Increased hardness of the underlying pancreas correlates with the presence of intraductal papillary-mucinous neoplasm in a limited number of cases

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Abstract

Purpose Pancreatic fibrosis or fibrosing reactions have been reported in intraductal papillary-mucinous neoplasm (IPMN) patients. We assessed whether a higher elastic modulus (EM) measured using shear wave elastography (SW-EG) correlated with the existence of branch-duct (BD) IPMN.

Methods In total, 183 normal pancreas (NP) and 123 BD-IPMN cases were enrolled. First, we assessed the difference in pancreatic EM (PEM) at different sites (head or tail side of the cyst). Second, a comparison was done between the median PEM of the NP and the BD-IPMN cases. Receiver-operating characteristic analysis was performed to determine the BD-IPMN diagnostic capabilities. Finally, in patients whose cyst was not visualized, the test-positive rate was determined.

Results No significant difference was seen between the cyst head side PEM (4.61 kPa) and the tail side PEM (5.35 kPa) ($P = 0.471$). Among these cases matched by age, 73 were selected each from NP and BD-IPMN cases (median age 65 years). The median PEM of the BD-IPMN cases (5.18 kPa) was significantly higher than that of the NP cases (3.17 kPa) ($P < 0.001$). When the cut-off value was set at 4.75 kPa, the sensitivity, specificity, PPV, NPV, and accuracy were 75.3%, 64.4%, 72.3%, 67.9%, and 69.9%, respectively. The cut-off value of 4.75 kPa helped for the indirect selection of BD-IPMN patients (10/17, 58.8%) whose cyst was not detected on B-mode ultrasonography.

Conclusion SW-EG measurement of the underlying pancreatic parenchyma may correlate with the presence of BD-IPMN.

Keywords Intraductal papillary-mucinous neoplasm · Shear wave elastography · Pancreatic fibrosis

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Introduction

Intraductal papillary-mucinous neoplasm (IPMN) is a risk factor of concomitant pancreatic cancer, in addition to its cancerization as an infiltrating cancer through carcinoma in situ [1–3]. While transabdominal ultrasonography (US) is considered a useful method for detecting pancreatic cystic lesions, about 25% of the entire pancreas cannot be observed by US, and overlooking of potential lesions is a concerning issue [4].

By contrast, fibrosis observed in the pancreas during IPMN has been previously reported [5], and ultrasound elastography is a possible method for noninvasively evaluating pancreatic fibrosis [6, 7]. There are two methods of ultrasound elastography: strain elastography, which images the distribution of distortion utilizing heart or vascular pulsations, and shear wave elastography (SW-EG), which quantitatively assesses tissue elasticity by measuring the shear

wave velocity. We previously reported that ultrasound elastography was useful in diagnosing fibrosis of the pancreatic parenchyma using either method [8, 9].

If the modulus of elasticity is high in the background pancreas of a branch-duct (BD)-IPMN, the possibility exists that it can be applied to indirect observational diagnosis of the presence of BD-IPMN. In this study, we investigated the potential of diagnosing the presence of IPMN by comparing the modulus of elasticity between a normal pancreas (NP) and a pancreas in patients with BD-IPMN.

Methods

Subjects

A total of 183 patients with NP and 123 patients with BD-IPMN in whom SW-EG measurements of the normal pancreatic parenchyma and background pancreas were performed were enrolled prospectively and analyzed retrospectively at Nagoya University Hospital between October 2012 and June 2016. The exclusion criteria were severe complications; serious psychiatric symptoms; development of multiple, branched pancreatic duct-type IPMN in two or more of the head, body, and tail regions; and non-measurable SW-EG. Patients in whom SW-EG was not measurable were defined as those in whom the pancreas could not be clearly visualized, those with difficulty holding their breath, and those in whom the region of interest (ROI) could not reach the pancreas. In addition, the measurement success rate was defined as the ratio of the number of successful measurements to the total number of measurements in patients in whom shear wave measurements were performed at least five times. Patients with a measurement success rate below 60%, based on five or more measurements, were regarded as having a low reliability and were, thus, excluded, as reported previously [8]. An NP was defined as a pancreas with no tumors, cysts, or main pancreatic duct dilatation on endoscopic ultrasonography or contrast-enhanced CT; no habitual alcohol drinking of 80 g/day or more; and amylase and lipase levels within normal ranges on blood testing. BD-IPMN was defined as a cystic lesion communicating with the main pancreatic duct on endoscopic ultrasonography (EUS) or contrast-enhanced CT and clinically diagnosed as BD-IPMN. Out of the 123 cases, 13 cases were diagnosed as low grade-to-intermediate dysplasia, five cases were diagnosed as having invasive carcinoma histopathology through surgery, and 105 cases were being conservatively observed. All IPMNs in our study were BD-IPMNs and had no dilated main pancreatic duct. It was possible to set the ROI in all patients. In this study, we excluded cases diagnosed with invasive cancer to rule out the effects of fibrosis due to direct invasion of the cancer. During this

