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**Endoscopic ultrasound elastography for solid pancreatic lesions**

Chantarojanasiri T *et al.* EUS elastography for SPL

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**Abstract**

Elastography is one of technologies assisting diagnosis of solid pancreatic lesions (SPL). This technology has been previously used for measuring the stiffness of various organs based on a principle of “harder the lesions, higher chance for malignancy”. Two elastography techniques; strain and shear wave elastography, are available. For endoscopic ultrasound (EUS), only the former is existing. To interpret results of EUS elastography for SPL, 3 methods are used: (1) pattern recognition; (2) strain ratio; and (3) strain histogram. Based on results of existing studies, these 3 techniques provide high sensitivity but low to moderate specificity and accuracy rate. This review will summarize all available information in order to update current situation of using elastography for an evaluation of SPLs to readers.

**Key words:** Elastography; Endoscopic ultrasound; Pancreatic cancer; Solid pancreatic lesions; Chronic pancreatitis

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**Core tip:** Elastography is a technology that can measure tissue stiffness. Endoscopic ultrasound (EUS) elastography has been increasingly used for an evaluation of solid pancreatic lesions (SPL). Several interpretation methods of EUS elastography for this purpose have been described in many previous studies. This review focuses on how to read and interpret findings of EUS elastography obtained from SPL. Readers should be competent for applying EUS elastography for diagnosing SPL after finishing reading the review.

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**INTRODUCTION**

The diagnosis of solid pancreatic lesions (SPL) is a challenging clinical problem. Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) is the most commonly used diagnostic method. It has high specificity but moderate sensitivity. Due to the aggressiveness and poor outcomes of pancreatic cancer, several methods such as elastography or contrast enhancement have then been developed to assist in the diagnosis of SPL. Certainly, these software technologies cannot replace EUS-FNA because they are not pathological diagnostic tools, but they can help clinicians in many clinical scenarios such as in lesions with remarkably low EUS-FNA diagnostic yield including mass-forming chronic pancreatitis. Several previous studies have shown various efficacy values for these adjunctive technologies in their results. Elastography is one of these current assisting technologies diagnosing SPL. This technology measures the stiffness of the target lesion. In this review, the results of EUS elastography in the evaluation of SPL will be summarized.

This review summarizes characteristic findings of each SPL by EUS elastography. We searched the PubMed database for English-language journals with human studies published between 1988 and 2016. The following keywords were used in combination with EUS: Elastography, pancreas, and solid lesions. References to those identified articles were also examined for potentially relevant studies.

**HISTORY OF ELASTOGRAPHY**

Since 1988, the concepts of tissue deformability and elasticity of solid tumor has been described[1]. In 1991, tissue elasticity measurements were made by evaluation of the elastic modulus after applying a pressure (Figure 1); hence, the term “elastography” was first reported[2]. This led to the development of real-time imaging and the combination of elastography imaging with B mode imaging using a combined autocorrelation method in 2001[3]. Since then, elastography has been applied to the diagnosis of solid tumors of various organs such as breast, thyroids, lymph nodes and liver. In 2006, elastography for SPL was firstly reported[4]. The interpretation of elastography findings from SPL have been developed and applied to clinical management.

**TYPES OF ELASTOGRAPHY**

Elastography is classified into two categories based on different mechanical properties: Strain and shear wave elastography. The former evaluates tissue stiffness by measuring tissue distortion after applying pressure and the latter assess tissue stiffness by measuring tissue distortion after applying the acoustic radial force impulse[5]. However, only strain elastography is available for EUS.

**STRAIN ELASTOGRAPHY MEASUREMENT METHODS**

Strain elastography evaluates tissue stiffness *via* the displacement caused by manual compression or cardiovascular pulsation[6]. Larger strain or tissue displacement values represent softer tissue (Figure 2). The degree of strain-the relative indicator-can be displayed *via* three methods[6].

