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Original Article

Quantitative evaluation of pancreatic tumor fibrosis using shear wave elastography

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ABSTRACT

Background & aims: There is no established non-invasive method for diagnosis of pancreatic fibrosis. Shear wave elastography (SW-EG) may be a candidate for this purpose. The aims of this study were to assess the reproducibility of SW-EG in the normal imaging pancreas (Phase 1) and to evaluate the diagnostic performance of SW-EG for pancreatic fibrosis classified histologically (Phase 2).
Methods: Phase 1: This included 127 cases that underwent SW-EG of the normal imaging pancreas. SW-EG was measured at least five times in the pancreatic parenchyma and the median of repeated measurements was defined as the pancreatic elastic modulus (PEM). Phase 2: This included 53 cases that underwent SW-EG of the pancreatic parenchyma preoperatively and in which pancreas parenchyma were evaluated histologically. Histological fibrosis was graded in 4 stages: normal, mild, moderate, and severe.
Results: Phase 1: Median PEM in the head, body, and tail of the pancreas were 3.23, 3.17, and 2.91 kPa, respectively, with no significant difference among regions ($P = 0.554$). The intraclass correlation coefficient showed good reproducibility ($\rho = 0.71$) after 5 measurements. Phase 2: There was a significant positive correlation between PEM and the histological pancreatic fibrosis stage ($r_s = 0.63$, $P < 0.001$). Areas under the receiver operating characteristic curve for the accuracy of SW-EG for diagnosis of pancreatic fibrosis were 0.85 (≥mild), 0.84 (≥moderate), and 0.87 (severe).
Conclusion: SW-EG can be used to determine the stage of pancreatic fibrosis non-invasively with high accuracy and reproducibility.

1. Introduction

Chronic pancreatitis is characterized by a relentless and progressive loss of pancreatic parenchymal tissue and is often diagnosed at an advanced stage [1]. Although chronic pancreatitis and pancreatic fibrosis are theoretically not the same disease, early detection of pancreatic fibrosis may be important to improve the prognosis. However, there is no non-invasive method for diagnosis. Endoscopic ultrasonography (EUS) B-mode imaging is relatively accurate for diagnosis of chronic pancreatitis (sensitivity: 83.3–84.0%, specificity: 80.0–100.0%), but this method is subjective and cannot be used for objective diagnosis of pancreatic fibrosis [2–5]. Therefore, its reproducibility is likely to be low. A standard and objective method for detection of pancreatic fibrosis is needed and elastography may be a candidate.

Ultrasound elastography is a new technique for measuring the elasticity (hardness) of tissue [6,7] that has been used for diagnosis of tumors in the mammary gland [8], thyroid [9], prostate [10], and

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abdominal organs [11,12], and for diagnosis of fibrosis in solid organs [13]. There are two types of ultrasound elastography: strain elastography, in which tissue elasticity is visualized using tissue strain; and shear wave elastography (SW-EG), which quantifies tissue elasticity as the elastic modulus by measuring the shear wave velocity. We have shown that strain elastography using EUS (EUS-EG) is an accurate diagnostic method for pancreatic fibrosis [14]. However, SW-EG performed using transabdominal ultrasonography (US), so SW-EG is less invasive and simpler method than EUS-EG [7].

SW-EG has been used for non-invasive diagnosis of liver fibrosis [13] and may also be useful for diagnosis of pancreatic fibrosis. However, measurements using SW-EG in the pancreas have not been established. To assess the reproducibility of SW-EG, we conducted a retrospective observational study in subjects with a normal imaging pancreas (Phase 1). Then, using method established in this study, we evaluated the diagnostic accuracy of SW-EG for pancreatic fibrosis that was classified histologically (Phase 2).

2. Methods

2.1. Subjects

Phase 1: The subjects were 127 cases (males 66, females, 61) with a normal imaging pancreas that was defined as a pancreas without apparent pancreatic diseases such as tumors, cysts, or a dilated main pancreatic duct, and without a history of alcohol consumption>80 g per day. The serum levels of lipase and amylase in all subjects were normal. The mean age was 59.2 ± 15.9 years (range 21–89 years).

Phase 2: The subjects were 53 cases (males 24, females, 29) who underwent SW-EG preoperatively and in whom pancreas parenchyma were evaluated histologically. The mean age was 63.1 ± 12.4 years (range 18–81 years). Subjects who underwent neoadjuvant chemotherapy or radiotherapy, pancreatic stenting, or tumor enucleation were excluded.

All subjects were consecutively recruited and provided informed consent before evaluation from October 2012 to July 2014 at Nagoya University Hospital. The study was approved by the hospital IRB, performed in conformity with the Declaration of Helsinki, and registered at UMIN-CTR (000016497).

