted to a confidence level that could range from 0 to 1, as described in the previous paper (7). Two observers performed each evaluation twice, with the second evaluations being done one week after the first so they would not remember their previous judgment. The reliability of visual analysis was assessed by intraclass correlation coefficient (ICC).

For the semi-quantitative analyses, we measured the maximum standardized uptake value (SUVmax) and the mean standardized uptake value (SUVmean) of the lesion. When it was difficult to discern the range of the lesion with PET/CT, we used contrast-enhanced CT or magnetic resonance imaging (MRI) to set the region of interest on the very limit of the inside of the lesion, so as to not extend over the border of the lesion and not pick up uptake from the surrounding area. The correlations between visual analysis value and SUVmax as well as visual analysis value and SUVmean were examined from the correlation coefficients. Multiple comparisons of the three analyses were controlled by the Bonferroni method. Performance in detecting malignant and borderline pancreatic lesions through visual analysis, SUVmax, and SUVmean were evaluated using receiver operating characteristic (ROC) analysis. The most suitable cutoff values for balancing the sensitivity and specificity were obtained using the ROC analysis. Correlation between lesion size and degree of uptake was also measured.

Pathological classification

After surgery, pathological evaluation was done to establish that the pancreatic lesions were other than invasive ductal carcinoma. Patient characteristics, distribution by pathology, and imaging findings are summarized in Table 1. The breakdown by pathology was as follows : benign lesions in 14 patients (5 well-differentiated neuroendocrine tumors [WDNET] of benign behavior, 5 serous cystadenomas [SCA], and 4 intraductal papillary-mucinous adenomas), 7 borderline (low malignant) lesions (4 WDNET of uncertain behavior, 3 SPN), and 11 malignant lesions (3 acinar cell carcinomas, 1 mucinous cystadenocarcinoma, 5 intraductal papillary-mucinous carcinomas [IPMC], 2 well-differentiated neuroendocrine carcinomas [WDNEC]). Five IPMC cases include 2 cases (Patients 26 and 27) diagnosed with intraepithelial carcinoma (carcinoma in situ). The NET group of tumors was classified according to

Table 1 Pathology and SUVmax, SUVmean, and visual analysis value in each patients

No.	pathology	age	gender	SUVmax	SUVmean	visual analysis value	size (mm)
(Benign)							
1	SCA	73	m	1.0	0.8	0.055	50×44×42
2	SCA	69	f	2.2	1.6	0.525	39×30×35
3	SCA	79	m	1.6	1.3	0.080	22×24×22
4	SCA	71	f	2.0	1.8	0.150	41×22×27
5	SCA	49	f	2.2	1.8	0.385	31×24×30
6	IPMA	69	m	1.3	1.0	0.045	29×16×33
7	IPMA	67	m	2.0	1.8	0.390	15×11×16
8	IPMA	61	m	1.3	1.2	0.345	30×21×37
9	IPMA	64	m	1.2	0.6	0.120	46×37×55
10	WDNET (benign)	70	f	1.3	1.0	0.290	13×12×10
11	WDNET (benign)	66	m	1.5	1.2	0.475	16×15×13
12	WDNET (benign)	71	f	2.0	1.7	0.500	13×10×11
13	WDNET (benign)	63	m	2.2	1.7	0.560	14×13×5
14	WDNET (benign)	56	f	3.9	3.3	0.720	15×13×15
(Borderline)							
15	SPN	38	f	3.5	2.7	0.690	20×19×22
16	SPN	28	f	5.3	3.9	0.850	39×30×28
17	SPN	28	f	6.6	2.5	0.945	77×43×73
18	WDNET(uncertain)	66	m	2.4	1.1	0.165	50×48×47
19	WDNET(uncertain)	64	f	2.5	1.9	0.565	30×25×31
20	WDNET(uncertain)	72	f	9.8	6.3	0.965	76×64×72
21	WDNET(uncertain)	34	m	4.6	3.4	0.750	46×44×44
(Malignant)							
22	Acinar cell carcinoma	68	f	4.3	3.1	0.755	57×32×31
23	Acinar cell carcinoma	71	m	6.1	5.0	0.890	47×46×33
24	Acinar cell carcinoma	64	m	2.6	2.2	0.525	29×29×28
25	Mucinous cystadenocarcinoma	74	f	3.9	2.6	0.675	35×33×39
26	IPMC	79	f	2.0	1.0	0.430	52×26×33
27	IPMC	75	f	2.4	1.8	0.565	33×14×21
28	IPMC	78	m	4.1	3.2	0.765	25×19×20
29	IPMC	73	m	4.5	1.9	0.795	53×41×49
30	IPMC	77	f	10.4	6.0	0.985	29×15×25
31	WDNEC	38	m	3.9	3.4	0.715	60×44×44
32	WDNEC	59	f	7.8	5.5	0.955	23×18×31

