Endoscopic ultrasound elastography for small solid pancreatic lesions with or without main pancreatic duct dilatation

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ABSTRACT

Background: /Objectives: Endoscopic ultrasound elastography (EUS-EG) is useful for diagnosis of small solid pancreatic lesions (SPLs), particularly in excluding pancreatic cancer (PC), but its dependence on main pancreatic duct dilatation (MPDD) has not been examined. We aimed to investigate EUS-EG for diagnosis of small SPLs with and without MPDD.
Methods: Patients with pathologically diagnosed SPLs of ≤20 mm were included and retrospectively analyzed. Using the blue:green ratio, an EUS-EG image was classified as blue-dominant, equivalent, or green-dominant. Using multiple EUS-EG images per patient, a lesion with a greater number of blue-dominant than green-dominant images was classified as stiff, and the others as soft. EUS-EG images in random order were judged by three raters. Considering stiff SPLs as PC, diagnostic performance of EUS-EG was examined for SPLs with and without MPDD.
Results: Of 126 cases analyzed, 65 (52%) were diagnosed as PC, and 63 (50%) had MPDD. A total of 1077 EUS-EG images were examined (kappa coefficient = 0.783). Lesions were classified as stiff in 91 cases and soft in 35 (kappa coefficient = 0.932). The ratio of stiff to soft lesions was significantly higher in PC than in non-PC (62:3 vs. 29:32, $P < 0.001$). The sensitivity, specificity, and negative predictive value of a stiff lesion with vs. without MPDD for diagnosis of PC were 94%, 23%, and 50% vs. 100%, 60%, and 100%, respectively.
Conclusions: Using the EUS-EG stiffness classification for small SPLs, PC can be excluded with high confidence and concordance for a soft lesion without MPDD.

Introduction

Pancreatic cancer (PC) accounts for about 40% of cases of solid pancreatic lesions (SPLs) of ≤15 mm and other lesions identified were pancreatic neuroendocrine tumor (PanNET), metastasis, mass-forming pancreatitis (MFP), and solid-type serous cystic neoplasm, based on a multicenter study [1]. The outcome of PC is improved by early discovery and treatment. It has been reported that the smaller the tumor diameter at the time of resection, the better the prognosis is, with a 5-year overall survival rate of patients with a tumor of ≤10 mm of as high as 80.4% [2].

It is also important to diagnose small SPLs accurately to avoid unnecessary radical surgery for benign lesions, since this surgery has relatively high rates of complications and mortality. Small lesions are diverse in origin and many are not cancerous. The diagnostic performance of endoscopic ultrasound (EUS)-guided fine needle aspiration (FNA) is limited for these lesions [3—5], and imaging diagnoses are important. Ignee et al. categorized 218 lesions of ≤15 mm into stiff and soft lesions using EUS elastography (EUS-EG), and found a negative predictive value (NPV) for diagnosis of PC among stiff lesions of 98%; i.e., for a soft lesion, PC can be excluded with high confidence [6]. This is clinically useful since it supports the judgment that radical surgery is not needed if the lesion is classified as soft.

Main pancreatic duct dilatation (MPDD) is an important finding

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for diagnosis of PC [7], with one study showing MPDD in about 80% of 200 early PC cases [8]. However, the differences in diagnostic ability according to the presence of MPDD on EUS-EG diagnosis was not examined by Ignee et al. Therefore, the objective of this study was to investigate the usefulness of EUS-EG for diagnosis of small SPLs focusing on the presence or absence of MPDD.

Methods

Study design

A single-center retrospective study was performed at Nagoya University Hospital after approval by the hospital Ethics Committee (the date registered: December 8, 2015, the approval number: 2015-0316).

Patients

Patients with SPLs of ≤20 mm examined by EUS-EG and pathologically diagnosed by surgical resection or EUS-FNA between May 2005 and November 2019 were identified in the hospital database. For the tumor diameter, the larger value measured by CT or EUS was used. Since the image quality of EUS-EG varies markedly among ultrasound apparatuses, only cases examined with Hitachi and Olympus systems were included, since these have relatively similar image quality. Patients in whom a biliary stent was placed at the time of EUS-EG were excluded because the stent can influence the images. For reproducibility, evaluation of multiple EUS-EG images per case is needed. Therefore, only cases with two or more images without a defect within the lesion on the EUS-EG color map were included in the study, and to eliminate selection bias, all these EUS-EG images were evaluated for each case.

