Chapter

Endoscopic Ultrasound Elastography: New Advancement in Pancreatic Diseases

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Abstract

Elastography opened up new frontiers for pancreatic disease, as it may aid in tumor mass differentiation. Ultrasound strain elastography and ultrasound shear-wave elastography have been used so far by transabdominal transducers. New technological advancements have embedded elastography techniques in endoscopic ultrasound (EUS), thus enabling a better evaluation of patients with pancreatic tumors, chronic pancreatitis, autoimmune pancreatitis, gastrointestinal subepithelial lesions, and lymph node involvement. Moreover, EUS-E might help in guiding EUS-Fine Needle Aspiration or EUS-Fine Needle Biopsy when addressing solid pancreatic tumors, for proper tissue harvesting. Furthermore, artificial intelligence methods may bypass the human factor and lead to better diagnostic results.

Keywords: endoscopic ultrasound, elastography, pancreatic disease

1. Introduction

Elastography has surfaced in the early 1990s as a new noninvasive technique capable of offering new diagnostic opportunities for malignant diseases [1]. Initially, considered for superficial organs such as the breast [2, 3] or thyroid [4], elastography became to have an upward trend by covering most of the parenchymatous organs from the digestive system [5]. Over the years, new elastography techniques were integrated into ultrasound devices trying to create a foundational stage and to develop new standards by enhancing the spectrum of the available techniques [6]. However, the pancreas still stands as a challenge as it is hard to reach by elastography measurements.

When compared with other organs, the pancreas has by far a more limited number of studies. Due to its' retroperitoneal position, transabdominal ultrasound elastography may be rather difficult to be properly executed, and it may lead to an inaccurate or imprecise examination. The evolving field of evidence-based medicine has then focused on more precise imaging techniques used for the pancreas examination such as endoscopic ultrasound (EUS) [7]. This enhanced the spectrum of available techniques that might enable pancreatic disease diagnosis and lead to a path-breaking development along with the endoscopic ultrasound fine-needle aspiration

(EUS-FNA) implementation as a standard and necessary method [8]. While EUS-FNA has laid the grounds for the current therapeutic techniques for pancreatic disease complications, it has also contributed to the elastography imaging, mainly by providing a pathological result, which is helped as the standard method for the elastography evaluation.

In the evolutionary steps of elastography, the first introduced method was strain elastography [9]. This technique measures the strain developed during external pressure, and its' results are considered inversely related, meaning that the tissue stiffness will be softer if the strain will be greater. The manual compression is acknowledged as a limitation in a pancreatic setting thus, it requires strain to be obtained from nearby structures. However, several limitations are encountered, as measurements may be obtained usually at the level of the pancreatic body, provided that no vascular elements are in the elastography region of interest.

Further on, other elastography techniques have tried to enlarge the current spectrum and to extend elastography to a more precise tool. Shear-wave elastography [10], which is based on a different principle, was then proposed to outcome the flaws of strain elastography. By generating shear waves from the transducer, pancreatic tissue is measured and its stiffness becomes more evident as the shear wave velocity is faster. This technique was recently introduced to a EUS setting and might strengthen the available data [11].

As part of ongoing technical developments, artificial intelligence methods have also been introduced in pancreatic elastography assessment [12]. Their potential is nonetheless beneficial, as they may avoid the human factor in some situations, thus covering new grounds in pancreatic elastography.

With this chapter, we try to explore the potential of elastography in different pancreatic diseases and try to answer some of the available questions about the future of elastography.

2. Endoscopic ultrasound elastography (EUS-E) techniques

Probably the major outcome of EUS-E is that it may reach structures that are rather hard to examine, such as the pancreas or adjacent lymph nodes. As mentioned above, there are two elastography techniques available on EUS systems that have been tested on pancreatic diseases: strain elastography and the recently introduced shear wave method [11].

