Int Surg 2015;**100**:497–502
DOI: 10.9738/INTSURG-D-14-00040.1

Quantification of Pancreatic Stiffness on Intraoperative Ultrasound Elastography and Evaluation of its Relationship With Postoperative Pancreatic Fistula

Masahide Hatano[1], Jota Watanabe[1], Fumiki Kushihata[1], Taiji Tohyama[1], Taira Kuroda[2], Mitsuhito Koizumi[2], Teru Kumagi[2], Yoshiko Hisano[3], Atsuro Sugita[3], Yasutsugu Takada[1]

[1]*Department of Hepato-Biliary-Pancreatic Surgery and Breast Surgery, Graduate School of Medicine, Ehime University, Ehime, Japan*

[2]*Department of Gastroenterology and Metabology, Graduate School of Medicine, Ehime University, Ehime, Japan*

[3]*Pathology Division, Ehime University Hospital, Ehime, Japan*

"Soft pancreas" has often been reported as a predictive factor for postoperative pancreatic fistula (POPF) after pancreatectomy. However, pancreatic stiffness is judged subjectively by surgeons, without objective criteria. In the present study, pancreatic stiffness was quantified using intraoperative ultrasound elastography, and its relevance to POPF and histopathology was investigated. Forty-one patients (pancreatoduodenectomy, 30; distal pancreatectomy, 11) who underwent intraoperative elastography during pancreatectomy were included. The elastic ratio was determined at the pancreatic resection site (just above the portal vein) and at the remnant pancreas (head or tail). Correlations between the incidence of POPF and patient characteristics, operative variables, and the elastic ratio were examined. In addition, the relationship between the elastic ratio and the percentage of the exocrine gland at the resection stump was investigated. For pancreatoduodenectomy patients, main pancreatic duct diameter < 3.2 mm and elastic ratio < 2.09 were significant risk factors for POPF. In addition, the elastic ratio, but not main pancreatic duct diameter, was significantly associated with the

Corresponding author: Masahide Hatano, MD, Department of Hepato-Biliary-Pancreatic Surgery and Breast Surgery, Ehime University Graduate School of Medicine, Shitsukawa 454, Toon, Ehime 791-0295, Japan.
Tel: +81 89 960 5327; Fax: +81 89 960 5329; E-mail: m-hatano@m.ehime-u.ac.jp

percentage of exocrine gland area at the pancreatic resection stump. Pancreatic stiffness can be quantified using intraoperative elastography. Elastography can be used to diagnose "soft pancreas" and may thus be useful in predicting the occurrence of POPF.

Key words: Elastography – Exocrine gland – Pancreatectomy – Pancreatic stiffness – Postoperative pancreatic fistula

Despite current advances in surgical techniques, pancreatectomy is a very difficult procedure associated with the risk of multiple postoperative complications. The morbidity and mortality are reported to be 20–50% and 1–5%, respectively.[1] In particular, a postoperative pancreatic fistula (POPF) can sometimes lead to life-threatening complications, such as hemoperitoneum and sepsis. The worldwide incidence of POPF is reported to be 5–50%. Several predictive factors for POPF have been reported to date, and, of these, "soft pancreas" has often been mentioned.[2–4] However, in all of these reports, evaluation of pancreatic stiffness has depended on subjective judgment by the surgeon, without objective parameters as criteria.

Elastography has recently been developed to enable real-time visualization of the relative stiffness of tissue elasticity, and its usefulness in various clinical disciplines for tumor diagnosis and differential diagnosis has been described.[5] In gastroenterology, evaluation of liver fibrosis and diagnosis of pancreatic tumors and chronic pancreatitis using endoscopic ultrasound (EUS) have been reported,[6,7] but the use of elastography in surgery has not been reported. An objective assessment of pancreatic stiffness as a predictive risk factor for POPF can help in choosing the intraoperative surgical technique and in planning the postoperative management strategy. Therefore, in the present study, pancreatic stiffness was quantified using intraoperative ultrasound elastography, and its relevance to POPF and histopathology was investigated.