study period, there were no evident morphological changes in the observed cases. This study was approved by the Institutional Review Board (IRB) of our hospital, registered in the UMIN-CTR (000016497), and performed in conformity to the Declaration of Helsinki.

Devices used for observation

With regards to the observation device, an iU22 (Philips Healthcare, Bothell, WA, USA) was used. SW-EG was performed using a convex probe (C5-1) in ElastoPQ mode. When the measurement result was 0.00 kPa, the measurement was considered unsuccessful. The ROI in this study was set as a rectangular shape with a size of 5 mm (horizontal) and 15 mm (vertical).

Study protocol

Shear wave elastography measurements were performed from the epigastric fossa in a supine or semi-sitting position after the patients had fasted for > 9 h. The ROI was placed using a trackball. The patients were instructed to hold their breath while the physician pressed a button to launch the data acquisition. The ROI was set, so that it avoided blood vessels and the main pancreatic duct, in a region wherein the pancreas was clearly visualized on B-mode imaging, as previously reported [8]. According to this research, sufficient reproducibility was achieved by more than five measurements from the results calculated using the intraclass correlation coefficient. The median of the values of the successful measurements was defined as the pancreatic elastic module (PEM). We measured the elasticity at different sites, because we are not always able to set the ROI at a specific location depending on the location of the cyst and the form of the pancreas. However, we followed the data in the previous study, which showed no significant differences in PEM between the different pancreatic positions in the normal subject [8]. This study was a retrospective study, and no specific blind conditions were adopted. The examiners were three board fellows of the Japanese Society of Ultrasonics in Medicine, with more than 15 years of experience.

Investigation 1 To confirm the absence of differences due to the position of the ROI relative to the cyst, measurements were performed on the head and tail sides of the lesion in BD-IPMN patients, and the PEM was compared between the head and tail sides.

Investigation 2 To exclude the influence of aging, the subjects were divided into 5-year increment groups, in the normal and BD-IPMN groups, and the age factor was adjusted using a 1:1 caliper matching. PEM and background factors (sex, BMI, subcutaneous fat thickness, distance between the pancreas and body surface, and distance between the aorta and pancreas) were then compared between the NP and

BD-IPMN groups (NP group: N-PEM; BD-IPMN group: B-PEM). To determine the PEM-based BD-IPMN diagnostic performance, receiver-operating characteristic (ROC) analysis was performed in age-matched subjects.

Investigation 3 In the 17 patients in whom the cyst was not visualized directly on US (Fig. 1), the region containing the lesion and measurement site was evaluated, and the test-positive rate was determined using the cut-off value set by the ROC analysis. These 17 cases were diagnosed by EUS, CT, and magnetic resonance cholangiopancreatography (MRCP).

Statistical analysis

The analyses were performed using the Mann–Whitney U test for continuous variables. For comparison between the groups that were age-matched using a 1:1 caliper matching, the Wilcoxon signed-rank test was used for continuous variables, and the McNemar test was used for comparison of sex. Continuous parameters were presented as median (range). Regarding the accuracy of the PEM-based diagnosis of BD-IPMN, the cut-off value was set at a point maximizing the Youden index using the area under the ROC curve (AUC), and the sensitivity, specificity, positive and negative predictive values, and accurate diagnosis rate were calculated. These were analyzed using SPSS ver. 22.0 (SPSS, Chicago, IL, USA). A P value less than 0.05 was regarded as significant.

Results

Of the 183 cases with an NP and the 123 cases with BD-IPMN in which SW-EG was measured, 108 and 89 (103 sites in total), respectively, were included in the analysis

(Fig. 2). The cyst could not be visualized directly by transabdominal ultrasonography in 17 (19.1%) of the 89 BD-IPMN patients, and the region containing the lesion was the pancreatic tail in 15 cases and pancreatic head in two cases.