Diagnosis of a lesion as benign based on EUS-FNA required a follow-up period of at least 12 months. Lesion types were classified based on the method described by Terada et al. [9] with modifications: lesions were divided into MPDD and parenchymal tumor (PT) types based on CT or EUS findings for the main pancreatic duct. MPDD type represents a lesion accompanied by ≥ 3 mm dilatation of the main pancreatic duct on the caudal side of the lesion. All other lesions were regarded as PT type.

EUS-EG

EUS was performed by three experts with experience of ≥10 years (YH, EO, and TI) or trainees under their supervision. Vital signs were monitored in the left lateral position under sedation with midazolam. After conventional EUS, strain elastography was performed using Real-time Tissue Elastography (Hitachi, Tokyo, Japan) or ELST (Olympus, Tokyo, Japan) system. The region of interest (ROI) was set to include the whole lesion with a sufficient surrounding area, such that the lesion occupied < 50% of the whole ROI. Strain elastography is used to estimate relative tissue stiffness based on the distortion generated by an aortic pulse. For relative tissue elasticities (stiffness) of stiff, average, and soft, the tissues are visualized as blue, green, and red, respectively. Since the EUS-EG color map changes rapidly, a video was acquired for several seconds and still images of the lesion were extracted from the video. This procedure was repeated multiple times, as needed.

Evaluation criteria

Each EUS-EG image was classified as blue-dominant, equivalent, or green-dominant based on the blue:green ratio in the lesion, using a modification of the method described by Iglesias-Garcia et al. [10]. Using multiple EUS-EG images from the same patient, a lesion with a greater number of blue-dominant than green-dominant images was classified as stiff, and all other lesions were defined as soft, as shown in Figs. 1 and 2, respectively.

Data analysis and statistics

Three raters (KK, TI, and EO) classified the colors of lesions separately using EUS-EG images presented in random order and while blinded to clinical information. When the judgment differed among the raters, a majority decision was used. If all three raters differed, the EUS-EG image was classified as equivalent. Kappa coefficients for the EUS-EG color and stiffness classifications were calculated to evaluate concordance among the raters, with values of 0.01−0.20, 0.21−0.40, 0.41−0.60, 0.61−0.80, and 0.81−1.00 regarded as minor, fair, moderate, good, and excellent, respectively.

For comparison between two groups, a Fisher exact test or a chi-square test was used for categorical variables and a Mann-Whitney U test for continuous variables, with $P < 0.05$ regarded as significant. The sensitivity, specificity, positive predictive value (PPV), and NPV were calculated to evaluate diagnostic performance of the EUS-EG stiffness classification for PC, with the 95% confidence interval (CI) determined using the Clopper-Pearson method. Diagnostic performance based on main pancreatic duct findings was also investigated using this approach. All analyses were performed using SPSS Statistics version 27.0 (SPSS, Chicago, IL, USA).

Results

### Final diagnoses of the SPLs included in the study

Between May 2005 and November 2019, 244 patients were examined by EUS and pathologically diagnosed with a SPL of ≤20 mm at our hospital. Of these patients, 172 were examined by EUS-EG, and finally, 126 patients were included in the study (Fig. 3). The final diagnoses of the 126 patients were PC (n = 65), PanNET (n = 31), solid pseudopapillary neoplasm (SPN) (n = 8), MFP (n = 13), and others (n = 9: pancreatic metastasis of renal cell carcinoma (RCC) (n = 5) and of gallbladder cancer (n = 1); arteriovenous malformation (n = 1); accessory spleen (n = 1); and hematoma (n = 1)). There were no G3 lesions in PanNET. Based on the International Consensus Diagnostic Criteria [11], the cause of MFP was definitive type 1 autoimmune pancreatitis (AIP) in 7 cases, probable type 2 AIP in 1 case, and chronic pancreatitis (CP) in the remaining 5 cases. Surgery was performed in 59 (91%) of the 65 patients with PC and 47 (77%) of the 61 patients with non-PC.

Overall EUS-EG classification

The results of EUS-EG are shown in Table 1. A median of 7 EUS-EG images (IQR, interquartile range: 5−10) was acquired per patient and a total of 1077 images were analyzed for the 126 patients. The color classification was blue-dominant in 675 images, equivalent in 158, and green-dominant in 244. The kappa coefficient of this classification was 0.783, indicating good concordance among the raters. The EUS-EG stiffness classification was stiff in 91 patients and soft in 35, with a kappa coefficient of 0.932, indicating excellent concordance among the raters.