SCA : serous cystadenoma

IPMA : intraductal papillary-mucinous adenoma

IPMC : intraductal papillary-mucinous carcinoma

SPN : solid-pseudopapillary neoplasm

WDNET : well-differentiated neuroendocrine tumor

WDNEC : well-differentiated neuroendocrine carcinoma

World Health Organization criteria (8). WDNET can be classified into two categories, benign behavior and uncertain behavior, based on presence of angio-invasion and size of the tumor. We considered WDNET of benign behavior as a benign lesion, WDNET of uncertain behavior as a borderline lesion, and WDNEC as a malignant lesion. SPN of the pancreas is a relatively rare neoplasm with low-grade malignant potential and most often follows a benign clinical course, although approximately 15% of patients with SPN go on to develop metastatic

disease (9-11). Therefore, we classified SPN as a borderline lesion.

FDG PET/CT technique

FDG was synthesized with the nucleophilic substitution method using an FDG-synthesizing instrument (F100, Sumitomo Heavy Industries, Ltd., Tokyo, Japan) and a cyclotron (CYPRIS, Sumitomo Heavy Industries, Ltd.) at our institution. All patients were examined with a PET/CT scanner (Aquiduo, Toshiba Medical Systems Corporation, Tochigi,

Japan) 1 hour after FDG injection (3.7 MBq/kg). Patients were imaged from the top of the head to the mid thigh. The attenuation-corrected PET images, non-attenuation-corrected PET images, and CT images were reviewed, and the attenuation-corrected PET and CT images were co-registered using a commercial workstation (Aquarius NET, TeraRecon, Inc., USA).

Statistical analyses

Statistical analyses, including ICC and ROC analysis, were conducted using SPSS Statistics V21.0 (IBM Corp., Armonk, NY, USA). A p-value of less than 0.05 was considered statistically significant.

RESULTS

Visual analysis and semi-quantitative analyses

The results of visual analysis and semi-quantitative analyses are shown in Table 1. Visual analysis value was 0.33 ± 0.21 for the benign lesions, 0.70 ± 0.28 for the borderline lesions, and 0.73 ± 0.18 for the malignant lesions. The results for the semi-quantitative analyses were as follows : SUVmax and SUVmean were 1.8 ± 0.7 and 1.5 ± 0.7 for the benign lesions, 5.0 ± 2.6 and 3.1 ± 1.7 for the borderline lesions, and 4.7 ± 2.5 and 3.2 ± 1.6 for the malignant lesions, respectively. The differences between benign and borderline lesions as well as benign and malignant lesions were statistically significant in each visual analysis value ($p < 0.01$), SUVmax ($p < 0.01$) and SUVmean ($p < 0.05$) as shown in Fig. 1.

