Review Article

Do we need elastography for EUS?

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ABSTRACT

We recently introduced a series of papers "What should be known prior to performing EUS exams." In Part I, the authors discussed which clinical information and whether other imaging modalities are needed before embarking EUS examinations. In Part II, technical controversies on how EUS is performed were discussed from different points of view. In this article, important practical issues regarding EUS elastography will be raised and controversially discussed from very different points of view.

Key words: Elastography, EUS examinations, EUS

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INTRODUCTION AND REVIEW OF THE LITERATURE

Since ancient times, physicians have considered palpation as an essential part of the physical examination of the patient, with changes in the elasticity of tissues and organs, in particular increased firmness, traditionally associated with a pathologic process. The evolution of imaging techniques has added elastography to physical palpation, a sort of "palpation by imaging," which allows real-time estimation of tissue stiffness. As stiffer tissues deform less under compression (*i.e.*, have a lower strain) than softer tissues, comparing echosets before and after applying a compressive force give valuable information on tissue stiffness. The differences in strain measurements are easily displayed sonographically using semi-transparent color scales overlaying the B-mode images.[1] Elastography based on the strain technique is also available as a real-time method for EUS.[2,3] Cancer and inflammation modify tissue elasticity to differing degrees, with malignant tumors being typically significantly stiffer than healthy surrounding tissues. The ability to differentiate between softer and harder tissues may help in refining the differential diagnosis of pancreatic lesions and lymph nodes (LNs).[4]

Elastography began as a qualitative technique, where green areas, corresponding to soft tissues, were considered benign, while blue areas indicative of stiff tissues were considered more likely malignant.[2,5] With second-generation EUS elastography, semi-quantitative analysis could be performed using either the strain ratio or the strain histogram technique.[6] The strain ratio (SR) is calculated as follows: the operator positions a round-shaped region of interest (ROI) sized on the target lesion (A) and a smaller ROI (B) above a homogeneous soft reference area either in the surrounding normal parenchyma or in the wall of the gastrointestinal tract. The strain ratio is calculated by dividing the strain data from A by B (A/B), the value of which is displayed automatically by the software of the ultrasound processors. It has been shown that both surrounding pancreatic parenchyma and gastrointestinal wall are useful positions for the reference ROI to differentiate between malignant and benign pancreatic lesions (parenchymal strain ratio and wall strain ratio).[7]

An alternative method of quantitative elastographic analysis is the strain histogram. Modern ultrasound processors provide the opportunity to calculate average hue histograms over several compression cycles. These are graphical representations of the colors (hues) distribution within a lesion, thereby describing the stiffness or elasticity of the lesion. Consequently, the mean value of the histogram reflects the global stiffness or elasticity of a focal lesion based on calculations inside a selected ROI positioned over the lesion. In addition, standard deviation (SD) and other parameters may be used to further describe the hues distribution with the ROI.[8]

Elastography histogram analysis is helpful in diffuse diseases such as chronic hepatitis and pancreatitis, where the spatial color pattern displayed in the elastogram is related to the fibrous tissue alterations caused by chronic inflammatory processes. The distribution of recorded strain measurements can be displayed as a histogram (Gaussian distribution curve) from which a number of statistical parameters can be derived for quantitative evaluation. The key parameters (features extracted from the strain image) are mean strain (MEAN); SD of the mean; percentage of blue area (%AREA); and complexity of the blue areas (COMP) (relation between the circumference and the area of blue patches). The shape of the histogram described mathematically by skewness and kurtosis also reflects the distribution and the homogeneity of the tissue stiffness recorded.[9]

Computerized analysis based on artificial neural network[10] and fractals[7] have also been applied to EUS elastography with promising results, but more studies are needed to establish the real clinical impact of these techniques. Theoretically, strain elastography just gives the relative stiffness inside an ROI, not providing an absolute measurement of tissue stiffness. However, comparisons of strain elastography between individuals are limited due to lack of both objectivity and methods of standardization. Recently, EUS-guided shear wave measurement allowed immediate and repeated measurement of the objective elastic value, which may provide us more reliable absolute values of tissue elasticity.[11-13] Clinical applications of EUS-elastography include characterization of pancreatic masses, LNs, subepithelial lesions, and tumor staging.[6,14,15]

PANCREATIC MASSES

Qualitative elastographic findings in the pancreas have been categorized into four different patterns to provide a classification of solid pancreatic lesions.

