Chapter

Pancreatic Elastography

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Abstract

Pancreatic elastography represents a challenging new procedure for inflammatory pathology or tumour masses. There are technical difficulties for accurate assessment of pancreatic stiffness due to deep localization. But the new software for both conventional and endoscopic ultrasound are promising techniques for differential diagnosis between malignant tumours and different forms of chronic pancreatitis (groove pancreatitis or autoimmune pancreatitis). Early diagnosis of chronic pancreatitis, noninvasively by transabdominal shear wave elastography, is actively studied nowadays. Elastography might offer a predictive tool for the occurrence of pancreatic fistula after pancreatoduodenectomy. This chapter introduces the recent innovation of pancreatic elastography and makes recommendations for its use.

Keywords: pancreas, elastography, pancreatic cancer, chronic pancreatitis

1. Introduction

The pancreatic pathology assessment represents a challenge even today when many imaging techniques are available. The differentiation between chronic pancreatitis and malignant lesions requires sometimes many imaging combined procedures, even histology, without an accurate assessment. The elastography development used the principle that the assessment of a tissue elasticity of tissue might differentiate a benign soft lesion from a malignant hard tissue. But the stiffness assessment and measurement of this small organ, deeply localised in the retroperitoneum, are difficult. High accuracy and reproducibility of pancreatic elastography are not easily obtained, as the histology is not always available [1].

Nowadays both transabdominal ultrasound (US) and endoscopic ultrasound (EUS) allow pancreatic elastography assessment. There are two types of pancreatic elastography: strain elastography and shear wave speed elastography [1]. In the case of strain elastography, the stiffness of pancreatic tissue is estimated by measuring the grade of strain generated by external pressure. For shear speed elastography, the stiffness is estimated by measuring the propagation speed of the shear wave (the transverse wave) generated by acoustic radiation force impulse (ARFI) [1].

The results of elastography can be the strain, which has a negative correlation with tissue stiffness, and the shear wave speed, which has a positive correlation with tissue stiffness [2].

Elastography that measures shear wave speed is classified into shear wave elastography, which uses ARFI as the method to excite shear waves, and transient elastography, in which shear waves are excited in a mechanical manner. Fibroscan™, the only transient elastography device, is not used for the pancreas due to its localization [2]. Shear wave speed might be displayed by two different methods: as

the average speed within a small region (target ROI) and as an image reflecting the distribution of the speeds in the ROI [2].

2. Transabdominal ultrasound: strain elastography

The stiffness of pancreatic tissue is estimated through transabdominal ultrasound by measuring the grade of strain generated by aortic pulsation [1–4]. The relationship between the grade of strain and the stiffness of target tissue is negative correlation: the greater the strain, the softer pancreatic tissue is. For a proper assessment, the target tissue should be located in line between the probe and the aorta [1]. A fine elastogram can be easily obtained in the pancreatic body, except for the patients with severe arteriosclerosis. The elastograms obtained in the pancreatic head and tail should be interpreted with caution [1].

Strain elastography of the pancreas can be obtained with transabdominal ultrasound (US) and with EUS.

First clinical application of US elastography had been reported with real-time tissue elastography™ (RTE) produced by Hitachi Aloka [5, 6]. In the conventional RTE, only qualitative diagnosis using colour map was possible. This technique measures compression-induced tissue deformation (strain) within a region of interest (ROI), which is visualised using a transparent colour overlaying on the B-mode image. In this colour map, the hardest tissue is displayed as blue, and the softest tissue is displayed as red. In RTE, pancreatic cystic lesions cannot be evaluated, due to artefacts, when fluid component of cyst was assessed.

The first report of the usefulness of US elastography for the pancreas in clinical practice was published by Uchida et al. in 2009 [7]. They defined typical colour map observed in US-RTE for different clinical scenarios: homogeneous colour in normal pancreas, markedly hard area with soft spots, was in pancreatic ductal adenocarcinoma, uniform and soft comparable to parenchyma in neuroendocrine tumour and mixture of various colours in chronic pancreatitis. The same authors reported the 70–80% diagnostic accuracy for pancreatic tumours of B-mode alone; when B-mode was combined with US-RTE, the diagnostic accuracy was more than 90% [7].