2.1 Strain elastography

This technique was first considered a qualitative technique, with the elastography region of interest (ROI), which covered the ultrasound image showing a pattern of green and blue colors in correspondence to the tissue stiffness [12, 13]. Green areas were considered benign, whereas blue areas were related to a possible malignant tissue. Since this method requires the transducer to be placed near the examination tissue, it is recommended to cover up at least 50% of the targeted tissue. Also, since the compression will be performed with the echoendoscope, it is important not to produce too strong compressions, so that reproducible types of elastograms may be achieved. The targeted lesion should be in the center of the transducer so that the elastography image should cover it and avoid adjacent tissue as much as possible [14, 15].

Semiquantitative analysis was introduced by determining strain ratio [16, 17]. This concept allows the practitioner to select an ROI by highlighting a round-shaped area in the targeted tissue and a smaller ROI within the nearby normal tissue, which might be either the normal parenchyma or the gastrointestinal tract wall. Then, the strain ratio has resulted from the two selected areas, with a value displayed by the ultrasound software.

Another method is represented by the strain histogram, which is based on the hue histograms averaged over several compression cycles [18, 19]. The results are usually described by mean values and standard deviation, as well as other parameters characteristic to histograms (Kurtosis, skewness, etc.). This strain histogram will cover a scale of 256 colors, being now embedded in the software of most ultrasound systems.

2.2 Shear-wave elastography

Shear-wave elastography (SWE) also became recently available in the EUS setting [11]. While the concept of SWE is similar to strain elastography, it does not use a transducer to create pressure, but it creates an elasticity map by measuring shear wave parameters. Directed by the ultrasound beam, the tissue is targeted by a perpendicular "push-pulse," which generates shear waves. SWE is capable of providing direct stiffness measurements, which are translated either in kilopascal (kPa) or meter/second (m/s). This technique might be easier to use, as it may be performed much easier, and most of all since will directly provide quantitative values. However, it will require establishing cutoff values for every organ, which will be examined.

3. Clinical applications

Both strain and shear-wave elastography are available in the EUS setting for pancreatic disease [20, 21]. One of the major differences between these techniques is that when strain elastography is used only relative values are obtained as this is only a semiquantitative method, whereas shear-wave elastography produces absolute values, which may be more relevant. Thus, color pattern assessment with strain ratio and strain histogram analysis, as well as definite values for shear wave elastography may aid for pancreatic disease assessment and may represent an adjuvant method to confirm the diagnosis.

3.1 Pancreatic masses

There is always room for techniques improvement when discussing pancreatic tumors. Even though EUS-FNB is now considered the main method to confirm the diagnosis of a pancreatic tumor [22], elastography might aid in providing a larger panel when imaging examinations are performed.

Solid pancreatic lesions were classified by qualitative elastography into four different patterns presumably with their correspondent, normal tissue—green pattern, malignant tumor—mostly blue with small green areas and red lines, inflammatory mass—green with yellow and red lines or neuroendocrine tumor—homogeneous blue pattern [23]. When performing this procedure, it is important to avoid a smaller ROI, as the measurements will show a relative elasticity difference. Thus, the ROI should be large enough to include the tumor as well as normal adjacent tissue, and this is easily achievable in a clinical setting with a ratio of 50% for lesions and 50% for nearby tissues [24].

Along with the first study in 2006 [25], EUS was introduced as an optimistic technique that might be at least as useful as it was introduced in breast cancer. Moreover, due to the pancreatic adenocarcinoma characteristics as a tumor with high desmoplastic reaction, when performing EUS-E, the tumors should be much stiffer than the surrounding tissue [26]. However, no reliable correlation was successful so far with tumor grading.

Further on, the use of quantitative EUS-E suggested more reliable results, even though there were no differences in accuracy between these two techniques [27]. Iglesias-Garcia et al [28] mentioned that the strain ratio method had a higher accuracy (97.7%) and specificity (92.2%) than the qualitative analysis and that a cutoff value of the strain ratio higher than 6.04 with a lower elasticity index than 0.05% might be sensitive enough the difference between malignant and benign pancreatic tumors. He also concluded that this technique might properly differentiate from inflammatory masses with a sensitivity of 100% and a specificity of 96% and neuroendocrine tumors (sensitivity 100% and specificity 88%).