2.2. Shear wave elastography

In all cases, SW-EG was performed using an iU22 ultrasound system (Philips Healthcare, Bothell, WA, USA) with a convex probe (C5-1) in ElastPQ mode. As with other SW-EG methods, the ElastPQ technique generates shear waves inside the organ using the acoustic radiation force impulse (ARFI). The ultrasound machine monitors the shear wave propagation using a Doppler-like ultrasound technique and measures the velocity of the shear wave. The shear wave velocity is displayed in kilopascals (kPa) or in meters per second through Young's modulus $E = 3\ (vS^2\rho)$, where E is Young's modulus, vS is the shear wave velocity, and ρ is the tissue density [15]. The stiffer the tissue, the faster the shear wave propagates. If the amount of non-shear wave motion exceeds a threshold, the result is defined as unreliable and “0.00 kPa” is displayed on the lower left of the screen [7].

SW-EG measurements were performed from the epigastric fossa in the supine or semi-sitting position after the patients had fasted for ≥9 h. A region of interest (ROI) of 5 × 15 mm was placed using trackball. The patients were instructed to hold their breath while the physician pressed a button to launch the data acquisition.

In the Phase 1 study, SW-EG was measured in one region of the head, body, or tail of the pancreas parenchyma in each subject. The measurement ROI was selected as the most clearly visualized region of the head, body, or tail of the pancreas on B-mode imaging that was not close to a gas or liquid component such as a blood vessel or the stomach because shear waves are easily refracted and reflected. If the result was 0.00 kPa, the measurement was regarded as invalid. All other measurements were regarded as valid and measurements were repeated until a valid value was obtained at least 5 times in each case. The median value was defined as the pancreatic elastic modulus (PEM) and the results are presented in kPa. The total number of measurements (invalid + valid), the number of valid measurements, and the interquartile range (IQR) were calculated. The measurement success rate (number of valid measurements/total number of measurements × 100) and intraclass correlation coefficient (ICC) were then calculated. Only cases with measurement success rates of ≥60%, which is regarded as highly reliable in transient elastography (TE), were included in this study [16].

In the Phase 2 study, SW-EG was measured in pancreatic parenchyma on the cranial or caudal side of the tumor or pancreatic parenchyma in the head of the pancreas in cases of bile duct carcinoma. Using the same methods as those described above for the Phase 1 study, we selected the measurement region with more clearly visualized parenchyma on the cranial or caudal side of the tumor. When parenchyma on both the cranial and caudal sides were clearly visualized, both regions were selected.

2.3. Histological assessment

Pancreas parenchymal specimens were fixed in buffered formalin, embedded in paraffin, and stained with hematoxylin-eosin. All specimens were analyzed by two pathologists who specialized in pancreatic diseases and were blinded to the SW-EG results. For pancreas fibrosis, the degree of perilobular and intralobular fibrosis were separately graded from 0 to 6, as defined by Kloppel et al., and the total fibrosis score (0–12) was calculated. This score was then used to classify the stages as normal (score = 0–3), mild fibrosis (4–6), moderate fibrosis (7–9), or severe fibrosis (10–12) [14,17].

2.4. Statistical analysis

Continuous variables are expressed as mean ± SD, or median and IQR, where indicated. A Chi-square test was used for categorical variables, and a Kruskal-Wallis test followed by a Mann-Whitney U test with Bonferroni correction were used for continuous variables. Correlations between success rate, PEM, and patient characteristics were analyzed using Spearman correlation coefficients (r_s), which were defined as indicating a weak correlation ($|r_s| \leq 0.2$), mild correlation ($|r_s| = 0.2–0.4$), moderate correlation ($|r_s| = 0.4–0.7$), or strong correlation ($|r_s| = 0.7–1.0$). The ICC was used to assess the intra-rater reproducibility of the normal PEM in SW-EG. ICC values were defined as indicating slight ($\rho \leq 0.2$), fair ($\rho = 0.2–0.4$), moderate ($\rho = 0.4–0.6$), substantial ($\rho = 0.6–0.8$), and almost perfect ($\rho = 0.8–1.0$) reproducibility. A receiver operating characteristic (ROC) curve was generated and the area under ROC (AUCROC) was calculated to determine the cut-off value of PEM for diagnosis of pancreas fibrosis. AUCROC was defined as indicating low (AUCROC = 0.5–0.7), moderate (AUCROC = 0.7–0.9) or high (AUCROC = 0.9–1.0) accuracy. Cut-off values were determined to maximize the Youden index (sensitivity + specificity −1), and sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated for these cut-off values. SPSS ver. 22.0 (SPSS, Inc, Chicago, IL) was used for all analyses. All tests were 2-tailed and $P < 0.05$ was considered to be significant.

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