This qualitative diagnosis using colour map was subjective and highly operator dependent; quantitative diagnosis using strain ratio was established since the second generation of RTE. Strain ratio was defined as the ratio of the strain of reference tissue (B) divided by the strain of target tissue (A).

Strain ratio was adapted from the theory called “fat lesion ratio” reported in the breast, which means the ratio of the strain of fat around the mammary gland divided by the strain of target tissue. The initial principal considered that the stiffness of fat was almost equal in different individuals [1]. To date no consensus exists for the reference area, on non-tumorous area inside the pancreatic parenchyma [8, 9] or on red area around the pancreas, estimated to be fat [10, 11]. There is no evidence if red area around pancreas is really fat. The strain ratios calculated for the same target tissue quite differ according to wherever the reference area is set [1].

The cutoff levels of strain ratio for differential diagnosis between malignant and benign varied in reported studies [9–11], meaning that pancreatic RTE is highly operator dependent and lacks adequate reproducibility.

A fine B-mode image is required for a fine elastogram, and this is obtained within 6 cm in depth from the body surface in US. Therefore, pancreatic elastogram is quite difficult in the obese. Also B-mode image is easily affected by gastrointestinal gas in US. These problems will occur less frequently in EUS.

Recommendations to obtain a quality elastogram on B-mode US [2]:

- The most important is to obtain a quality B-mode images with as few artefacts as possible.

- Examination is made from the epigastric fossa in a dorsal position, (semi) sitting position, or left lateral decubitus position.

- No vibration should be caused by the probe, which should lightly touch the abdominal wall.

- The patient should hold his breath.

- Two settings for ROI are accepted [12]: (1) ROI is set only within the target area; (2) ROI is set both within the target area and the surrounding tissue. The second is recommended for neoplastic cancer assessment.

- The colours in an elastogram minutely vary with the passage of time according to cardiovascular pulsation. It is desirable that elastograms with good reproducibility are taken at every pulsation by recording the images of elastograms in a range of 5–10 pulsations.

3. Transabdominal ultrasound: shear wave elastography

For this type of elastography, emission of ARFI is possible for the entire pancreas. Virtual Touch™ quantification (VTQ) produced by Siemens is a representative instrument. VTQ displays the stiffness of pancreatic tissue digitally shear wave velocity being measured. SWV is expressed in m/s. If an error occurs, X,XX m/s is displayed on the right part of the screen instead of digits [1].

Even if this technique is very promising for the pancreas, there are some issue to be considered. There is a limit to the acoustic radiation force impulse that is certainly safe within the body [2]. Also, when the tissue in the ROI is hard, measurement error tends to occur, because it is difficult to generate sufficient shear waves. When SWV of a pancreatic tumour cannot be assessed, ROI should be placed on a tip of the tumour [2]. If the target area is far from the probe, the attenuation of the focused ultrasound reduces the acoustic radiation force impulse, which in turn reduces the amplitude of the shear waves, making it difficult to detect the shear waves [12]. The safety standards are accomplished by the focused ultrasound [2], but the transmission waveform and wavelength are different from the usual ultrasonic pulses. A concern is represented by its influence on the body, through a possible increase in temperature [13]. Its safety in simultaneous use with contrast media is not confirmed yet [14].

It is recommended to repeat three times the same measurement for the same site about if the reproducibility is high. If the reproducibility is low, a measurement should be repeated 10 times for the same site and the median is used [2].

New ARFI software are developed (ElastPQ™ (Philips), Virtual Touch™ IQ: VTIQ (Siemens)), but their use for the pancreatic pathology is still limited.