Histogram analysis also showed some promising results (**Figures 1** and **2**). In our own study published in 2008 [29], we reported a 91.4% sensitivity, 87.9% specificity, 88.9% positive predictive value (PPV), and 90.6% negative predictive value (NPV) for the diagnosis of pancreatic malignancies, based on a cutoff of 175. Even more, better results were obtained by Schrader et al [30], who obtained 100% sensitivity and 100% specificity for pancreatic ductal adenocarcinoma (PDAC) detection; however, they did mention the controls were patients with a normal pancreas. This might not be relevant, since chronic pancreatic or other masses would be the main objective to be compared with.

Currently, there are seven meta-analyses (**Table 1**) [31–37] that include strain EUS-E for pancreatic cancer and showed a specificity of 92–98% and a specificity of 67–76%. However, two studies assessed small pancreatic tumors of less than 15 and 20 mm, respectively, and pointed out that EUS-E might be confident in suggesting that PDAC is a stiff tumor [38, 39]. Kataoka et al [38] analyzed 126 cases of small pancreatic lesions associated or not with main pancreatic duct dilation. They concluded that a stiffness ratio was definitely higher for pancreatic cancer 62:3 vs. 29:32, $P < 0.001$. Also, when comparing lesions with PC vs. without main pancreatic duct dilation, the sensitivity (94 vs 100%), specificity (23 vs 60%), and predictive value (60 vs 100%) were different suggesting that a small lesion might be excluded from being pancreatic cancer without main pancreatic duct dilation with high confidence and concordance.

As this technique may be used as an adjuvant tool for pancreatic masses diagnosis, it may be included in a panel of procedures to enhance the diagnosis process. Combining EUS-E with contrast-enhanced endoscopic ultrasound (CEUS), it could help patients with a negative FNA, if a PDAC is strongly suspected. For EUS-FNA negative cases, we compared PDAC patients with chronic pancreatitis and suggested that a hypovascular, hard tumor might suggest a PDAC with 75.8% sensitivity, 85.2% specificity, 83.3% PPV, and 96.2% NPV [40].

A different approach was tested by Yamada et al [41], which tried to assess vascular invasion of PDAC using EUS-E. They defined vascular invasions as seen in EUS by their exerting pressure characteristics. They considered that if two tissues with different stiffness are in close contact, but not fixed, their border will move when compression is made, which will translate in EUS-E as a softer tissue with adjacent artifacts with red, yellow, and green. On the other hand, if their border moves at a time, they will not have any artifacts there, thus they might have a vascular invasion. EUS-E showed a high diagnostic ability with a sensitivity of 0.917 a specificity of 0.900, and