***Pattern recognition***

This method is to display as colors, with the green color as the mean stiffness, blue color represents harder tissue and red color represents softer tissue. This is the only method considered qualitative method whereas following methods are quantitative ones.

***Strain ratio***

This method is to display as gray scale image and compare strain ratio (SR) of area of interest with reference area.

***Strain histogram***

**Pattern recognition:** Color pattern analysis of elastography was first described in transcutaneous ultrasound elastography of the breast[7]. The EUS elastography pattern in pancreatic lesion was first described by Giovannini (Figure 3)[4] with 100% sensitivity but only 67% specificity in differential diagnosis of benign and malignant SPL. The same author later classified the previous 5-scale elastic score into 3 scores: A, B and C, representing benign, indeterminate, and malignant lesions, respectively[8]. This classification has 92.3% sensitivity and 80% specificity in differential diagnosis between benign and malignant SPL. Reports of different pattern analyses results in different clinical efficacy have been published. Another report by Janssen *et al*[9] classified color patterns into 3 types: Type 1 with homogeneous pattern, type 2 with 2 or 3 colors, and type 3 with a honeycomb pattern. In this report, however, the use of elastography in differential diagnosis between benign and malignant lesions was disappointing. Another study done by Iglesias-Garcia[10], classified the elastography into 4 patterns with 100% sensitivity and 85.5% specificity in the diagnosis of malignant SPL. The comparison of each report as well as sensitivity and specificity is shown in Table 1.

**SR:** SR compares the strain between the target area and other reference areas to provide more objective qualitative data[11]. In breast lesions, the strain of the lesion is compared to the strain of the surrounding fat tissue. Many studies use SR to differentially diagnose pancreatic carcinoma and chronic pancreatitis[11-14]. In some studies, the strain of the area surrounding the pancreas was used as the baseline compared with the strain of the lesion[11,15]. The peripancreatic surrounding the soft tissue was used as the baseline in other studies[12,13]. Moreover, according to the phantom study, the depth of the reference area has a significant impact on the evaluation of the SR[16]. The area of selection and cut-off point in each study are demonstrated in Table 2. Studies have correlated SR and chronic pancreatitis. Iglesias-Garcia reported a cut-off of 2.25 for the diagnosis of chronic pancreatitis with a sensitivity of 91.2% and a specificity of 91% using the surrounding soft tissue as a reference[17]. Another study reported the correlation of SR and the presence of pancreatic exocrine insufficiency (PEI) with 87.0% probability of PEI in those with SR higher than 4.5 compared with 16.3% probability of PEI in those with SR lower than 4.5[18]. In this study, the normal surrounding gut wall was used as the reference. Iglesias-Garcias reported the mean elastic value to be 0.47%, 0.23%, 0.02% and 0.01% for normal pancreas, chronic pancreatitis, pancreatic cancer, and endocrine tumor, respectively[14]. Another report from South Korea demonstrated a mean elastic value of 0.53% for the normal pancreas and 0.02% for pancreatic cancer[19].

Many studies are based on the SR method, but there is no standardization for the reference area yet[5]. Moreover, the distance of the reference area from the ultrasound probe significantly impacted the SR measurements[16]. These two factors significantly impacted the reliability of the SR methods as a diagnostic test for SPL.

***Strain histogram***

The strain histogram is another type of the quantitative image analysis. To analyze the strain histogram, the color image of the elastography is converted into the gray scale (value) of 256 tones. It ranged from 0 to 255 with 0 representing the blue area (hard) and 255 representing the red area (soft) (Figure 4). The distribution of the gray scale is then calculated into various parameters as shown (Table 3). In some reports, the histograms were performed separately from the individual red/green/blue color[20]. The correlations of the parameters with the degree of pancreatic fibrosis have been published[21]. With increasing fibrosis, the mean and standard deviation decrease, while skewness and kurtosis increase. On the other hand, the histogram could be analyzed using the neural network analysis. The correlation between a cut-off mean level > 175 in pancreatic carcinoma had a sensitivity of 91.4%-93.4% and a specificity of 66%-87.9%[22,23]. Another report analyzed the histogram by comparing the histogram of the tumor over the adjacent part of the pancreas[24]. The strain histogram’s ratio with cut-off value of 1.15 indicated pancreatic malignancy with 98% sensitivity, 58% specificity, and 69% accuracy.