Investigation 1 PEM was investigated at 103 sites by measuring the ROI of the cyst in 89 BD-IPMN patients. PEM was measured only on the head side in 28 cases, only on the tail side in 47, and both sides in 14. The PEM (interquartile range) was 4.61 (3.54–6.54) kPa on the head side (42 sites) and 5.35 (3.53–7.75) kPa on the tail side (61 sites), thus showing no significant difference ($P = 0.471$). In the 14 patients in whom PEM was measured on both sides, the values were 5.38 (3.76–9.36) kPa on the head side and 5.25 (4.75–6.81) kPa on the tail side, showing no significant difference ($P = 0.549$) (Table 1).

Investigation 2 In the 73 age-matched subjects in the normal group, the median age was 65 (60–75) years and the male:female ratio was 39:34. In the BD-IPMN group, the median age was 65 (60–75) years and the male:female ratio was 33:40. N-PEM was 3.27 (2.51–4.73) kPa, and B-PEM was 5.38 (3.98–8.54) kPa, which was significantly higher ($P < 0.001$) (Fig. 3). In the univariate analysis, no significant differences between the NP and the BD-IPMN groups were noted in terms of BMI, subcutaneous fat thickness, distance between the pancreas and body surface, or distance between the aorta and pancreas (Table 2).

When the cut-off value obtained from the ROC curve was set at 4.75 kPa, the sensitivity was 75.3%, specificity was 64.4%, PPV was 72.3%, NPV was 67.9%, and the accurate diagnosis rate was 69.9% (Table 3).

Investigation 3 The 17 patients in whom the pancreatic cyst could not be visualized directly on US were diagnosed using the cut-off value (4.75 kPa) determined by the ROC analysis, and 10 (58.8%) of the 17 patients were found

Fig. 1 The patient was a 60-year-old man. The cyst in the tail was not detected on transabdominal ultrasonography. When the parenchyma pancreatic elastic modulus (PEM) was measured in the pancreatic body, the value was 6.17 kPa (**a**). On magnetic resonance cholangi-opancreatography (MRCP), a 16-mm multilocular cystic lesion suspected of communicating with the main pancreatic duct was observed in the pancreatic tail (**b**)
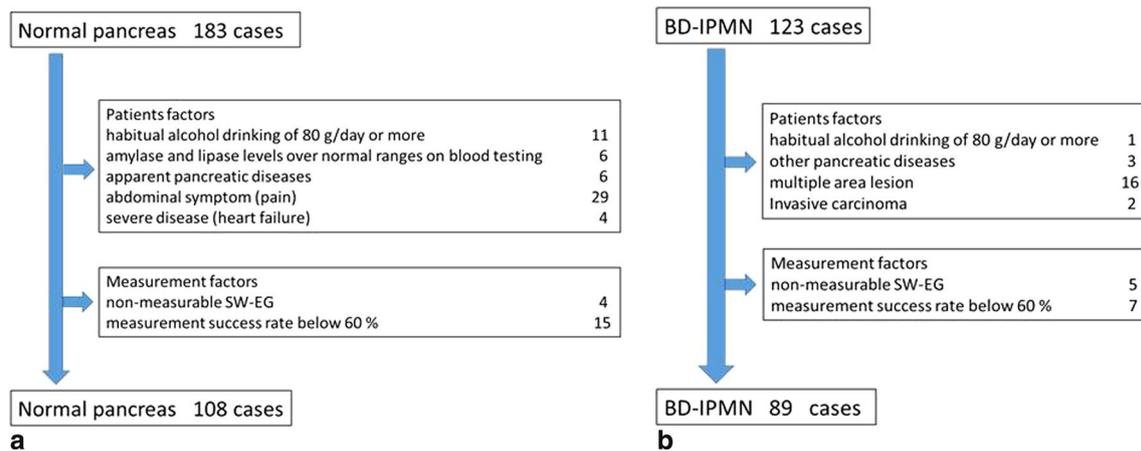
Fig. 2 Flowchart of the enrolled patients. **a** Normal pancreas: We initially enrolled 183 subjects in the study. We excluded 56 cases because of patient-associated factors and 19 cases because of measurement factors. **b** Branch-duct intraductal papillary-mucinous neo-

plasm (BD-IPMN): we initially enrolled 123 subjects and excluded 22 cases because of patient-associated factors and 12 cases because of measurement factors

Table 1 Comparison of PEM by site (Investigation 1)

	PEM[a] (kPa)	*P* value
Pancreas head side (*n*=42)	4.61 (3.54–6.54)	0.471
Pancreas tail side (*n*=61)	5.35 (3.53–7.75)	
Both sides (*n*=14)		
Head side	5.38 (3.76–9.36)	0.549
Tail side	5.25 (4.75–6.81)	

A Mann–Whitney *U* test was used for comparison of PEM on the head side and tail side of the cyst

IQR interquartile range, *PEM* parenchyma pancreatic elastic modulus

[a]Data are median

to be positive (median PEM in the positive cases: 9.69 (5.50–13.87) kPa) (Table 4).