Patients and Methods

This study included 41 patients who underwent intraoperative elastography during pancreatectomy at our hospital between July 2010 and February 2013. The patients were recruited into the study before surgery and agreed to enroll in this study. The protocol and study design of the present trial were approved and conducted according to the guidelines of the Ethics Committee at our hospital.

The pancreatectomy procedures were standardized using the same methods. For pancreatoduodenectomy (PD), pancreatic anastomosis was performed by duct-to-mucosal, end-to-side pancreatico-jejunostomy in all enrolled patients. A pancreatic duct stent tube was inserted. For distal pancreatectomy (DP), the main pancreatic duct was ligated, and the pancreatic stump was closed in a "fish-mouth" fashion. POPF was evaluated according to the criteria of the International Study Group of Pancreatic Fistula (ISGPF).[8] Incidence of POPF was evaluated with respect to various patient and operation factors.

For measurement of pancreatic stiffness, a real-time tissue elastography measurement system, EZU-TE3 HITACHI EUB-7500 (Hitachi Medical Systems, Tokyo, Japan), was used for ultrasound

Table 1 Clinical characteristics of patients with pancreatectomy

Characteristics	Total (n = 41)	PD (n = 30)	DP (n = 11)
Male sex, n (%)	29 (70.7)	19 (63.3)	10 (90.9)
Age, y, median (range)	71 (43–82)	71.5 (43–81)	71 (59–82)
BMI, kg/m^2, median (range)	21.1 (16.2–28.7)	20.5 (17.6–28.7)	21.1 (16.2–26.7)
HbA1c, %, median (range)	5.4 (4.1–9.2)	5.5 (4.7–9.2)	5.4 (4.1–6.9)
PFD test, %, median (range)	58.3 (12.6–96.1)	59.3 (12.6–85.4)	53.8 (17.0–96.1)
Main pancreatic duct, mm, median (range)	2.7 (1.5–10.7)	2.6 (1.5–10.7)	2.8 (2.1–9.9)
Operative time, min, median (range)	590 (265–855)	600 (510–810)	415 (265–855)
Intraoperative blood loss, mL, median (range)	870 (35–4280)	890 (340–2680)	500 (35–4280)
Elastic ratio, median (range)	1.95 (1.4–6.56)	1.97 (1.4–6.56)	1.98 (1.65–4.07)

PD, pancreatoduodenectomy; DP, distal pancreatectomy.

Table 2 Postoperative pancreatic fistula outcomes

	Total (n = 41) n (%)	PD (n = 30) n (%)	DP (n = 11) n (%)
Postoperative pancreatic fistula	18 (43.9)	11 (36.7)	7 (63.6)
Grade A	9 (22.0)	4 (13.3)	5 (45.5)
Grade B	6 (14.6)	4 (13.3)	2 (18.2)
Grade C	3 (7.3)	3 (10.0)	0 (0.0)
Mortality	1 (2.4)	1 (3.3)	0 (0.0)

PD, pancreatoduodenectomy; DP, distal pancreatectomy.

elastography. Measurements were performed intraoperatively by the same examiner at the pancreatic dissection site (just above the portal vein), at the pancreatic head, and at the pancreatic tail site. The mean value of 3 measurements at each site was used. Elastic ratio measurements were based on our previously reported studies using same method as for the spleen and liver.[6] As for the elastic ratio, the mean values of 2 measurement results at the dissection site and at the remnant pancreatic site were used for analysis.

Specimens were stained with hematoxylin-eosin for examination. Slides from the resection stump were selected from the specimen slides in all cases. The ratio of the exocrine gland area to the total area of the stump tissue specimens was measured in a double-blind manner by two pathologists and one gastroenterological surgeon. This was based on previous reports by Mathur *et al*.[9] Patients were classified by the percentage of exocrine gland area into the following three groups: the poor group (< 25%), the rich group (> 75%), and the moderate group (intermediate values).