Characteristics of the patients included in the study

The characteristics of the 126 patients are shown in Table 2. Patients with PC were significantly older than those with non-PC (70 years (IQR: 62−75.5) vs. 61 years (49−69), $P < 0.001$), and significantly more frequently had lesions that were in the
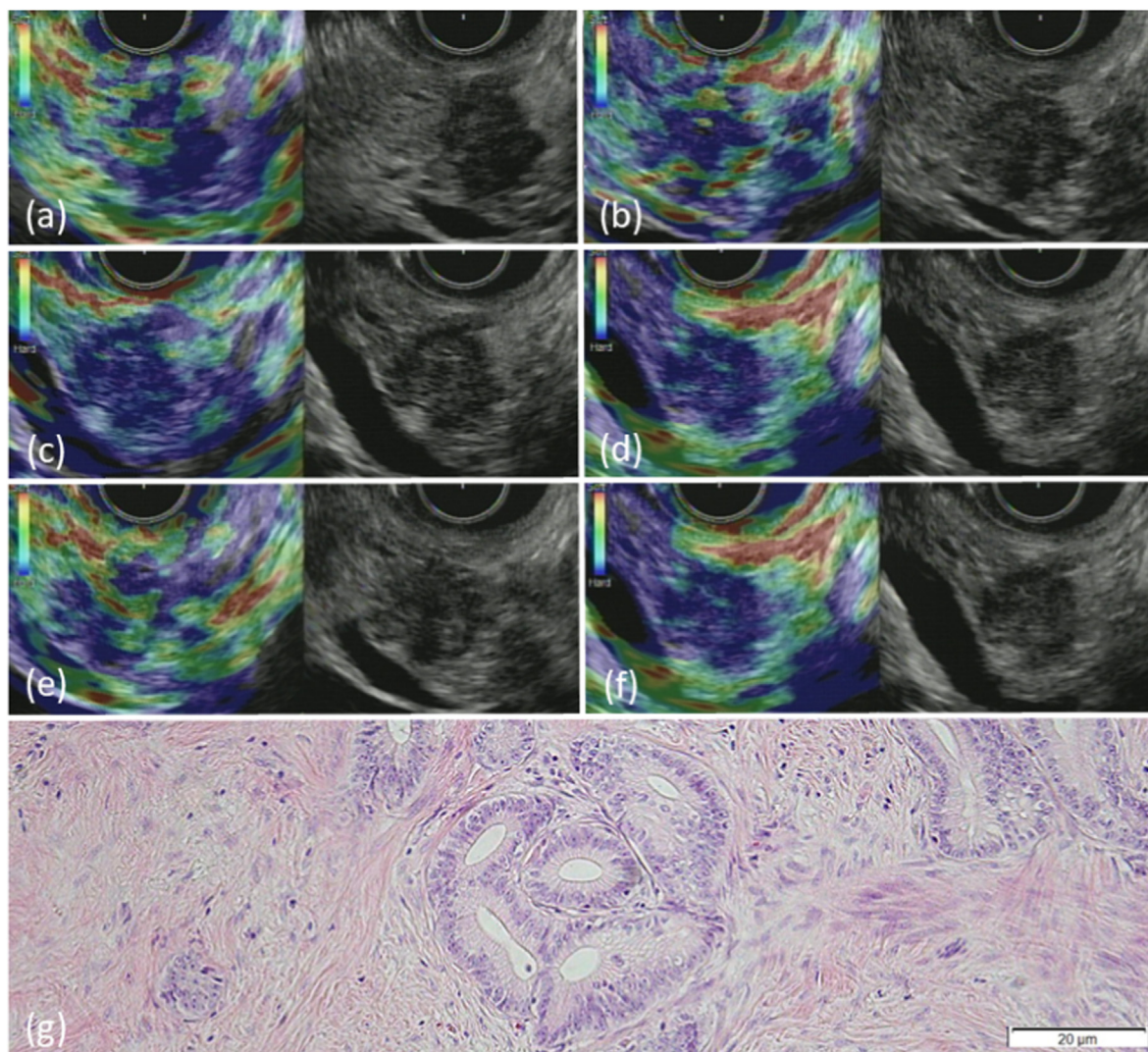
Fig. 1. A 15-mm lesion in the pancreatic body without main pancreatic duct dilation in a 62-year-old man. The lesion was resected, with the histology revealing invasive ductal adenocarcinoma. The endoscopic ultrasound elastography color classification that we finally judged were, (a) blue-dominant, (b) blue-dominant, (c) blue-dominant, (d) blue-dominant, (e) equivalent, and (f) blue-dominant, respectively. So, this lesion was classified as stiff. The echoendoscope and ultrasound apparatus used was a combination of EG-3670URK (Pentax, Tokyo, Japan) with HiVision Ascendus (Hitachi, Tokyo, Japan). (g) Hematoxylin and eosin staining showed small to medium-sized irregular glands were surrounded by large amounts of fibrous components.