**CLINICAL IMPLICATIONS**

***Pancreatic adenocarcinoma vs mass-forming chronic pancreatitis***

Pancreatic adenocarcinoma is the most common type of pancreatic tumor, and it is characterized by many desmoplastic reactions[25]. Increased amounts of extracellular matrix including type I and type V collagen and fibronectin are found similar to those found in alcoholic chronic pancreatitis and tumor-induced chronic pancreatitis[26]. The differential diagnosis between pancreatic adenocarcinoma and mass-forming pancreatitis-especially on the background of chronic pancreatitis-remains a challenging problem. It is well known that the incidence of pancreatic adenocarcinoma is higher in patients with chronic pancreatitis[27]. Moreover, some features of chronic pancreatitis, such as calcification, may hinder the detection of pancreatic cancer[28]. Moreover, EUS-FNA of the pancreatic cancer (standard method for tissue acquisition from SPL) results in only 50%-73.9% sensitivity but with 73.7%-100% specificity in the presence of chronic pancreatitis[29-31]. In elastography, pancreatic adenocarcinoma usually manifests as a hard tumor with a predominate blue color pattern (Table 1 and Figure 5). It has a higher SR than mass-forming chronic pancreatitis. Another single report compared pancreatic adenocarcinoma and autoimmune pancreatitis. This demonstrated that in autoimmune pancreatitis the stiffness area not only forms the mass area but also the surrounding pancreatic tissue[32].

***Pancreatic neuroendocrine tumor***

Pancreatic neuroendocrine tumors (PNETs) are a rare type of solid pancreatic tumor that are characterized histologically by tumor cells arranged in solid nest, trabecular, or gland like formation surrounded by thin vascular stroma[33]. The elastography pattern of PNET was described as homogeneous blue and heterogeneous blue by Giovannini[4] and Iglesias-Garcia[10], respectively. In one prospective study that included 6 patients with PNET, the SR of PNET is 56.73-higher than the 17.41 SR seen in pancreatic adenocarcinoma[17].

***Solid pseudopapillary neoplasm***

Elastography studies in solid pseudopapillary neoplasm (SPN) are rare. Only one study with 1 SPN case was found. It had a SR near 15[17].

**OTHER UNCOMMON TUMORS**

For pancreatic acinar cell carcinoma, there are limited reports of EUS elastography. Only one report of elastography in pancreatic acinar cell carcinoma has been published[34]. In this report, there was no specific pattern of elastography, and the pattern varied according to the acinar cell tumor pathologic phenotype. The data for more uncommon types of pancreatic cancers such as anaplastic cell carcinoma and adenosquamous cell carcinoma have not yet been reported.

***Chronic pancreatitis***

Elastography has been used in both the diagnosis of chronic pancreatitis and as a predictor of post-operative pancreatic fistula. Despite the usefulness of EUS in the diagnosis of pancreatic lesions, there are only limited data in EUS elastography studies in chronic pancreatitis. Many studies of elastography in chronic pancreatitis using transabdominal ultrasound with shear wave elastography for the detection of pancreatic fibrosis both in chronic pancreatitis and tumor-related fibrosis have been reported[35-38]. Apart from the transabdominal ultrasonography, intraoperative ultrasound elastography has been published. This demonstrated correlation between “soft pancreas” and the development of a post-operative pancreatic fistula[39,40].