Instead the Shear Wave™ Elastography (SWE) (Super Sonic Imaging) uses a new approach. In SWE, ultrasonic beams are continuously emitted to different depths in the tissue, and thus a conically shaped wave surface of shear waves is formed [2]. By an ultrafast imaging method, the shear wave speed is measured. The transducers repeat outgoing/incoming transmissions of ultrasonic waves. A colour map is displayed in the ROI, which can be defined in any location [2]. The mean ± SD, the minimum value, and the maximum value of the shear wave speed

in the ROI are displayed. A ratio is calculated when two ROIs in different locations are compared. The study conducted by Arda et al. [15] reported measurement of stiffness for normal pancreas: 11.1 ± 3.2 kPa for males and 10.8 ± 3.1 kPa for females.

4. Echo-endoscopy elastography: strain elastography

The first report of EUS elastography was published in 2005 by Hirooka et al. [5]. Then many papers reported their experience using RTE for pancreatic EUS elastography, being for many years the only system available. In RTE obtained by EUS, the diagnosis is qualitative. It is recommended that the ROI to be set to include peripancreatic tissue [2]. Red colour corresponds to the softest tissue within ROI, and blue corresponds to the hardest tissue within ROI. The remaining tissue is displayed as a coordinated colour between red and blue according to its stiffness. As the colour map depends on the size of ROI in RTE, it is not an absolute one [1].

Some technique aspects should be kept in mind for a qualitative elastogram [2]. The EUS probe should be lightly touching the wall of the stomach or the duodenum. The selected image must be without artefacts. The ultrasonic beam should be towards the aorta, and the strain should be generated in the depth direction. The RTE image should be stably generated for a certain period (5 s or longer in normal cases). For the evaluation of vibration energy, it would be preferable to refer to a strain indicator or to a strain graph. A good-quality B-mode image should be obtained to suit the RTE image [2].

The main debated issue was the differentiation of benign vs. malignant. The diagnostic criteria to differentiate malignancy from benignancy considered two aspects: (1) the dominant colour within colour map and (2) the homogeneity of colour map [1].

In a multicentre study on 121 patients with pancreatic tumours (92 malignant and 29 benign), Giovannini et al. [16] proposed a scoring system: score 1, homogeneous green represents normal tissue; score 2, heterogeneous soft tissue (green, yellow, and red) corresponds to inflammatory tissue; score 3, mixed colour or honeycombed can be attributed to any pathology; score 4, small green central area surrounded by mainly blue; and score 5, mainly blue with heterogeneous green and red, represents advanced malignant lesion. Scores 1 and 2 were considered benign, and scores 4 and 5 were assigned to malignant pathology. The sensitivity and specificity for this score were 92.3 and 80% [16].

The (semi) quantitative evaluation is possible, being more objective, but the analytical procedure is complicated. The image quantitative analysis reported included strain ratio [9, 10, 17], strain histogram [18, 19], and neural network [20–22]. A comparison between different analysis methods has not been conducted, so there is no consensus about which of these methods is the best.

5. Clinical applications for pancreatic elastography

Uchida et al. [7] published the first report evaluating the usefulness of US elastography for the pancreas in 2009. They reviewed elastograms performed for 10 normal pancreas and reported the typical colour map for normal pancreas assessed by RTE as homogeneous colour.

The normal reference values of pancreas stiffness using ARFI elastography through Virtual Touch Tissue Quantification (Siemens) were reported by Zaro et al. in 2016 [23]: from the entire parenchyma—1.216 m/s ± 0.36 (head, 1.224 m/s; body, 1.227 m/s; and tail, 1.191 m/s) [23]. Another study found a significant correlation

between increasing age and elastographic parameters [24]. Using SWE (Super Sonic Imaging) Arda et al. [15] reported measurement of stiffness for normal pancreas: 11.1 ± 3.2 kPa for males and 10.8 ± 3.1 kPa for females.

6. Benign vs. malignant mass pancreatic lesions

The most frequent use of elastography in pancreatic pathology is for differential diagnosis between benign and malignant focal lesions.

The number of reports on strain elastography with US is extremely small in comparison with EUS.