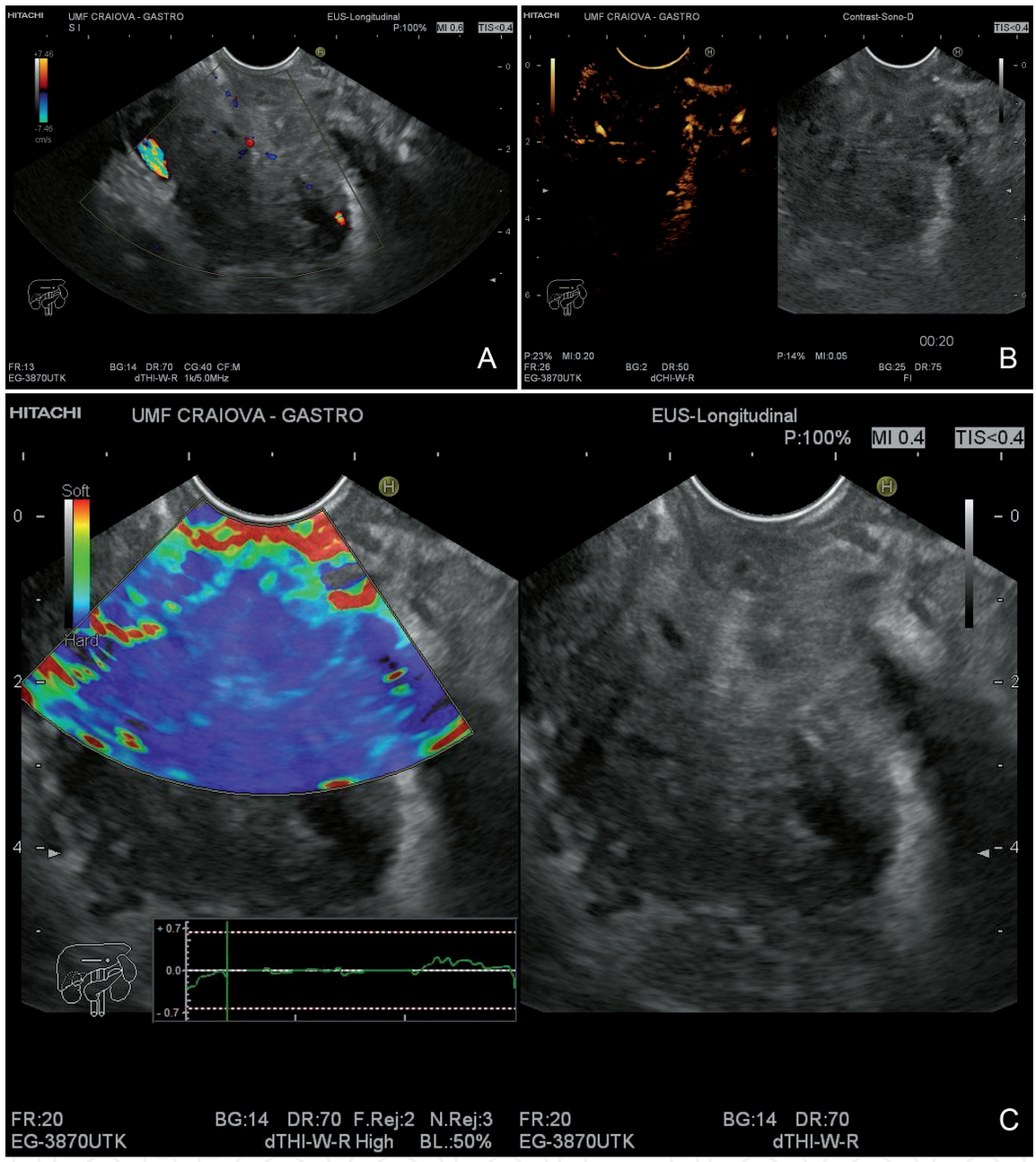

Figure 1.
Multimodal EUS imaging of a solid pancreatic tumor, pancreatic adenocarcinoma. A EUS – Doppler imaging. B Contrast-enhanced ultrasound imaging. C. EUS-E imaging with strain histogram.

an accuracy of 0.906, and after the interobserver agreement, they obtained higher k-coefficients than the B mode k −0.542 vs. $k = 0.625$, suggesting a possible method to assess vascular invasion. However, they used six different ultrasound settings, and this may hamper their results.

In a research setting, Mazzawi et al [42] published two cases where they tested EUS-E after radiofrequency ablation. Based on the fact that after ablation is difficult to distinguish residual from a recurrent tumor or fibrotic tissue, while the mass is only visible at CT/MR as decreased or unchanged by RFA, they USED EUS-E to figure out if there is any tumor tissue left. First, EUS-E was performed before the RFA procedure showing blue colored mass suggesting a hard tissue. Second, after RFA, the CT scan showed an increase in tumor diameter without any other characterization. While performing EUS-E, a mixture of blue and green areas was seen, suggesting central