In EUS studies, one prospective study demonstrated a higher SR in chronic pancreatitis with 91.2% sensitivity, 91.0%specificity, and 91.1% accuracy with a cut-off point of 2.25[17]. In this study, the SR also varied across groups according to Rosemond criteria for the diagnosis of chronic pancreatitis with a higher SR up to 8.12 in cases that fulfilled all criteria of chronic pancreatitis. Moreover, in patients with chronic pancreatitis, elastography with higher SR was seen in those with evidence of pancreatic enzyme insufficiency (SR 4.89 *vs* 2.99)[18]. This finding was consistent with another study demonstrating higher stiffness in more advanced pancreatic fibrosis using EUS elastography with histogram analysis[21]. A retrospective study of EUS elastography using histograms for analysis also demonstrate the correlation of mean value with the stage of chronic pancreatitis *via* the Rosemont criteria. This used cutoffs of 90.1 ± 19.3, 73.2 ± 10.6, 63.7 ± 14.2, and 56.1 ± 13.6, in normal pancreas, indeterminate for chronic pancreatitis, suggestive of chronic pancreatitis, and consistent with chronic pancreatitis, respectively[41].

Aging can cause several changes similar to early chronic pancreatitis[42]. A study using EUS also demonstrated abnormalities similar to chronic pancreatitis in elderly subjects without clinical chronic pancreatitis-particularly after the age of 60[43]. Elastography studies in aging populations also showed increased pancreatic stiffness with age demonstrated by both EUS[44]. and transabdominal ultrasonography[45]. These changes become significant after age 40 to 60[44,45]. In one study, the mean histogram below 50 was more suggestive of chronic pancreatitis than usual aging changes[44].

**COULD EUS ELASTOGRAPHY REPLACED TISSUE DIAGNOSIS?**

While many studies have demonstrated excellent efficacy of elastography in the diagnosis of SPL, the value of elastography in cases with negative EUS FNA remains inconsistently demonstrated in all studies. Moreover, the method of image analysis is not yet standardized. Most reports demonstrated high sensitivity but low specificity, and the interpretation was performed by a center with many experienced elastographers. Hence, elastography cannot replace EUS-FNA for diagnosis[46].

**CONCLUSION**

In summary, EUS elastography is an improvement in the differential diagnosis between benign and malignant SPL in many studies. The main role of elastography in SPL is as an adjunct with other modalities in making diagnoses. Especially in chronic pancreatitis, EUS still has a promising role in both the diagnosis of early chronic pancreatitis and the prediction of complication. However, the overlapping of early chronic pancreatitis and aging changes makes the decision more difficult.

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**Table 1 Results of 4 large studies using pattern recognition of elastography for diagnosis of solid pancreatic lesions**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author** | **Giovannini *et al*[4],2006** | | **Giovannini *et al*[8], 2009** | | **Janssen *et al*[9], 2007** | | | **Iglesias-Garcia *et al*[10], 2009** | |
| Score and interpretation | Elastic score /pattern | Interpretation | Score | Interpretation | Type | Color | Interpretation | Pattern | Interpretation |
| Distortion for entire low echo area | Normal pancreas | A (elastic score 1 and 2) | Benign | Homogeneous | A = blue | B = normal pancreas | Homogeneous green | Normal pancreas |
| No distortion on low echo area even for a part | Fibrosis, chronic pancreatitis | Heterogenous green | Inflammatory pancreas |
| Distortion at the edge of low echo area, even for a part | Small adenocarcinoma | B (elastoc score 3) | Indeterminate | 2 or 3 colors | B = green/yellow |  | Homogeneous blue | Ductal pancreatic adenocarcinoma |
| No distortion for entire low echo area | Endocrine tumor | C (elastic score 4 and 5) | Malignant | Heterogeneous | C = red | A/B = chronic pancreatitis and neoplasia | Heterogeneous blue | Neuroendocrine tumor |
| No distortion on low echo area and surrounding | Advanced adenocarcinoma |
| Sensitivity | 100 | | 92.3 | | 65.9 (chronic pancreatitis),  93.8 (neoplasia) | | | 100 | |
| Specificity | 67 | | 80 | | 56.9 (chronic pancreatitis),  65.4 (neoplasia) | | | 85.5 | |
| Accuracy | NA | | 89.2 | | 60.2 (chronic pancreatitis), 73.5 (neoplasia) | | | 94 | |

NA: Not available.