Results

For the total 41 patients (29 men, 12 women), the median patient age was 71 years (43–82 years). The operative procedure was pancreatoduodenectomy (PD) in 30 patients and distal pancreatectomy (DP) in 11. Table 1 shows the patients' background and surgical characteristics for each operative procedure.

In the PD group, POPF developed in 11 (36.7%), and in the DP group, POPF developed in 7 (63.6%) based on the ISGPF criteria (Table 2). In the PD group, main pancreatic duct (MPD) diameter was significantly smaller and the elastic ratio was significantly lower in the POPF group (Table 3). On the other hand, in the DP group, no significant differences were observed for any variables between the POPF and non-POPF groups.

The optimal cut-off values for MPD diameter and elastic ratio to predict the POPF for the PD group

Table 3 Univariate analysis of the risk factors for POPF

	PD (n = 30)			DP (n = 11)		
Clinical factors	POPF (+) (n = 11)	POPF (−) (n = 19)	*P* value	POPF (+) (n = 7)	POPF (−) (n = 4)	*P* value
Male sex, n (%)	9 (81.8)	10 (52.6)	0.1	7 (100)	3 (75)	0.2
Age, y, median (range)	73 (58–81)	70 (43–80)	0.6	68 (59–81)	73 (71–82)	0.2
BMI, kg/m^2, median (range)	22 (18.6–25.7)	19.8 (17.6–28.7)	0.4	21.1 (18.2–23.5)	22.2 (16.2–26.7)	0.7
Pancreatic cancer, n (%)	2 (18.2)	7 (36.8)	0.3	3 (42.9)	3 (75)	0.3
HbA1c, %, median (range)	5.5 (5.0–7.4)	5.4 (4.7–9.2)	0.5	5.3 (5.0–6.6)	5.6 (4.1–6.9)	0.6
PFD test, %, median (range)	61.1 (43.9–82.3)	55.2 (12.6–85.4)	0.4	58.3 (33.9–96.1)	45 (17.0–52.2)	0.1
Main pancreatic duct, mm, median (range)	2.3 (1.6–3.6)	3.6 (1.5–10.7)	0.02*	4 (2.1–9.9)	2.6 (2.4–3.2)	0.2
Operative time, min, median (range)	595 (535–810)	605 (510–735)	0.9	380 (265–855)	468 (380–590)	0.3
Intraoperative blood loss, mL, median (range)	1510 (400–2250)	870 (340–2680)	0.6	450 (35–4280)	1095 (460–2085)	0.3
Elastic ratio, median (range)	1.82 (1.53–2.23)	2.22 (1.4–6.56)	0.03*	1.98 (1.67–2.18)	2.39 (1.65–4.07)	0.09

PD, pancreatoduodenectomy; DP, distal pancreatectomy.

*Statistically significant: $P < 0.05$.

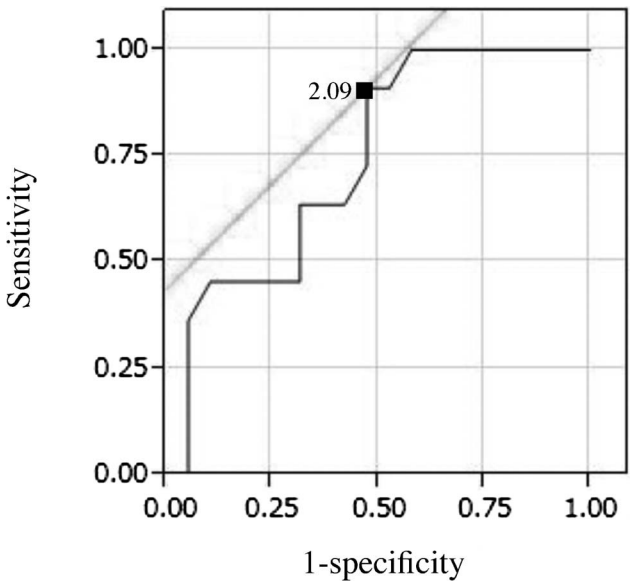

Fig. 1 Receiver operating characteristic (ROC) curve of the elastic ratio for postoperative pancreatic fistula. The optimal cut off value is 2.09 (sensitivity: 0.909, specificity: 0.526), and the area under the curve (AUC) is 0.739.