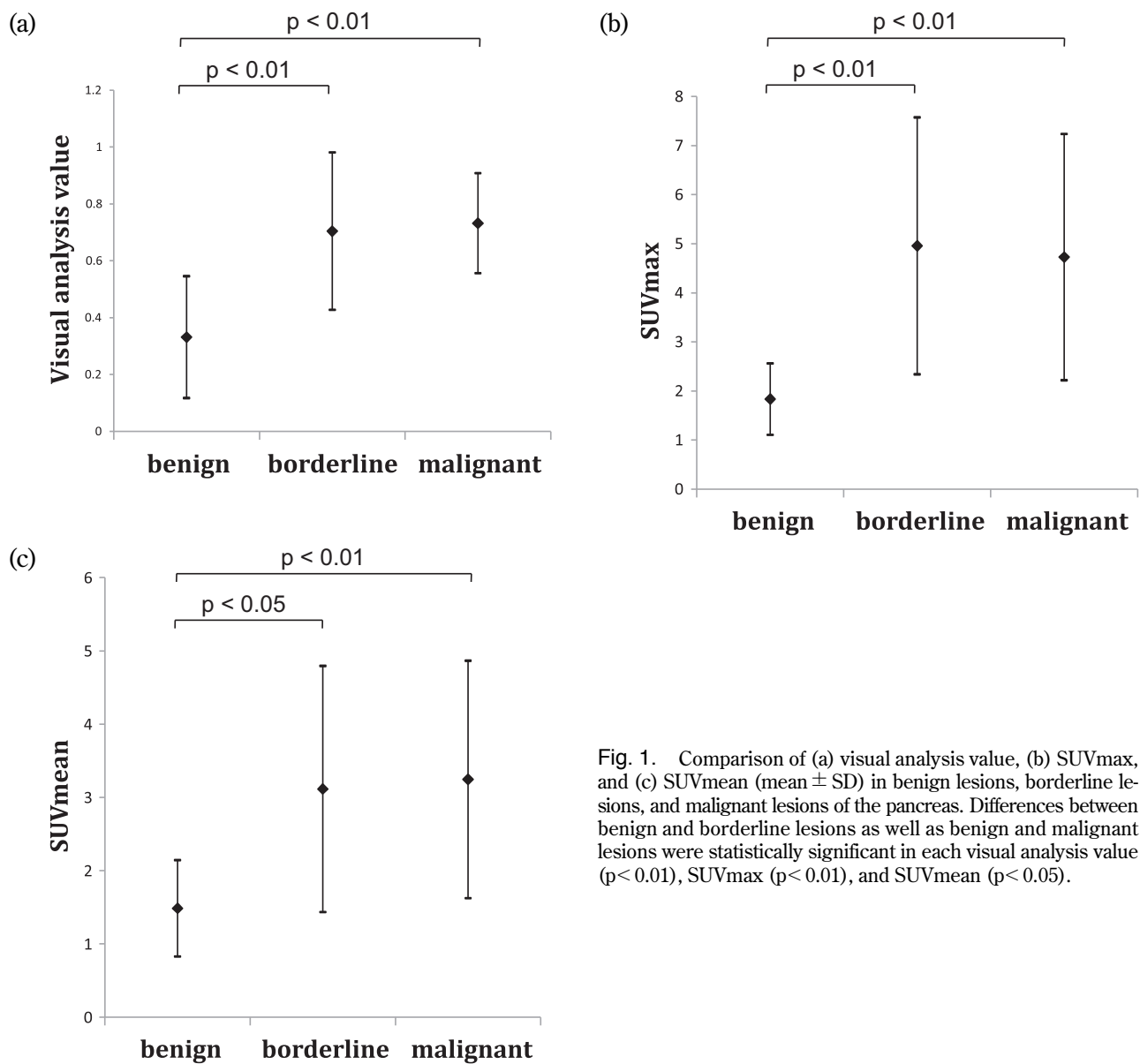


Fig. 1. Comparison of (a) visual analysis value, (b) SUVmax, and (c) SUVmean (mean \pm SD) in benign lesions, borderline lesions, and malignant lesions of the pancreas. Differences between benign and borderline lesions as well as benign and malignant lesions were statistically significant in each visual analysis value ($p < 0.01$), SUVmax ($p < 0.01$), and SUVmean ($p < 0.05$).

ICC for the average visual analysis values of the two observers was 0.953, indicating strong agreement between their evaluations. Furthermore, correlation coefficients for visual analysis value and SUVmax as well as visual analysis value and SUVmean were 0.949 and 0.896, respectively.

ROC analysis and cutoff value

Using ROC analysis, the area under the curve (AUC) for detecting non-benign (malignant or borderline) lesions through visual analysis, SUVmax, and SUVmean were 0.914, 0.954, and 0.875, respectively (Fig. 2), but the statistical differences between three AUC values were not confirmed ($p > 0.05$).

The suitable cutoff values for differentiating between non-benign (malignant or borderline) and benign lesions based on the ROC analysis were 0.57, 2.4, and 1.9 for visual analysis, SUVmax, and SUVmean, respectively. Applying these cutoff values, sensitivity and specificity were 83% and 93% for visual analysis, 94% and 93% for SUVmax, and 83% and 93% for SUVmean, respectively.