pancreatic head (head: body: tail; 35:19:11 vs. 17:27:17, $P = 0.012$), had a larger diameter (18 mm (IQR: 14−19) vs. 13 mm (10−17), $P < 0.001$), and were with MPDD (MPDD: PT type; 50:15 vs. 13:48, $P < 0.001$). In the EUS-EG stiffness classification, PC lesions were significantly more frequently stiff (stiff: soft; 62:3 vs. 29:32, $P < 0.001$).

Characteristics of stiff lesions

62 cases of PC were visualized as a stiff lesion and 47 were MPDD type. The other 29 stiff lesions were PanNET (n = 14), SPN (n = 6), MFP (n = 7), pancreatic metastasis of RCC (n = 1), and of gallbladder cancer (n = 1) (Table 2); and 10 of these cases were MPDD type lesions: MFP (n = 6) and PanNET (n = 4). Pathologically, the 4 PanNET cases with MPDD had invasive growth to main pancreatic duct with fibrosis. Two of the 6 MFP cases with MPDD were resected, and they were type 1 AIP and CP. Both cases were associated with abundant fibrosis.

Characteristics of soft lesions

Three cases of PC were visualized as a soft lesion and they were MPDD type. One of these was high-grade pancreatic intraepithelial neoplasia (PanIN). Pathologically, the region visualized as a solid lesion in this patient was due to inflammatory changes, and no tumor component was observed. The other 2 cases were anaplastic carcinoma and invasive ductal adenocarcinoma. The caudal pancreas of these 2 cases had highly fibrotic obstructive pancreatitis. The other 32 soft lesions were PanNET (n = 17), MFP (n = 6), SPN (n = 2), pancreatic metastasis of RCC (n = 4), arteriovenous malformation (n = 1), accessory spleen (n = 1), and hematoma (n = 1) (Table 2); and 29 of these cases (excluding 2 cases of MFP and 1 case of pancreatic metastasis of RCC) were PT type lesions.