**Table 2 Results of studies using strain ratio of elastography for an evaluation of solid pancreatic lesions**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Ref.** | **Diseases of comparison (*n*)** | **Reference area** | **Cut off point** | **Sensitivity** | **Specificity** |
| Iglesia-Garcia *et al*[[14](#_ENREF_14)] | PC (49) *vs* CP (27)  PC (49) *vs* PNET (6) | Soft tissue | 6.04 | 100 | 96.3 |
| 26.63 | 100 | 87.8 |
| Itokawa *et al*[[11](#_ENREF_14)] | PC (72), PNET (9), CP (20), normal pancreas (8) | Normal pancreas | 23.66 in MFP *vs* 39.08 in PC |  |  |
| Dawwas *et al*[[12](#_ENREF_14)] | Malignant (87): (PC, PNET, metastatic cancer)  And benign (17) (pancreatitis) | Soft tissue | 4.65 | 100 | 16.7 |
| Kongkam *et al*[[13](#_ENREF_14)] | PC (23), PNET (5), Meatastasis (1), CP (2), AIP (3), other (4) | Soft tissue | 3.17 | 86.2 | 66.7 |
| 6.04 | 75.9 | 77.8 |

PC: Pancreatic cancer; PNET: Pancreatic neuroendocrine tumor; CP: Chronic pancreatitis; AIP: Autoimmune pancreatitis.

**Table 3 The histogram parameters[5,21,45]**

|  |  |  |  |
| --- | --- | --- | --- |
| **Images** | **Parameters** | **Information** | **Interpretation** |
| Gray scale images | Mean | Mean of the gray levels | Higher mean value indicates softer tissue |
| Standard  deviation | Standard deviation of the gray levels | Higher value indicating heterogeneous hardness |
| ASM | Measure of the homogeneity on the gray scale image |  |
| Contrast | Measure of local gray level variation on the gray scale image |  |
| Correlation | Measure of gray level linear  dependence on the gray scale image |  |
| Entropy | Measure of the randomness of gray level distribution |  |
| IDM | Measure of the homogeneity on the gray scale image |  |
| Skewness | Measure of the asymmetry of the gray level distribution | Higher value indicating higher or lower hardness |
| Kurtosis | Measure of the “peakedness” of the gray level distribution | Higher value indicating concentration of a specific hardness |
| Black and  white  image | % area | Percentage of the white area (= hard area) |  |
| Mean of  Complexity | Complex ratio of the shape of the white area (= hard area) and is calculated as periphery2/area of the white area |  |



**Figure 1 The principle of strain elastography is illustrated by coil spring appearance.** A: after applying pressure, more deformation is demonstrated in tissue with higher elasticity; B: the strain on each tissue depends on the tissue stiffness; C: higher strain is seen in softer tissue after compression (Adapted from Ophir[2]).



**Figure 2 The principle of endoscopic ultrasound elastography for solid pancreatic lesions.** A:pancreatic carcinoma has more stiffness than normal pancreas; B: the strain elastography measured the degree of displacement after applying manual pressure or vascular pulsation; C: the degree of displacement is represented as colors: green is the average stiffness, blue is stiffer tissue, and red is softer tissue.



**Figure 3 Classification of elastography findings proposed by Giovannini[4].**

A



B



C



**Figure 4 Histogram analysis using MATLABver 1.6.7. A and B:** the color image of the elastography is converted into the gray scale (value) of 256 tones ranging from 0 to 255:0 represents the blue area (hard) and 255 represents the red area (soft); C: The distribution of the gray scale is presented as a histogram from which the parameters are calculated.



**Figure 5 Endoscopic ultrasound elastography of pancreatic adenocarcinoma.** The color pattern showed predominant blue color pattern without distortion of surrounding area.