Correlation between lesion size and degree of uptake

Spearman's rank correlation coefficients for tumor size compared with average visual analysis value, SUVmax, and SUVmean were 0.141, 0.260, and 0.123 and were not significantly different. The

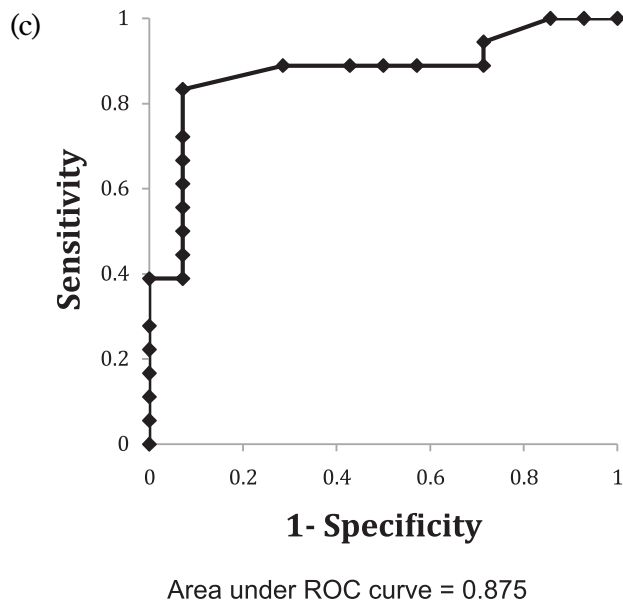
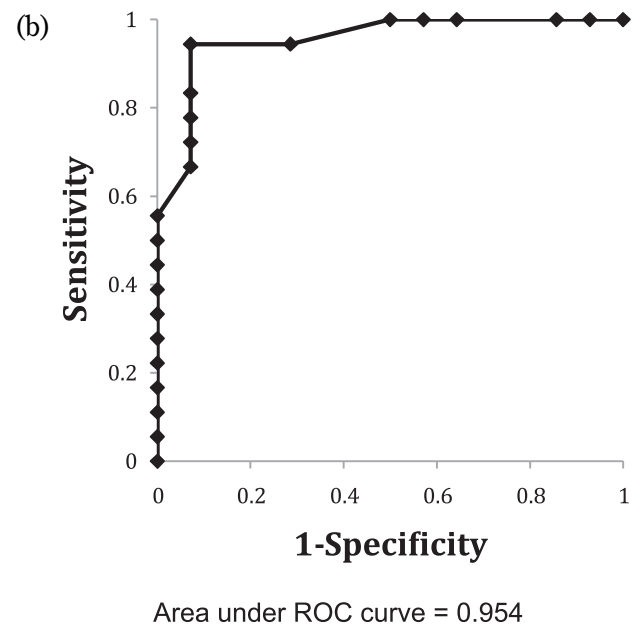
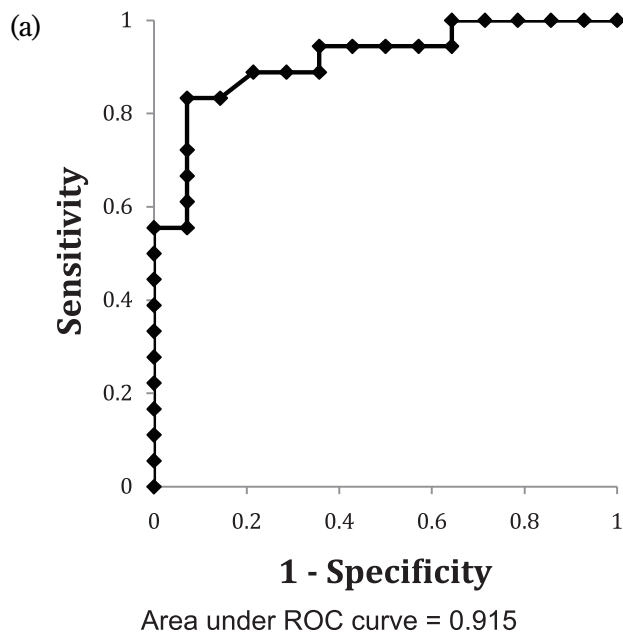


Fig. 2. ROC curves for (a) visual analysis value, (b) SUVmax, and (c) SUVmean of FDG PET/CT for detecting non-benign (malignant or borderline) lesions. Cutoff values for visual analysis, SUVmax, and SUVmean were 0.57, 2.4, and 1.9, respectively. Applying the cutoff values, AUC was 0.915 with 83% sensitivity and 93% specificity for visual analysis, 0.954 with 94% sensitivity and 93% specificity for SUVmax, and 0.875 with 83% sensitivity and 93% specificity for SUVmean, respectively.

size of borderline tumors was significantly greater than that of benign tumors ($p < 0.05$), but no significant difference in tumor size was seen when comparing benign to malignant tumors and borderline to malignant tumors.