Discussion

Shear wave elastography is considered to be a technique that is capable of noninvasive quantitative evaluation of fibrosis in the pancreas, and a high positive correlation has been observed between the histopathological pancreatic fibrosis stage and PEM calculated from SW-EG [8]. While inflammation and obstructive pancreatitis have been reported to be the causes of pancreatic parenchymal fibrosis [8], aging also causes fibrosis [10] and increases the shear wave velocity [11], resulting in a high PEM value. However, after adjustment by age matching, the median B-PEM was significantly higher than the N-PEM (Table 2), suggesting that IPMN promotes fibrosis of the background pancreatic parenchyma, which is not explained by aging.
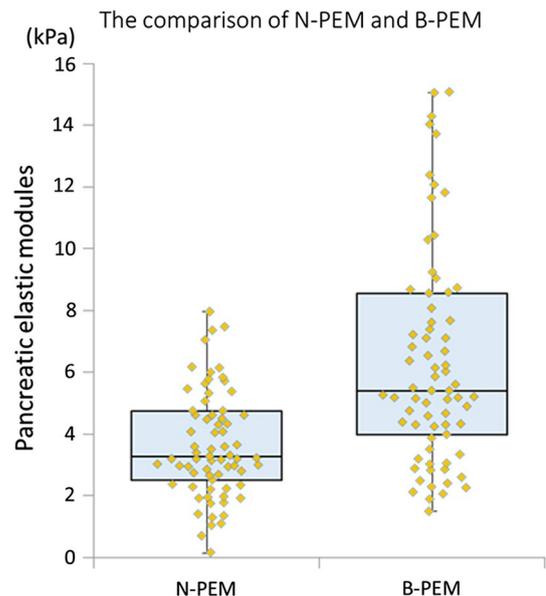
Fig. 3 Normal pancreatic elastic modulus (N-PEM) and branch duct-type intraductal papillary-mucinous neoplasm parenchyma pancreatic elastic modulus (B-PEM). Box and whisker plot of the N-PEM and B-PEM. The bottom and top of the boxes are the first and third quartiles (interquartile), respectively, and the band inside the boxes is the median. The ends of the whiskers are the minimum and maximum values of the data. The median N-PEM value was 3.27 kPa and the median B-PEM value was 5.38 kPa, which was significantly higher ($P < 0.001$)

Regarding the cause, mucus produced by the tumor increases the viscosity of the pancreatic juices and causes obstructive pancreatitis in IPMN [12–14], and fibrosis has been observed upon pathological examination of resected cases [15, 16]. It has been reported that the fibrosis is

Table 2 Patient characteristics (Investigation 2)

	Normal pancreas ($n=73$)	BD-IPMN ($n=73$)	P value
Age (years)[a]	65 (60–75)	65 (60–75)	0.557
Sex (male/female)	39/34	33/40	0.211
BMI (kg/m^2)[a]	22.2 (20.3–24.1)	21.7 (19.6–24.1)	0.816
Subcutaneous fat thickness (mm)[a]	13.2 (8.7–16.3)	11.8 (7.1–17.2)	0.329
Distance from pancreas to body surface (mm)[a]	55.2 (37.5–68.9)	54.7 (33.6–68.0)	0.476
Distance from pancreas to aorta (mm)[a]	25.2 (21.2–29.9)	24.6 (20.8–29.4)	0.314
PEM (kPa)[a]	3.27 (2.51–4.73)	5.38 (3.98–8.54)	<0.001*

BMI body mass index, *BD-IPMN* branch duct-type intraductal papillary-mucinous neoplasm, *IQR* inter-quartile range, *PEM* parenchyma pancreatic elastic modulus

*Normal pancreas PEM was 3.27 (2.51–4.73) kPa, and BD-IPMN PEM was 5.38 (3.98–8.54) kPa, which was significantly higher ($P < 0.001$)

[a]Data are median

Table 3 Ability of SW-EG to diagnose BD-IPMN

	Diagnostic ability
AUCROC	0.73
Cut-off value (kPa)	4.75
Sensitivity (%)	75.3
Specificity (%)	64.4
PPV (%)	72.3
NPV (%)	67.9
Accuracy (%)	69.9

SW-EG shear wave elastography, *BD-IPMN* branch duct-type intraductal papillary-mucinous neoplasm, *AUCROC* area under the receiver-operating characteristic curve, *PPV* positive predictive value, *NPV* negative predictive value

typically distributed between and within the lobules on the tail side of the obstructed region in obstructive pancreatitis [17], but Kakizaki et al. reported that fibrosis was distributed heterogeneously in the interstitium around the dilated pancreatic duct in IPMN, and fibrosis was also observed around the dilated pancreatic duct in BD-IPMN [5]. Furthermore, they proposed that the presence of fibrosis around dilated pancreatic ducts indicated an interaction between IPMN and the surrounding interstitial fibrosis.