EUS-EG stiffness classification with or without MPDD

The EUS-EG stiffness classification with or without MPDD is
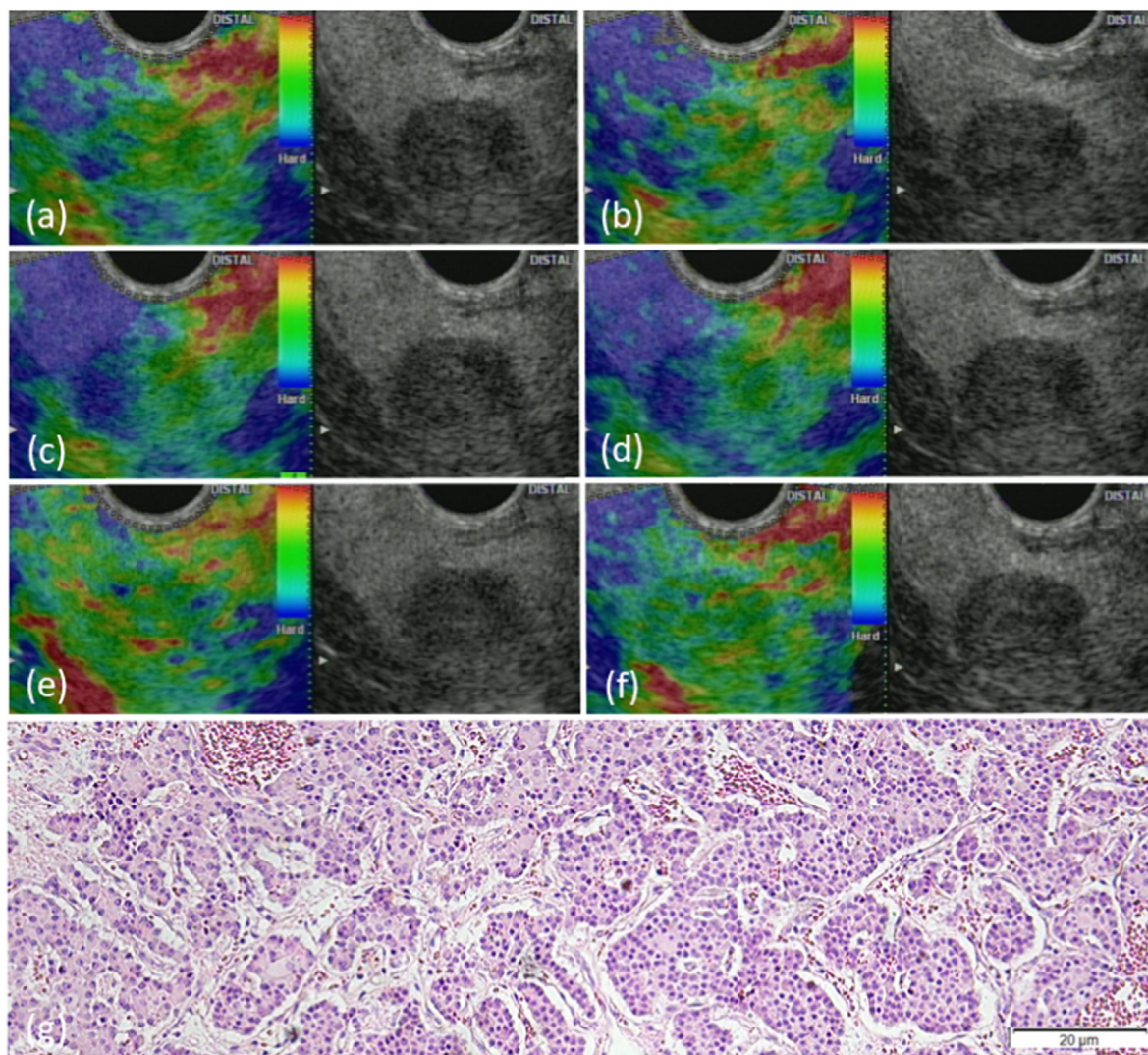
Fig. 2. An 18-mm lesion in the pancreatic tail without main pancreatic duct dilation in a 71-year-old man. The lesion was resected, with the histology revealing neuroendocrine tumor G1. The endoscopic ultrasound elastography color classification that we finally judged were, (a) green-dominant, (b) green-dominant, (c) equivalent, (d) equivalent, (e) green-dominant, and (f) green-dominant, respectively. So, this lesion was classified as soft. The echoendoscope and ultrasound apparatus used was a combination of EG-3670URK (Pentax, Tokyo, Japan) with HiVision 900 (Hitachi, Tokyo, Japan). (g) Hematoxylin and eosin staining showed atypical cells formed neuroendocrine features such as ribbon and trabecular patterns. There were few fibrous components within the tumor.

shown in Table 3. This classification did not differ significantly for MPDD type PC and non-PC (stiff: soft for PC vs. non-PC; 47:3 vs. 10:3, $P = 0.096$), but for PT type lesions, stiff lesions were significantly more frequently diagnosed as PC (15:0 vs. 19:29, $P < 0.001$). There was a significantly higher rate of stiff lesions in MPDD type non-PC than PT type non-PC (stiff: soft for MPDD type vs. PT type; 10:3 vs. 19:29, $P = 0.027$).

Lesion location based on the presence or absence of MPDD

Lesion location based on the presence or absence of MPDD is shown in Table 3. There was a significant difference in lesion location between PC cases and non-PC for both MPDD and PT types. MPDD type PC and PT type PC showed no significant differences in lesion location (head: body: tail for MPDD type vs. PT type; 25:16:9 vs. 10:3:2, $P = 0.519$).
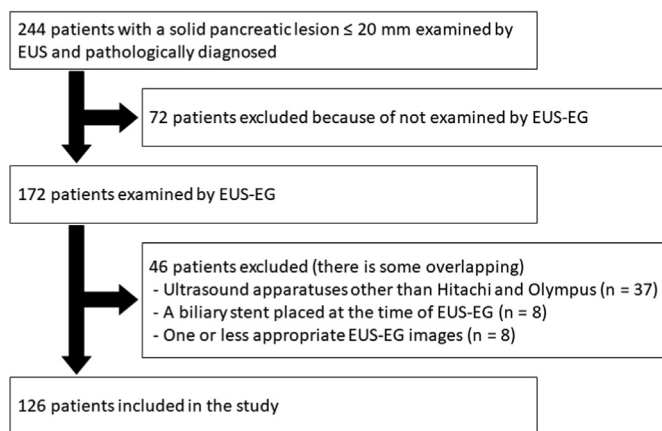
Fig. 3. Flowchart showing the selection of the study population. EUS, endoscopic ultrasound; EUS-EG, EUS elastography.