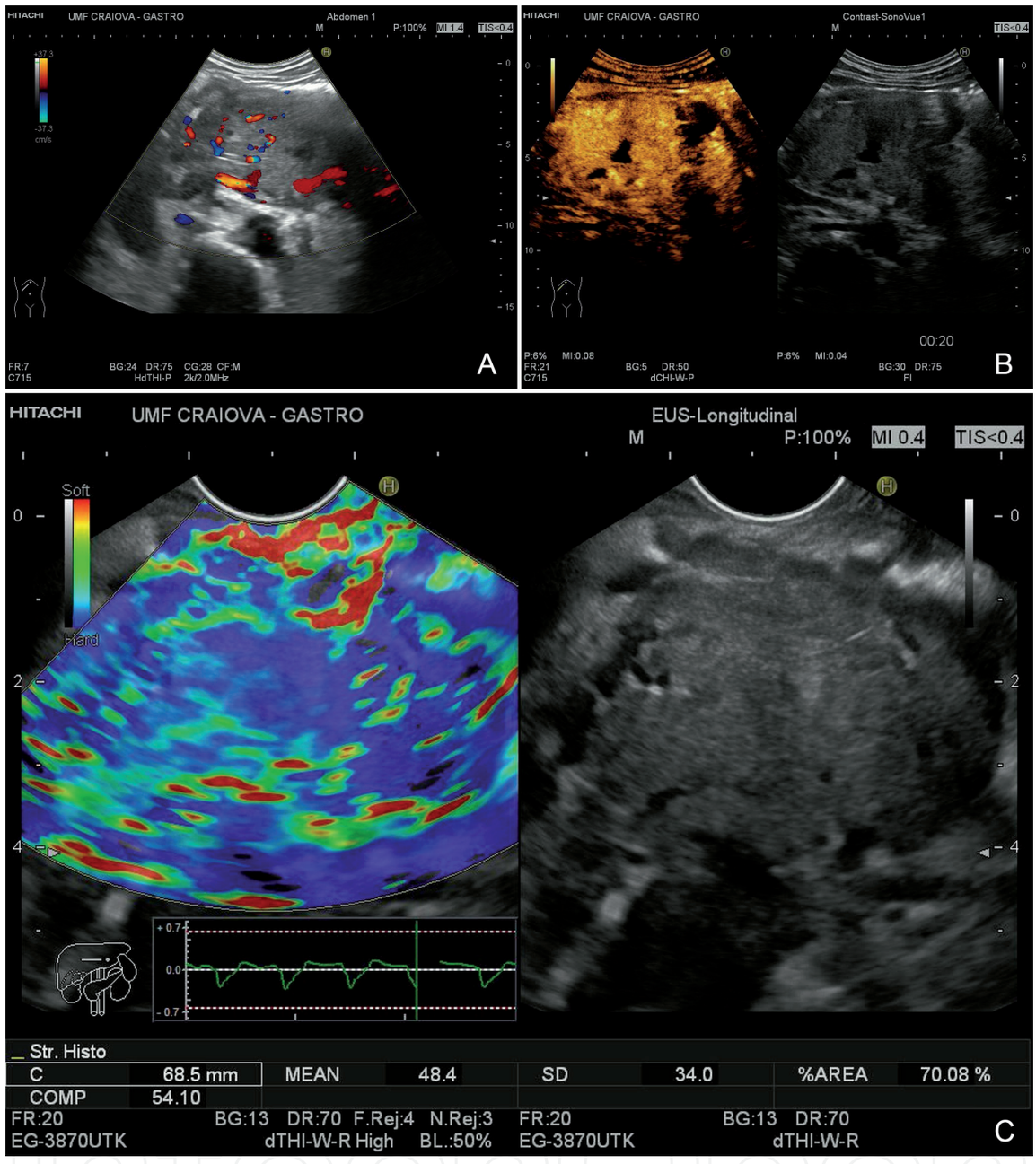

Figure 2.
Multimodal imaging of a solid pancreatic tumor, neuroendocrine tumor. A. EUS – Doppler imaging. B Contrast-enhanced ultrasound imaging. C. EUS-E imaging with strain histogram.

anechoic areas indicating necrosis and another hypoechoic region of the tumor mass. Thus, they suggest that since RFA could be performed sequentially, EUS-E might help in determining which region should be reassessed on future procedures.