Case presentation

A representative and typical case (Patient 30) of

the malignant lesions that show high uptake is presented in Fig. 3, and a representative and not typical case (Patient 26) of malignant lesions that show no high uptake is presented in Fig. 4.

Case 1

A 77-year-old woman (Patient 30) had no complaints. She had a history of subarachnoid hemorrhage and rectal cancer, for which surgery had been

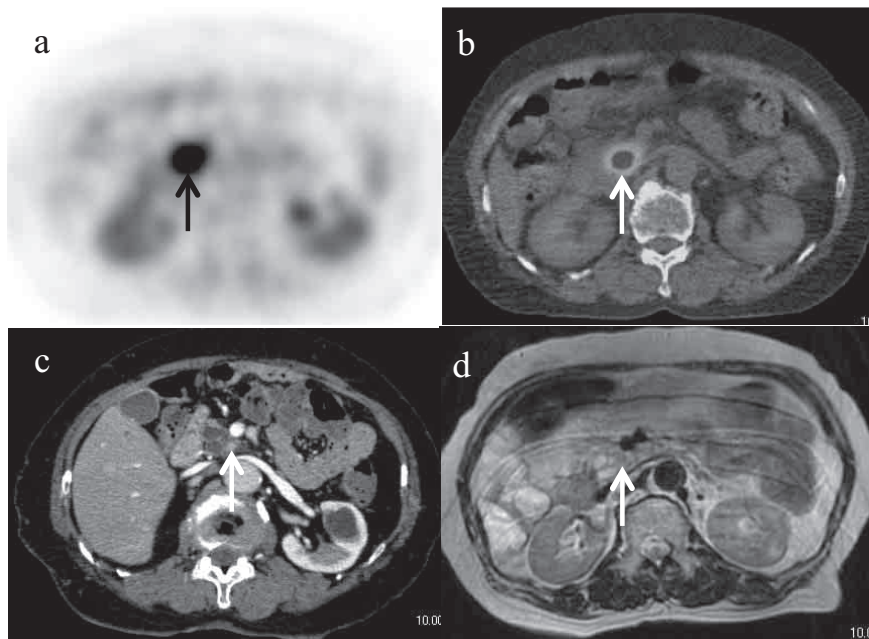


Fig. 3. (a) FDG PET, (b) PET/CT fusion, (c) contrast-enhanced CT, and (d) T2-weighted images of the abdomen in a 77-year-old woman (Patient 30) with IPMC of the pancreas. High FDG uptake (arrow) in the solid area on PET/CT that was observed as an enhancing nodule in contrast-enhanced CT suggests malignancy. Visual analysis value, SUVmax and SUVmean were 0.985, 10.4 and 6.0.