were obtained from receiver operating characteristic (ROC) analysis. They were 3.2 mm (sensitivity 0.909, specificity 0.579) for MPD diameter and 2.09 for the elastic ratio (sensitivity 0.909, specificity 0.526), and the areas under the curve (AUCs) were 0.77 and 0.739, respectively (Fig. 1). Univariate analysis (Table 4) showed that MPD diameter < 3.2 mm and elastic ratio < 2.09 were significant risk factors for POPF ($P = 0.009$ and $P = 0.02$, respectively). However, multivariate analysis demonstrated that neither variable was an independent factor.

Based on the classification of the percentage (distribution) of exocrine gland area of the pancreatic resection stump, 9 patients had poor, 9 had moderate, and 23 had rich exocrine gland distribution. Fig. 2 shows the distribution of exocrine gland area in pancreatic resection stumps in a typical histology specimen. The median elastic ratios at the pancreatic dissection site were 2.53, 2.04, and 1.78 for the poor, moderate, and rich groups, respectively (Fig. 3). The values were significantly different between the poor and moderate groups ($P < 0.05$) and between the poor and rich groups ($P < 0.001$). On the other hand, there were no significant differences in the median MPD diameters among the three group (2.63 mm, 2.46 mm, and 2.78 mm for the poor, moderate, and rich groups, respectively).

Discussion

Several studies of predictive risk factors for POPF have been reported to date. In particular, "soft pancreas" has often been mentioned as a significant risk factor.[2–4] That a "soft pancreas" is more likely to

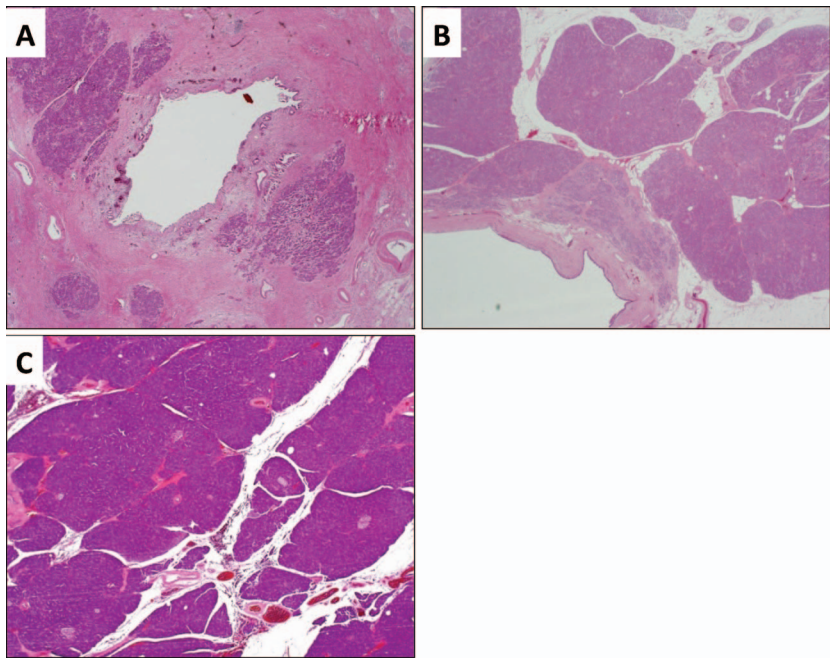

Fig. 2 Typical histologic specimen showing the distribution of exocrine gland area in pancreatic resection stumps. (A) Poor group: percentage (distribution) of exocrine gland area is 0–25%. (B) Moderate group: percentage (distribution) of exocrine gland area is 26–75%. (C) Rich group: percentage (distribution) of exocrine gland area is 76–100%. (magnification × 4, H & E stain.)