Table 1
The color and stiffness classifications based on EUS-EG images by each rater and final judgement.

	Rater 1	Rater 2	Rater 3	Kappa coefficient	Final Judgment
Color classification (1077 EUS-EG images)				0.783	
Blue-dominant	679	698	614		675
Equivalent	155	119	225		158
Green-dominant	243	260	238		244
Stiffness classification (126 patients)				0.932	
Stiff	92	92	93		91
Soft	34	34	33		35

EUS-EG, endoscopic ultrasound elastography.

Table 2
Baseline characteristics of the 126 patients included in the study.

	PC (n = 65)	Non-PC (n = 61)	P value	PanNET (n = 31)	SPN (n = 8)	MFP (n = 13)	Others (n = 9)
Age, median (IQR), years	70 (62—75.5)	61 (49—69)	<0.001*	58 (49—67)	41.5 (31—51)	66 (63—69.5)	73 (56—77.5)
Gender			0.714**				
Male	42 (65%)	37 (61%)		18 (58%)	4 (50%)	9 (69%)	6 (67%)
Female	23 (35%)	24 (39%)		13 (42%)	4 (50%)	4 (31%)	3 (33%)
Location			0.012***				
Head	35 (54%)	17 (28%)		12 (39%)	1 (13%)	3 (23%)	1 (11%)
Body	19 (29%)	27 (44%)		10 (32%)	6 (75%)	8 (62%)	3 (33%)
Tail	11 (17%)	17 (28%)		9 (29%)	1 (13%)	2 (15%)	5 (56%)
Size, median (IQR), mm	18 (14—19)	13 (10—17)	0.001*	14 (9—17)	12.5 (10.25—17.25)	13 (11—19)	10 (9—16)
Type			<0.001**				
MPDD	50 (77%)	13 (21%)		4 (13%)	0 (0%)	8 (62%)	1 (11%)
PT	15 (23%)	48 (79%)		27 (87%)	8 (100%)	5 (38%)	8 (89%)
Stiffness classification			<0.001**				
Stiff	62 (95%)	29 (48%)		14 (45%)	6 (75%)	7 (54%)	2 (22%)
Soft	3 (5%)	32 (52%)		17 (55%)	2 (25%)	6 (46%)	7 (78%)

PC, pancreatic cancer; PanNET, pancreatic neuroendocrine tumor; SPN, solid pseudopapillary neoplasm; MFP, mass forming pancreatitis.
MPDD, main pancreatic duct dilation; PT, parenchymal tumor; IQR, interquartile range.
*Mann-Whitney U test, **Fisher exact test, ***chi-square test.
Values are shown as numbers (percentage) or medians (IQR).

Table 3
The EUS-EG stiffness classification or lesion location based on the presence or absence of MPDD.

	MPDD type (n = 63)			PT type (n = 63)		
	PC (n = 50)	Non-PC (n = 13)	P value	PC (n = 15)	Non-PC (n = 48)	P value
Stiffness classification			0.096*			<0.001*
Stiff	47 (94%)	10 (77%)		15 (100%)	19 (40%)	
Soft	3 (6%)	3 (23%)		0 (0%)	29 (60%)	
Location			0.011**			0.031**
Head	25 (50%)	3 (23%)		10 (67%)	14 (29%)	
Body	16 (32%)	10 (77%)		3 (20%)	17 (35%)	
Tail	9 (18%)	0 (0%)		2 (13%)	17 (35%)	

EUS-EG, endoscopic ultrasound elastography; PC, pancreatic cancer; MPDD, main pancreatic duct dilation; PT, parenchymal tumor.
*Fisher exact test, **chi-square test.
Values are shown as numbers (percentage).

Diagnostic performance of the EUS-EG stiffness classification

The diagnostic performance of the EUS-EG stiffness classification is shown in Table 4. For diagnosis of PC, the sensitivity, specificity, PPV, and NPV of stiff lesions were 95% (95% CI: 87%—99%), 53% (39%—65%), 68% (58%—78%), and 91% (77%—98%), respectively. The sensitivity was also high, at 94% (83%—99%), for MPDD type lesions, but the specificity of 23% (5%—54%) and NPV of

Table 4
Comparison of diagnostic performance of the EUS-EG stiffness classification for PC based on the presence or absence of MPDD or lesion location.