In the present study, the PEM on the pancreatic head side of the cyst was higher than that in the NP, so fibrosis of the pancreas in IPMN cannot be explained by the mechanism of obstructive pancreatitis alone, which is consistent with the report of Kakizaki et al. that IPMN directly induced interstitial fibrosis around the dilated pancreatic duct. Therefore, if fibrosis is present in the pancreas regardless of the position of the cyst within the pancreas, it may be possible that the presence of IPMN can be predicted based on the presence of fibrosis. If fibrosis can be detected by measuring PEM with ultrasonography of the pancreas, it may be useful for predicting the presence of IPMN not visualized on US, leading to further close examination using CT and EUS, and subsequently leading to early discovery of the risk factors for pancreatic cancer. In addition, PEM is higher in fibrosis associated with pancreatic inflammation including chronic pancreatitis and tumors [9]. Thus, PEM measurement is not specific for the detection and diagnosis of BD-IPMN, and it may detect other inflammatory and tumorous diseases that may lead to fibrosis of the pancreatic parenchyma including aging-related changes.

There were two limitations of this study. First, this was a retrospective study and the BD-IPMN group involved elderly subjects, thus indicating differences in the demographic factors. While this was corrected by matching, the results may not have been reflected accurately. A prospective study is needed using the cut-off value in this study. Second, this study was in a limited cohort comparing cases diagnosed with BD-IPMN and NP. We intended to rule out chronic pancreatitis and pancreatic cancer by EUS and CT, but a high PEM might indicate other pancreatic fibrotic disease, or a small cyst not visualized.

Conclusion

The PEM of the BD-IPMN was higher than that of the normal pancreatic parenchyma on both the head and tail sides of the cyst. This finding suggests that an SW-EG measurement of the background pancreatic parenchyma is useful for diagnosing the presence of BD-IPMN, even after taking aging-related changes into consideration.

Table 4 Seventeen patients in whom the cyst was not directly visualized on US

Age (y.o.)	Sex	Cyst localiza- tion	Measure- ment site	B-PEM (kPa)	BMI (kg/m^2)	Subcutaneous fat thickness (mm)	Distance from pancreas to body surface (mm)	Distance from pancreas to Aorta (mm)
83	M	Pt	Pb	1.37	26.8	17.5	88.1	29.3
85	M	Pt	Pb	2.48	30.1	10	101.9	53.1
38	F	Pt	Pb	2.59	24.5	5.8	26.2	16.9
73	M	Pt	Ph	4.22	19.4	10	59.38	22.21
66	M	Pt	Pb	4.57	20.2	8.42	67.9	29.74
63	F	Pt	Ph	4.59	25.6	13.4	37.5	25
71	M	Pt	Ph	4.66	22.9	11.6	53.9	25.85
71	M	Pt	Ph	4.75	26.2	24.7	25.07	68.7
65	M	Ph	Pb	4.86	21	8.1	31.7	30.9
68	F	Pt	Pb	5.27	15.2	5	28.8	18.13
67	M	Pt	Pb	6.17	24.2	21.8	77.5	20.6
73	F	Ph	Pb	7.33	30.4	27.27	101.08	38.07
67	F	Pt	Pb	12.1	15.2	6.5	14.4	12
62	F	Pt	Ph	13.5	19.2	22.5	66.9	19.5
52	F	Pt	Pb	14.0	24.7	15.99	42.82	21
75	F	Pt	Pb	14.3	22.9	20	65	24
44	F	Pt	Ph	21.3	19.5	7.8	15.6	18.8

US ultrasonography, *y.o.* years old, *M* male, *F* female, *Ph* pancreatic head, *Pb* pancreatic body, *Pt* pancreatic tail, *B-PEM* branch duct-type intra-ductal papillary-mucinous neoplasm parenchyma pancreatic elastic modulus, *BMI* body mass index

Compliance with ethical standards

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