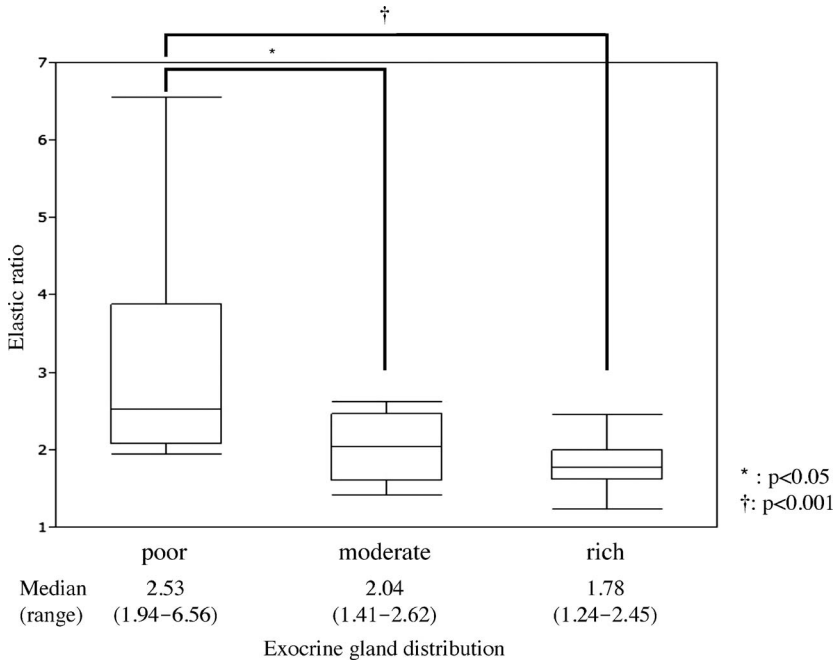

Fig. 3 Comparison of the elastic ratio by exocrine gland distribution. Statistical analysis: For comparisons among multiple groups, ANOVA was used. The Mann–Whitney U test was then performed for comparisons between 2 groups.

leak is common knowledge among surgeons. However, assessment of pancreatic stiffness is subjective and ill-defined, based only on palpation of the pancreatic tissue during surgery; no objective criteria have been reported.

In the present study, the elastic ratio was significantly associated with POPF in PD patients. Based on this finding, we have adopted several kinds of surgical approaches, such as modified anastomosis of pancreatico-jejunostomy in the PD procedure. However in DP patients, though there was a tendency for the POPF-positive group to have a lower elastic ratio, no significant association was observed. Given the heterogeneity between the 2 procedures, PD and DP should be investigated at multiple centers with a larger sample size for further clarification.

Ganjoux *et al*[10] examined whether soft pancreas and fat tissue content $>$ 10% in the pancreatic parenchyma were independent risk factors for POPF, but they found that soft pancreas did not correlate with fat tissue content. In the present study, the relationships between the elastic ratio and the histopathologic findings of the pancreas were investigated. It was found that the elastic ratio was significantly lower in the pancreas rich in exocrine gland tissue. This implies that a so-called "soft pancreas" reflected by a low elastic ratio has a high exocrine gland content on histopathology. This is the first study to identify this. Although the exact mechanisms that link POPF and exocrine gland content remain to be resolved, a greater amount of pancreatic juice might be one of the factors responsible for the occurrence of POPF.