	Sensitivity, % (95%CI)	Specificity, % (95%CI)	Positive predictive value, % (95%CI)	Negative predictive value, % (95%CI)
PC (n = 65)	95% (87%—99%)	53% (39%—65%)	68% (58%—78%)	91% (77%—98%)
Type				
MPDD (n = 50)	94% (83%—99%)	23% (5%—54%)	83% (70%—91%)	50% (12%—88%)
PT (n = 15)	100% (78%—100%)	60% (45%—74%)	44% (27%—62%)	100% (88%—100%)
Location				
Head (n = 35)	97% (85%—100%)	53% (28%—77%)	81% (66%—91%)	90% (56%—100%)
Body (n = 19)	95% (74%—100%)	41% (22%—61%)	53% (35%—70%)	92% (62%—100%)
Tail (n = 11)	91% (59%—100%)	71% (44%—90%)	67% (38%—88%)	92% (64%—100%)

EUS-EG, endoscopic ultrasound elastography; PC, pancreatic cancer; MPDD, main pancreatic duct dilation; PT, parenchymal tumor; CI, confidence interval.

50% (12%—88%) were low. For PT type lesions, the sensitivity of 100% (78%—100%), specificity of 60% (45%—74%), and NPV of 100% (88%—100%) were all high. The diagnostic performance according to lesion location was similar for the pancreatic head, body, and tail.

Discussion

As found in a similar previous multicenter study of SPLs of ≤15 mm [6], this study has shown that PC can be excluded with high confidence for a soft SPL ≤ 20 mm by using the EUS-EG stiffness classification. This conclusion is based on the high NPV for diagnosis of PC for a stiff lesion. When considering that the NPV of PT type lesions remained at 100% (95% CI: 88%—100%), but that of MPDD type lesions was only 50% (12%—88%), PC can only be excluded with high confidence for a lesion classified as a PT type soft lesion. On the other hand, lesion location had few effects on the diagnostic performance. Thus, this study evaluating the usefulness of EUS-EG based on the presence or absence of MPDD suggests that use of the EUS-EG stiffness classification for diagnosis of PC brings better results in PT type lesions.

High-grade PanIN is a cause of the decrease in NPV for EUS-EG diagnosis of MPDD type lesions because high-grade PanIN may be accompanied by surrounding MFP [9,12] and visualized as a soft lesion. In the current study, 6 (46%) of the 13 MFP cases were classified as soft lesions. In addition, MPDD type PC could be visualized as a soft lesion if the concomitant obstructive pancreatitis is stiff. On the contrary, even in non-PC, severe fibrosis may occur in a lesion causing MPDD, and this lesion is likely to be visualized as a stiff lesion. In fact, all the 6 MPDD type non-PC lesions that were resected were associated with abundant fibrosis. Thus, for PC lesions, the NPV of the MPDD type was lower because of the fewer soft lesions in non-PC, in addition to visualization of high-grade PanIN as a soft lesion and of obstructive pancreatitis as a stiff lesion.

The frequency of MPDD type lesions of ≤20 mm in this study was significantly higher in PC, with 50 (77%) of the 65 PC cases being MPDD type lesions. This is consistent with the results of another multicenter study [8] of early PC. Given the lower performance of EUS-FNA for diagnosis of small SPLs [3—5], exclusion of PC must be performed with care in an EUS-FNA-negative case, especially for a MPDD type lesion. Since progression of PC is rapid [13], there should only be a short interval until the next follow-up examination in such a case. In contrast, a longer interval may be acceptable for a soft lesion given the lower chance of PC. Surgery is recommended for PT type soft lesions of PanNET, SPN, and pancreatic metastasis of RCC, but these grow slowly. Limited surgery is also an option for these lesions [14—16]. For PT type soft lesions, radical surgery should be avoided if there is no clear rationale, given the increased rate of benign lesions, and follow-up should be considered in some cases.

This study included 31 cases of PanNET, which was the second most frequent. The EUS-EG stiffness classification was stiff in 14 (45%), which are similar rates to those in a previous study [6]. Only 4 PanNET cases (13%) were MPDD type lesions and all of them were stiff. In PanNET, it has been reported that aggressive tumors, such as those with invasive growth, have decreased intratumoral microvascular density and increased fibrosis [17]. In this study, the 4 PanNET cases with MPDD pathologically had invasive growth to main pancreatic duct with fibrosis, which may be related to be visualized as a stiff lesion.