Uchida et al. [7] used strain elastography with US to evaluate the colour patterns of the pancreatic cancers, pancreatic endocrine tumours, and chronic pancreatitis. They concluded that adding strain elastography to the B-mode observations the

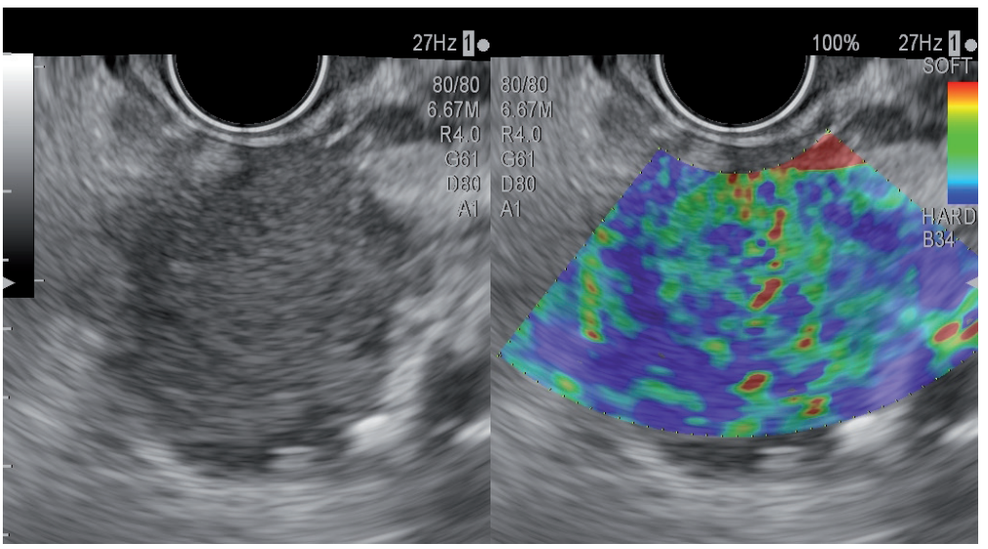

Figure 1.
Advanced pancreatic adenocarcinoma assessed by EUS-RTE. Elastogram is mainly blue with heterogeneous green and red corresponding to score 5 from Giovannini classification.

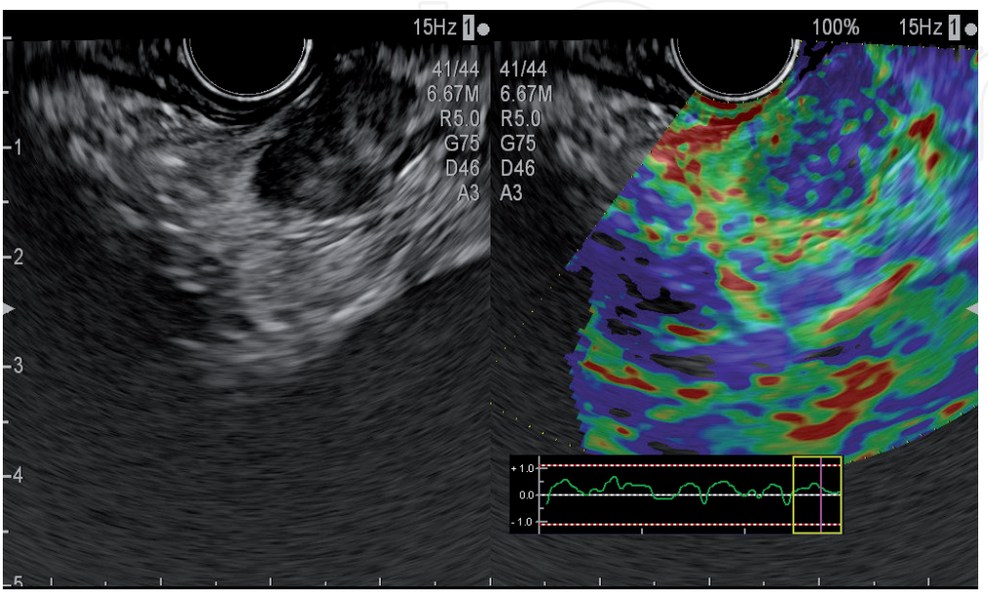

Figure 2.
Small neuroendocrine tumour at the tail of the pancreas assessed by EUS-RTE. Elastogram depicts heterogeneous small points surrounded by mainly blue corresponding to score 4 from Giovannini classification.