The second technique available for EUS-E in a pancreatic setting, the shear-wave measurement, has only one study published so far on pancreatic masses with inconclusive results [43]. Shear wave velocity is measured, and faster propagation will be related to greater tissue elasticity. Ohno et al [43] compared EUS-SWM and EUS-E for 64 consecutive cases with solid pancreatic lesions and pointed out that the velocity of the shear wave when comparing pancreatic cancer to mass-forming pancreatitis was not statistically significant (p 0.5687), while the mean strain value was lower for pancreatic cancer 45.4 vs. 74.5; p 0.0007. They used an Arietta 850 (Hitachi Medical Systems Europe, Zug, Switzerland) device, which unfortunately may not visualize

Year	Author	Number of patients	Sensitivity (%)	Specificity (%)
2012	Pei et al. [31]	1042	95	69
2013	Mei et al. [32]	1044	95	67
2013	Ying et al. [33]	893	98	69
2013	Li et al. [34]	781	99	76
2013	Hu et al. [35]	752	97	76
2013	Xu et al. [36]	752	99	74
2017	Lu et al. [37]	1537	97	67

Table 1.
Available meta-analyses that focus in EUS-E strain assessment on pancreatic cancer.

the propagation status of shear waves in the ROI. Moreover, as they mention, many artifacts may be encountered due to various reasons, such as tissue motion, nearby blood vessels, distortion, or precompression artifacts, as well as breathing, because the procedures are usually performed under conscious sedation. Thus, their conclusion was that this set of EUS-SWM is not feasible for pancreatic solid masses assessment and that EUS-E with strain ratios and histogram still remain the main adjuvant method to be considered.

3.2 Chronic pancreatitis

Currently, EUS-E is considered for pancreatic fibrosis assessment (as well as stiffness) by both strain and shear-wave elastography [44]. Even though transabdominal US-E has been reported at first [45, 46], EUS-E is the preferred method, due to its capability to better visualize the pancreas, regardless of the patient's body size. However, the technique still requires a highly experienced endoscopist (**Figure 3**).

Itoh et al [47] used quantitative analysis to diagnose pancreatic fibrosis using EUS-E of surgically resected specimens. They included 58 patients who underwent EUS-EG of the distal pancreas before performing a pancreatectomy of pancreatic tumor based on the concept that if a tumor is present in the pancreatic head, fibrosis might be present in the tail due to obstructive pancreatitis. When compared with histology, they maintained the same image as the EUS-E pattern by providing a median of 2.0 sections. They quantified four parameters of tissue elasticity (mean, standard deviation, skewness, and kurtosis) and obtained a significant correlation between all of them and the grade of pancreatic fibrosis. They concluded that with fibrosis progression, the skewness and kurtosis increased, whereas the standard deviation and mean decreased.

While this concept might be the ideal one, it is difficult to be introduced without comparing it to surgical specimens. On the other hand, EUS by itself is not standardized and has a low reproducibility in diagnosing chronic pancreatitis. Thus, by performing a histogram analysis, these drawbacks might be overcome. Kuwahara et al [48] published in 2017 their experience on using EUS on 96 patients. They performed EUS-E on the head of the pancreas and compared the mean values with no substantial difference (68.8 vs. 71.3); however, the interobserver reliability of chronic pancreatitis was substantial with a k value of 0.648 and a consistency ratio of 73%. They also mention that EUS characteristics with hyperechoic foci with shadowing and lobularity and honeycomb appearance, as well as the Rosemont Criteria, were correlated with