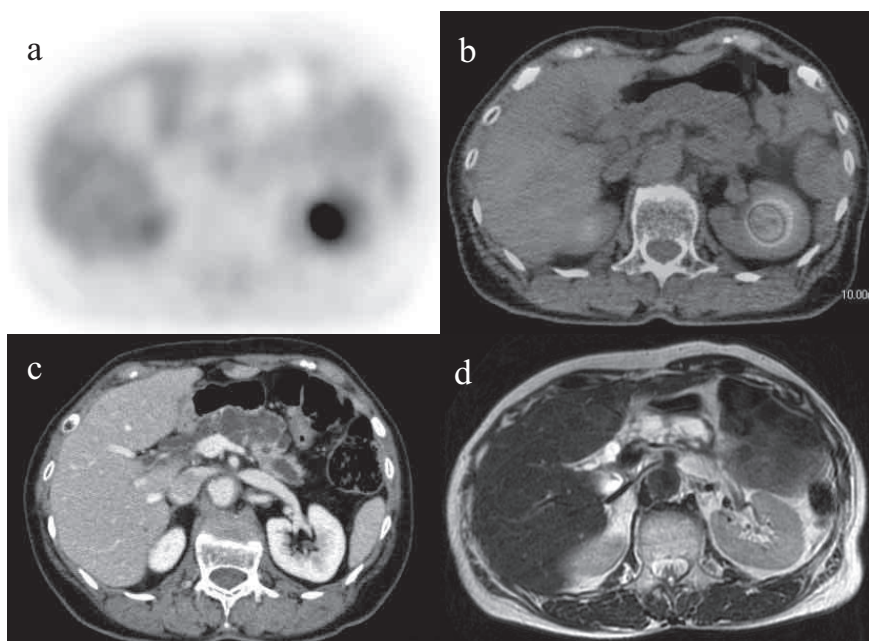


Fig. 4. (a) FDG PET, (b) PET/CT fusion, (c) contrast-enhanced CT, and (d) T2-weighted images of the abdomen in a 79-year-old woman (Patient 26) with IPMC of the pancreas. The cystic mass located in the pancreas body shows no increased FDG uptake. Visual analysis value, SUVmax and SUVmean were 0.430, 2.0 and 1.0.

performed. Serum amylase elevated (346 U/l : normal level 60-190). Serum carbohydrate antigen 19-9 (CA19-9) was within normal limits. She had a cystic mass located in the pancreas head with a dilated main pancreatic duct and showed high FDG uptake in the solid area that was visualized as an enhancing nodule in contrast-enhanced CT (Fig. 3). In this Fig. 3, (a) is FDG PET image, (b) is PET/CT fusion image, (c) is contrast-enhanced CT image, and (d) is T2-weighted image. The cystic mass was resected and confirmed pathologically as IPMC. Visual analysis value, SUVmax and SUVmean were 0.985, 10.4 and 6.0.

Case 2

A 79-year-old woman (Patient 26) had no complaints. She had a history of gastric cancer and breast cancer, for which surgery had been performed. A cystic lesion in pancreas was incidentally found by computed tomography before operation of breast cancer. Serum CA19-9 and carcinoembryonic antigen (CEA) were within normal limits. The cystic mass was located in the pancreas body and showed no increased FDG uptake on PET/CT (Fig. 4). In this Fig. 4, (a) is FDG PET image, (b) is PET/CT fusion image, (c) is contrast-enhanced CT image, and (d) is T2-weighted image. The cystic mass was resected and confirmed pathologically as IPMC. Visual analysis value, SUVmax and SUVmean were 0.430, 2.0 and 1.0.

DISCUSSION

Repeatability and reproducibility of the visual analysis results in this study were considered adequate due to the ICC of the two observers being 0.953, allowing us to use the average visual analysis values of the two observers. Using visual analysis, we were able to distinguish non-benign (malignant or borderline) lesions from benign lesions with relatively high sensitivity (83%), specificity (93%), and AUC (0.914).

We also examined semi-quantitative analyses SUVmax and SUVmean in comparison with visual analysis. From their correlation coefficients, we found visual analysis to be correlated with both SUVmax and SUVmean, with SUVmax showing the higher correlation of the two.

Using ROC analysis, the cutoff values for SUVmax and SUVmean in differentiating between non-benign (malignant or borderline) lesions and benign lesions were 2.4 and 1.9, respectively.

Visual analysis and semi-quantitative analyses all showed strong diagnostic performance for the pancreatic lesions in this study, but semi-quantitative analysis with SUVmax showed greater performance in detecting non-benign (malignant or borderline) lesions than the other two methods. Using semi-quantitative analysis with SUVmax, we were able to achieve high sensitivity (94%) and high specificity (93%). However, in a report including invasive ductal carcinoma and non-tumorous lesions such as autoimmune pancreatitis or tuberculosis, Sampath *et al.* reported a sensitivity of 88% and specificity of 41% for discriminating benign and malignant pancreatic lesions with an SUVmax cutoff value of 2.8 (12). In their study, they explained that the poor specificity, lower than that of our study, could be due to the increased inflammation in the patients with chronic pancreatitis. It has been reported that inflammation can give rise to focal FDG uptake in the same intensity range as pancreatic neoplasm, even when clinical, laboratory, and CT findings suggestive of an inflammatory etiology are equivocal or absent (13). Physicians should be cognizant of this when interpreting FDG-PET/CT images of pancreatic lesions.