diagnosis sensitivity is improved [7]. Kawada et al. [8] reported the use of strain ratio to distinguish between malignancy and benignancy of pancreatic solid tumours. The evaluation of the pancreatic tumours by transabdominal shear wave elastography was reported by Zaro et al. [25] in a pilot studied. The mean SWV

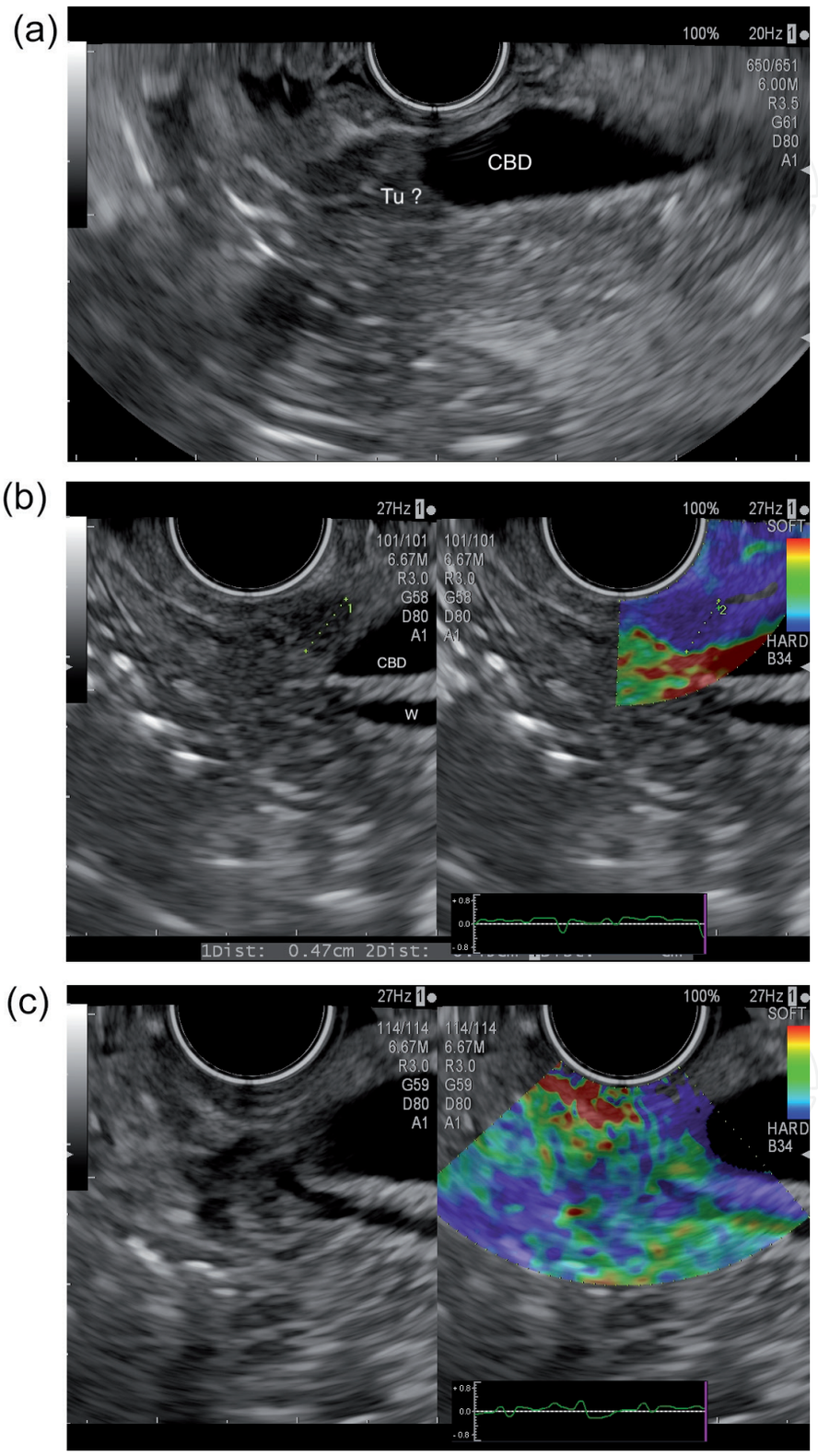

Figure 3.
(a) EUS B-mode. Dilated common bile duct and suspicion of periampular tumour. (b) A "tumour-like image, suspected of malignancy" on elastogram, due to its blue (hard) appearance. This false elastogram is due to the angulations of distal tip of echo-endoscope. (c) A correct assessment of the stiffness of the ampular region displays a mixed inflamed tissue: heterogeneous soft tissue (green and red) corresponding to score 2 in Giovannini classification.

of the pathological parenchyma indicated an increase of the SWV at the tumoral (cephalic) level corresponding to 1.54 ± 0.32 m/s compared to 1.21 ± 0.27 m/s for normal pancreas in the control group. Future research is needed to validate this data.

Most reports regarding EUS elastography for the pancreas are associated with the differential diagnosis between benign and malignant solid pancreatic tumours, being published several meta-analyses related to the differential diagnosis of pancreatic tumours [26, 27]. Elastograms for pancreatic adenocarcinoma and neuroendocrine tumours are displayed in **Figures 1** and **2**.

The sensitivity of EUS elastography for the differential diagnosis of pancreatic tumours is reported to be excellent ranging from 95 to 99%, while its specificity is reported to be inadequate ranging from 67 to 76% [1, 26, 27]. This low specificity is explained by the increased stiffness of benign nodule from chronic pancreatitis due to severe fibrosis. Fine needle aspiration through EUS is still mandatory even in cases with proper assessment of pancreatic tissue stiffness. There are few selective cases in which EUS-FNA cannot be performed, and the malignant diagnosis arguments include elastography [28]. But consensus criteria for differential diagnosis between malignant and benign pancreatic tumours were not established.