Qualitative evaluation of EUS-EG for SPLs using pattern classification was first reported by Giovannini et al., in 2006 [18] and then in further studies [6,10,19—22], but subjectivity was a concern in these studies. Subsequently, the strain ratio and strain histogram have been used for quantitative evaluation [23—35]. However,

these methods are complex and have limited reproducibility, which restricts their use in actual clinical practice. In a meta-analysis of EUS-EG, the pattern classifications for differentiation of benign and malignant lesions and the diagnostic performance of quantitative evaluation were equivalent, and both had high sensitivity and low specificity. Therefore, precise diagnostic performance based on stiffness is considered unreasonable [36]. Furthermore, EUS-EG is not suitable for large lesions because comparison with surrounding tissue is difficult. Satisfactory images can be acquired in 91% of cases with lesions limited to ≤35 mm, but in only 56% of all cases [37]. The recently introduced method of EUS shear-wave elastography allows quantitative evaluation, and a correlation with autoimmune pancreatitis has been reported [38]; however, the diagnostic performance of this method for SPLs remains to be investigated.

Ignee et al. [6] reported an EUS-EG stiffness classification of small SPLs based on comparison with surrounding tissue. A lesion that was stiffer than the surroundings was classified as stiff, and a lesion that was equivalent or softer was classified as soft. This is ideal with regard to the principle of strain elastography, but is difficult to judge, as shown in Figs. 1 and 2. In the pattern classification reported by Iglesias-Garcia et al. [10], the lesion was classified into 4 types based on the blue:green ratio: homogeneous blue, heterogeneous blue-predominant, heterogeneous green-predominant, and homogeneous green, but again judgement was not easy.

To improve the quality and objectivity of pattern classification, we used multiple images in the current study. In our database, multiple EUS-EG images are stored per case. Since reproducibility among images is not necessarily favorable, use of only one image may lead to selection bias. Thus, we decided to examine all images of the target lesion with no defect in the EUS-EG color map. In addition, as the study period was long (about 15 years), the improvement in image quality and learning curves for diagnostics may have affected the results of our study. To minimize these effects, the classification was simplified as much as possible, and images were classified based on the blue:green ratio in the lesion as blue-dominant, equivalent, or green-dominant. Using this method, 1077 images were classified by three raters and the kappa coefficient was 0.783, indicating good concordance among the raters. In the final classification, a lesion was classified as stiff if there were a greater number of blue-dominant than green-dominant images, and all other lesions were classified as soft. All 126 cases were evaluated using this method and the kappa coefficient was 0.932, showing excellent concordance among the raters and suggesting that the approach to EUS-EG stiffness classification using multiple images is appropriate.

Although reproducibility of EUS-EG images is a concern, many images can be acquired within a short time as a characteristic of this method. Contrast-enhanced EUS using an ultrasound contrast agent has recently enabled evaluation of hemodynamics, which is useful for differentiation of SPLs [1,39—41], but the characteristic of EUS-EG to obtain multiple images within a short time is an advantage that contrast-enhanced EUS does not offer. Certain ultrasound apparatuses can now extract three optimal still images at the time of acquiring EUS-EG video, which improves the accuracy of EUS-EG. Software to detect a lesion and analyze the blue:green ratio in the lesion may further increase objectivity and improve the usefulness of EUS-EG.

There are several limitations of this study. First, the number of cases was limited due to a single-center retrospective design. Second, many types of endoscopes were used, although with consistent use of only two ultrasound apparatuses (Hitachi and Olympus) that give relatively similar image qualities. Third, the number of EUS-EG images acquired per patient was also not the same which

ranged from 2 to 31, but this was to exclude a selection bias. Fourth, it is uncertain if an examination of diagnostic performance based on dividing cases into PC and non-PC is appropriate, since the non-PC group may contain lesions with malignancy equivalent to that of PC. However, there was only one case of pancreatic metastasis of gallbladder cancer in this category, and this was a PT type stiff lesion; therefore, this had a limited influence on the results. Finally, the histological findings could not be compared with the EUS-EG stiffness classification in all cases. This is because there is no established method for determining stiffness from histopathological findings, and because strain elastography reflects the relative stiffness within the ROI, which is not easy to compare with histological findings in detail. A prospective multi-center study of the histopathological findings and the EUS-EG stiffness classification would be desired to valid our results.

In conclusion, concordance among raters for the EUS-EG stiffness classification of SPLs of ≤20 mm using multiple images was very favorable. This classification permits exclusion of PC with high confidence for a PT type soft lesion, based on the high NPV of stiff lesions for diagnosis of PC.

Author contributions

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Critical revision of the article for important intellectual content: Fujishiro M.

Final approval of the article: All authors.

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