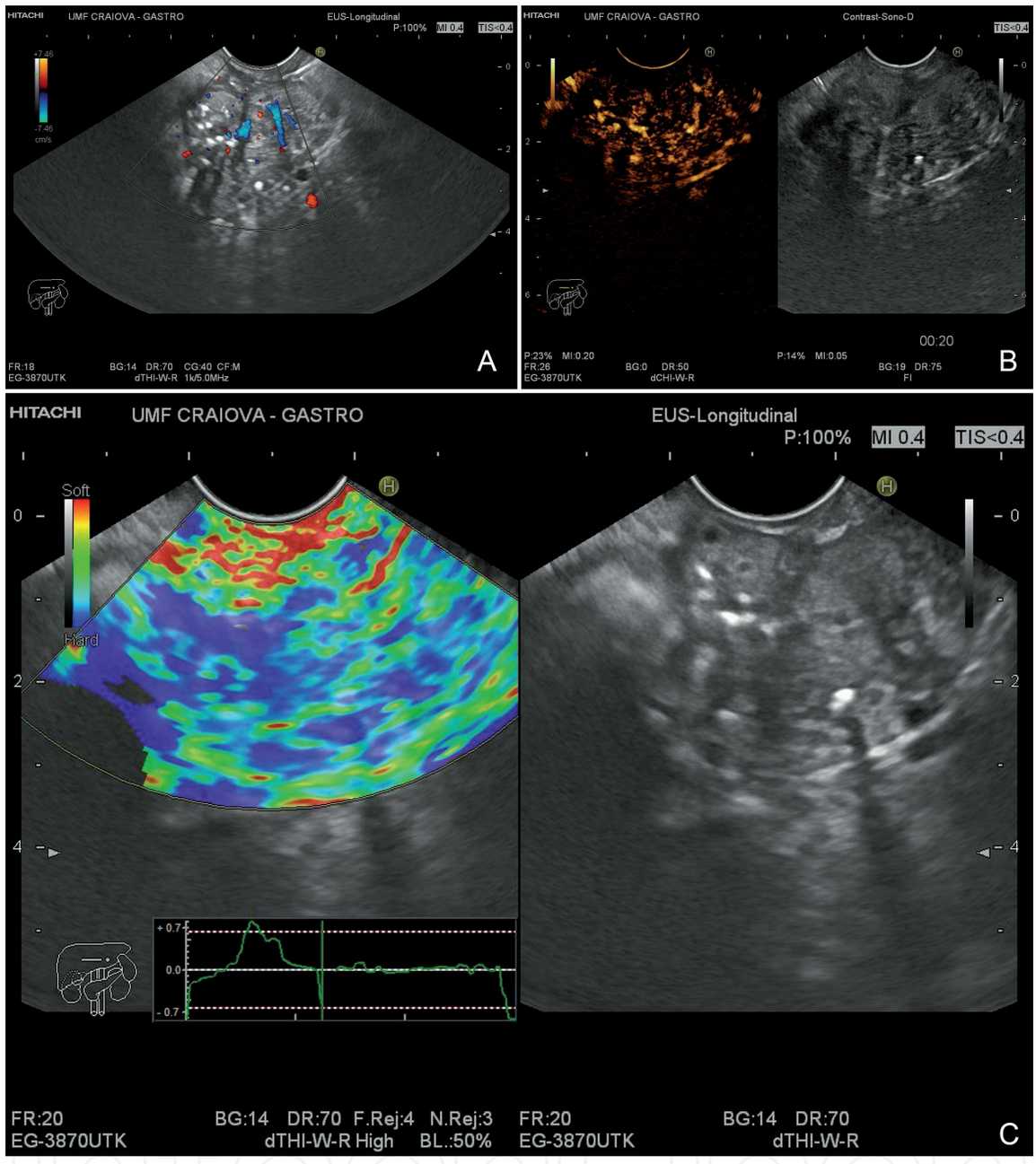

Figure 3.
Multimodal imaging of chronic pancreatitis A. EUS – Doppler imaging. B. Contrast-enhanced ultrasound imaging. C. EUS-E imaging with strain histogram.

EUS-E. In conclusion, they suggest that EUS-E is an objective method for the diagnosis of chronic pancreatitis and should be considered when performing EUS.