In clinical practice there are many challenging diagnosis. The images obtained with EUS elastography should be integrated in the clinical context of the patient, being complementary to other imaging techniques. Small tumour-like images, with suggestive malignant features at elastogram, should be interpreted with caution. To assess the quality and reproducibility of the elastography image, a consistent colour pattern obtained in a number of consecutive frames is indicated. If there are different elastograms obtained for the same tumour-like image (**Figure 3a–c**), all the technical adjustments should be rechecked.

7. Chronic pancreatitis

Chronic pancreatitis is frequently diagnosed in advance stages. Echo-endoscopy may be a useful method for the early diagnosis of chronic pancreatitis, even its diagnostic criteria are operator dependent.

Shear wave elastography using transabdominal US might be an objective and noninvasive method for the early diagnosis of pancreatic fibrosis. Yashima et al. [29] subjected 46 patients with chronic pancreatitis and 52 normal pancreas and measured SWV at the head, the body, and the tail of the pancreas for 10 times in each case and reported a sensitivity of 75% and a specificity of 72% for detection of chronic pancreatitis. They also determined the cutoff of SWV optimal for diagnosing chronic pancreatitis as 1.40 m/s by ROC analysis. Multivariate analysis detected that severe alcohol intake (OR = 3.87, p = 0.005) and deeper depth of the pancreas from the body surface ≥4.2 cm (OR = 0.10, p = 0.002) were associated with the stiffness of the pancreas (>1.40 m/s) [12]. Kuwahara et al. [30] reported that chronic pancreatitis might be diagnosed noninvasively and objectively using SW-EG without performing EUS, the diagnosis accuracy being 77%.