FDG PET may be effective in distinguishing benign from malignant cystic lesions of the pancreas, with 94% sensitivity and 95% specificity reported in previous studies (5, 6). For IPMN, FDG PET has also been reported to have higher diagnostic accuracy than conventional imaging modalities in differentiating IPMC. Sensitivity, specificity, and accuracy were reported as 100%, 87%, and 94% for FDG PET, and 94%, 60%, and 77% for CT, respectively (14). Takanami *et al.* showed sensitivity, specificity, and accuracy values of 77.8%, 100%, and 87.5% using an SUVmax cutoff value of 2.3 (15). Two of 5 IPMC cases (Patients 26 and 27) in our study were diagnosed with intraepithelial carcinoma (carcinoma in situ) and the size of their solid areas was small. It is possible that these lesions did not show high FDG uptake because they were small. Particularly for small lesions, the uptake may have been underestimated due to the partial volume effect (16, 17), although our cases did not show a high correlation between tumor size and SUV. In our study, the size of borderline tumors was significantly greater than that of benign tumors, but no significant difference in tumor size was seen between benign and malignant tumors or borderline and malignant tumors. The partial volume effect has been seen as a major source of bias in PET brain imaging measurements

for several years, leading to the development of partial volume correction methods especially for brain imaging (17, 18). Partial volume correction in the torso is considered more difficult than in the head or limbs because of the motion caused by respiration or cardiac contraction (17). Therefore, although the partial volume effect may have influenced the SUV of tumors in this study, we performed our evaluations without partial volume correction.

In a study of 19 lesions of histologically confirmed islet cell tumors, 8 showed positive PET results ($SUV > 2.3$), and localization was indicated in 2 lesions (19). This report also found that the sensitivity of PET was 53%, and PET did not demonstrate any advantage over ultrasonography, CT, or MRI for detecting islet cell tumors (19). All 2 WDNEC in our study showed high uptake. Although FDG-PET/CT is not useful for detecting NET, the results may suggest that low uptake is associated with benign or low malignant NET.

It is reported the mean apparent diffusion coefficient (ADC) of malignant IPMN was significantly lower than that of benign IPMN and the addition of diffusion weighted imaging (DWI) to magnetic resonance cholangiopancreatography (MRCP) with unenhanced MRI may improve the diagnosis of malignant IPMN (20). It is reported DWI may be helpful in distinguishing neuroendocrine carcinoma from benign NET by ADC values (21). DWI is also useful tool for detecting malignancy in pancreatic lesions. In a recent report, which included invasive ductal carcinoma, FDG PET/MRI fusion imaging showed significantly improved accuracy compared with that of PET/CT (96.6% vs. 86.6%) in diagnosing pancreatic tumors, particularly in differentiating malignant tumors from benign lesions (22). Dilatation of the main pancreatic duct, encasement of adjacent vessels, intratumor structures such as mural nodules, and the intracystic septum were also detected on FDG PET/MRI fusion imaging (22). To achieve higher diagnostic accuracy for pancreatic tumors, further studies on the combination of PET and MRI are warranted.

We understand that the combination of visual estimation and SUV may be useful to improve diagnosis capability. However, it was difficult to determine the diagnostic criteria for the combination of visual and SUV estimations. Furthermore, the accuracy of SUVmax (sensitivity of 94% and specificity of 93%) was considered to be enough high, therefore, the diagnostic capability by the combination of visual and SUVmax estimations would be almost the

same extent as only the SUVmax. Under such consideration, we did not evaluate combination diagnosis in this study.

The limitation of our study is a selection bias due to the retrospective study design and small number of cases. While it is necessary to accumulate additional cases to further evaluate diagnostic performance, we believe that, as with the case of invasive ductal carcinoma, FDG PET/CT has potential in other pancreatic lesions for differentiating malignant and borderline lesions from benign lesions.

In conclusion, the result of this study indicates that FDG PET/CT has potential in a variety of pancreatic lesions other than invasive ductal carcinoma for differentiating malignant and borderline lesions from benign lesions. Especially, semi-quantitative analysis with SUVmax is more accurate than visual analysis or semi-quantitative analysis with SUVmean for the purpose.

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