In conclusion, the present study is the first to show that pancreatic stiffness can be quantified using intraoperative elastography, and that the elastic ratio can be used to identify "soft pancreas," rendering it useful in predicting the likelihood of POPF following pancreatectomy. An elastic ratio $<$

Table 4 Univariate and multivariate analyses of risk factors for POPF

	Univariate			Multivariate		
	Odds ratio	95% CI	*P* value	Odds ratio	95% CI	*P* value
MPD diameter $<$ 3.2 mm	13.75	1.45–130.2	0.009	7.72	0.92–166.9	0.06
Elastic ratio $<$ 2.09	11.11	1.18–104.8	0.02	5.39	0.58–118.7	0.14

POPF, postoperative pancreatic fistula; MPD, main pancreatic duct; CI, confidence interval.

2.09 was a significant risk factor for POPF in the present cohort of PD patients. For patients with a soft pancreas or a lower elastic ratio, every effort is needed to reduce the risk of POPF by improving surgical procedures and perioperative patient care.

Acknowledgments

The authors would like to thank Dr. N. Azemoto and Dr. H. Yamanishi for their support and guidance. They are also deeply grateful to Professor M. Onji of the Department of Gastroenterology and Metabology. The article has been checked by a Statistician. None of the authors has any financial or personal conflicts of interest of any kind.

References

1. Winter JM, Cameron JL, Campbell KA, Arnold MA, Chang DC, Coleman J *et al*. 1423 pancreaticoduodenectomies for pancreatic cancer: a single-institution experience. *J Gastrointest Surg* 2006;**10**(9):1199–1210
2. Kim WS, Choi DW, Choi SH, Heo JS, Kim MJ, Song SC *et al*. Clinical validation of the ISGPF classification and the risk factor of pancreatic fistula formation following duct-to-mucosa pancreaticojejunostomy by one surgeon at a single center. *J Gastrointest Surg* 2011;**15**(12):2187–2192
3. Pecorelli N, Balzano G, Capretti G, Zerbi A, Carlo VD, Braga M. Effect of surgeon volume on outcome following pancreaticoduodenectomy in a high-volume hospital. *J Gastrointest Surg* 2012;**16**(3):518–523
4. Kawai M, Kondo S, Yamaue H, Wada K, Sano K, Motoi F *et al*. Predictive risk factors for clinically relevant pancreatic fistula analyzed in 1239 patients with pancreaticoduodenectomy: multicenter data collection as a project study of pancreatic surgery by the Japanese Society of Hepato-Biliary-Pancreatic Surgery. *J Hepatobiliary Pancreat Surg* 2011;**18**(4):601–608
5. Itoh A, Ueno E, Tohno E, Kamma H, Takahashi H, Shiina T *et al*. Breast disease: clinical application of ultrasound elastography for diagnosis. *Radiology* 2006;**239**(2):341–350
6. Ochi H, Hirooka M, Koizumi Y, Miyake E, Tokumoto Y, Soga Y *et al*. Real-time tissue elastography for evaluation of hepatic fibrosis and portal hypertension in non-alcoholic fatty liver disease. *Hepatology* 2012;**56**(4):1271–1278
7. Uchida H, Hirooka Y, Itoh A, Kawashima H, Hara K, Nonogaki K *et al*. Feasibility of tissue elastography using transcutaneous ultrasonography for the diagnosis of pancreatic diseases. *Pancreas*. 2009;**38**(1):17–22
8. Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Neoptolemos J *et al*. Postoperative pancreatic fistula: an international study group (ISGPF) definition. *Surgery* 2005; **138**(1):8–13
9. Mathur A, Pitt HA, Marine M, Saxena R, Schmidt CM, Howard TJ *et al*. Fatty pancreas: a factor in postoperative pancreatic fistula. *Ann Surg* 2007;**246**(6):1058–1064
10. Gaujoux S, Cortes A, Couvelard A, Noullet S, Clavel L, Rebours V *et al*. Fatty pancreas and increased body mass index are risk factors of pancreatic fistula after pancreaticoduodenectomy. *Surgery* 2010;**148**(1):15–23