Many reports evaluated the accuracy of EUS elastography for the diagnosis of pancreatic fibrosis. An elastogram in a patient with chronic pancreatitis is displayed in **Figure 4**. Itoh et al. [18] performed EUS elastography preoperatively for the proximal side of the pancreatic tumour and compared the elastograms with microscopic findings of the resected specimens. They found significant correlation between objective parameters assessed by elastography (mean, standard deviation, skewness, kurtosis) and the grade of fibrosis evaluated by histology. Iglesias-Garcia

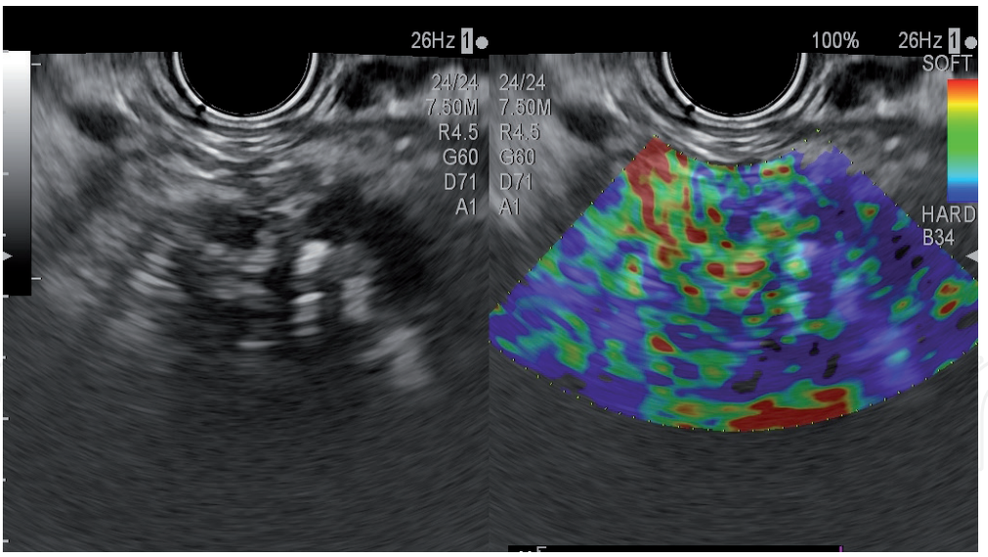

Figure 4.
An elastogram of chronic pancreatitis: heterogeneous soft tissue (green, yellow, and red) corresponding to score 2 in Giovannini classification.

et al. [31] reported a positive correlation between strain ratio and Rosemont classification ($r = 0.813$, $p < 0.0001$).

EUS elastography could predict pancreatic exocrine dysfunction in patients with chronic pancreatitis [32]. Iglesias-Garcia et al. [31] found significant correlation between strain ratio and pancreatic exocrine dysfunction evaluated by 13C-mixed triglyceride breath test.

In autoimmune pancreatitis the specific elastogram detected in five cases was homogenous stiffness of the whole organ, different from the circumscribed mass lesion in ductal adenocarcinoma [33].

8. Prediction of pancreatic fistula after pancreatic surgery

There are studies reporting that the stiffness of the pancreas measured preoperatively could predict the incidence of postoperative pancreatic juice fistula [34–36]. The postoperative fistula was observed more frequently in patients with lower stiffness of the pancreas (SWV < 1.54 m/s) than in patients with higher stiffness of the pancreas (63 vs. 17%, $p < 0.001$) [34].

9. Conclusions

The aim of pancreatic elastography for the pancreas is to reflect accurately the histological structure. The pancreatic elastography is challenging, as the access to this small organ is not easy, deep in the centre of the body. Also the biopsy specimens are difficult to obtain for direct comparison. Many of the challenges were resolved by the new technical achievements in the recent years. Both transabdominal US and EUS elastography might offer the clinicians an important tool for depiction of early chronic pancreatitis and a reliable tool for differential diagnosis between malignant and benign pancreatic masses.

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