The elastography spectrum was enhanced with the shear wave devices implemented on EUS systems. Nonetheless, chronic pancreatitis benefited from this breakthrough, and recent studies have already been published. The first reports of EUS shear wave elastography [43, 49] compared the resulting values with the Rosemont classification and EUS criteria with positive results and suggested that shear wave values may assess the fibrotic changes, which occur in chronic pancreatitis. They obtained a high sensitivity of 100%, specificity 94%, and an AUROC (Area Under the Receiver Operating Characteristics) of 0.97, which highlights the EUS-SWM diagnostic capability and that also may surpass other imaging techniques. The exocrine and endocrine functions were also discussed if they might be correlated with

EUS-SWM since in chronic pancreatitis, they are both altered [50]. The EUS-SWM sensitivity, specificity, and AUROC obtained for diagnosing chronic pancreatitis were 83%, 100%, and 0.92. When discussing exocrine dysfunction with pancreatic function diagnostic tests, the AUROC was 0.78 with a cutoff value of 1.96, whereas for the endocrine dysfunction associated with diabetes mellitus, it was 0.63 with a cutoff value of 2.34.

EUS-E is a promising asset for chronic pancreatitis; however, there is a need for more studies since some limitations are still encountered. While the proper way to validate its use is represented by histology as a reference, in chronic pancreatitis this might be rather difficult, thus another setting should be proposed. Also, the use of shear waves seems to provide better data, as they estimate the stiffness of the tissue.

3.3 Autoimmune pancreatitis

Exploring new diagnostic paths, EUS-E might be a valid tool for AP assessment. The first cases were reported by Dietrich et al [51] after suspicion of chronic pancreatitis but had a final diagnosis of AIP after EUS. The stiffness that covers the entire pancreas is characteristic for AIP, which enables to easily distinguish AIP and pancreatic adenocarcinoma. Only one study tested EUS-E with strain ratio on AIP. The authors tried to show a positive relationship after steroid treatment in AIP by examining the patient before and 2 weeks after therapy. The patients showed a decrease in the strain ratio from (8.04 ± 2.29 to 3.44 ± 1.97 ($P < 0.0001$). This might promote EUS-E as a response to the therapy, which might be useful for clinicians.

Additionally, there is also a study published on SWE that compared patients with AIP with controls, yielding different values of share wave velocity (2.57 m/s vs. 1.89 m/s) ($P = 0.0185$). The study also tested the response to steroid therapy, and Vs significantly decreased from 3.32 to 2.46 m/s ($n = 6$) (P 0.0234), which highlights the technique's capability in AIP [49, 51, 52].

3.4 Pancreatic fistulas

EUS-E has also been tested in the particular setting of pancreatic fistula following pancreaticoduodenectomy [53]. This is a possible complication that may occur and can have dramatic consequences. Mean elasticity was measured and proved to be significantly higher in patients with pancreatic fistula as compared with the ones without ($p < 0.001$). The AUROC for EUS-E to determine pancreatic fistula was higher than the operator who appreciated the tissue by hand; however, no statistical significance was present ($p = 0.132$).

4. Conclusions

EUS-E is a complementary tool for pancreatic disease assessment with a continuous endeavor to aid as a proper diagnosis method. While this method may not replace EUS tissue acquisition, it may be used as an additional method to help the decision-making process.

While strain EUS-E was the first technique used, with various results, the recent EUS-SWM in a pancreatic setting still requires more investigations. With only a few studies, and perhaps more to come in the next years, perhaps SWM will overcome the flaws of strain EUS-E and will be used more for pancreatic disease assessment.

Moreover, new software developments, such as artificial intelligence tools could also be an alternative, by enabling a more rapid diagnostic based on image analysis.

In conclusion, EUS-E might require more attention, because of its potential, and in combination with other methods, such as CEUS, may maximize the efforts for pancreatic disease management.

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Conflict of interest

The authors declare no conflict of interest.

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