A homogeneous green pattern usually represents normal pancreatic parenchyma; a heterogeneous, predominantly green pattern with slight yellow and red lines is present in inflammatory pancreatic masses; a heterogeneous, predominantly blue pattern with small green areas and red lines and a geographic appearance is present mainly in pancreatic malignant tumors (including pancreatic adenocarcinoma), while a homogeneous blue pattern is found in pancreatic neuroendocrine malignant lesions.[2,16]

When comparing the strain ratio of a mass over the normal surrounding pancreatic parenchyma, malignant pancreatic masses and neuroendocrine tumors produce higher strain ratios than inflammatory masses and normal parenchyma.[17,18]

It has been suggested that a strain ratio of >10 or a mean strain histogram value of <50 is associated with malignancy.[17] However, the reproducibility of EUS elastography in the evaluation of solid pancreatic lesions is still a matter of debate, even when semi-quantitative techniques are used.[17] It is anticipated that the new quantitative methods – shear wave elastography – will bring an interesting addition in this field.[12,19-24]

Several meta-analyses[25-30] have evaluated the diagnostic performance of EUS elastography for the characterization of malignant pancreatic tumors. Overall, their authors showed a high sensitivity (92%–98%), but a low specificity (67%–76%) of EUS elastography in this clinical application. Disappointingly, there was no significant advantage of semi-quantitative strain elastography over qualitative strain elastography. Interesting results have been reached by a recent multicenter study, including only small lesions (≤15 mm).[31] In this study, 50% of solid pancreatic lesions ≤15 mm proved to be soft, and the probability of a soft lesion to be malignant was negligible. Therefore, due to its very high negative predictive value for malignancy EUS elastography may be of particular value for small pancreatic lesions. In addition, combining the information obtained by elastography with contrast-enhanced harmonic EUS for the differential diagnosis of solid pancreatic masses could increase the overall diagnostic accuracy.[32-34]

PANCREATITIS

The diagnosis of chronic pancreatitis[5,35] represents another interesting application of EUS-elastography.[36] Fibrotic changes in chronic pancreatitis generally result in increased stiffness of the pancreatic parenchyma,[37] while acute pancreatitits and necrotic areas often appear softer on elastography. In chronic pancreatitis, EUS-elastography histogram analysis and strain ratio measurements correspond to the histological fibrosis score and the probability of exocrine pancreatic insufficiency.[38] The measured strain ratio correlates to the number of EUS B-mode criteria for chronic pancreatitis (Rosemont classification),[39] rendering elastography a complementary tool in the diagnosis of chronic pancreatitis. A similar correlation between elasticity values, Rosemont criteria, and endocrine dysfunction has been shown also using EUS-based shear-wave elastography.[12] Focal-type autoimmune pancreatitis can mimic pancreatic adenocarcinoma on B-mode EUS. EUS elastography may help in differentiating the two entities by demonstrating a diffuse homogenous increase in the stiffness of the entire organ in autoimmune pancreatitis as opposed to ductal adenocarcinoma, where the increased stiffness is generally seen only within the tumor itself.[40] A preliminary study using EUS-based shear-wave elastography not only showed a significantly higher stiffness of the pancreatic parenchyma in patients with autoimmune pancreatitis compared to healthy controls, but also that this technique may be useful to monitor the effect of steroid therapy.[13]

LYMPH NODES

EUS elastography can be helpful in differentiating benign and malignant LNs. Benign (physiological and reactive) LNs are characterized by a homogeneous or scattered soft pattern (predominantly green or mixed red-yellow-green).[41] In a meta-analysis, the pooled sensitivity of EUS elastography in differentiating benign and malignant LNs was 88%, with a specificity of 85%.[42] Two prospective studies using EUS fine-needle aspiration (EUS-FNA) as a gold-standard have shown that EUS elastography can be helpful in LN staging of esophageal cancer.[43,44] In a recent prospective study comparing EUS elastography results with histology after surgery for esophageal cancer, the technique had an accuracy of 93.9% in identifying metastatic LNs.[45] Such noninvasive elastographic evaluation of suspicious LNs may be particularly valuable if the nodes are not accessible by FNA needle, in patients with contraindications to FNA, and for selecting the best FNA target when multiple nodes are present.[15,46-49]

SUBEPITHELIAL LESIONS

Preliminary data suggest that EUS elastography could help in characterizing subepithelial lesions (SEL). In particular, it could be useful in differentiating gastrointestinal stromal tumors (GIST) from other types of SEL.[50-52] In a pilot study with strain ratio EUS-elastography, GISTs were harder than other types of gastric SEL such as lipoma and ectopic pancreas.[51] However, a subsequent larger study, including 62 SEL, which were classified according to histology, did not show a reliable differentiation between GISTs and leiomyomas using EUS-elastography. Based on qualitative strain elastography, 80% of (4/5) leiomyomas appeared blue as did the vast majority of GISTs that were included (61/62).[50] Another study using the strain ratio was able to differentiate between leiomyoma and GIST with a sensitivity and specificity of 100% and 94.1%, respectively.[52] Due to these conflicting data, further studies are needed to evaluate the capability of EUS elastography in differentiating leiomyoma from GIST.

FOCAL LIVER LESIONS

EUS has proven to be helpful in the detection and guidance of sampling of small liver metastases, for example, in pancreatobiliary malignancy. Preliminary experience is available showing that EUS elastography combined with contrast-enhanced EUS may facilitate characterization of solid focal liver lesions.[53]

TARGETED EUS-GUIDED TISSUE SAMPLING

In theory, EUS-elastography can highlight the hardest area within a pancreatic mass, a LN or another focal lesion by displaying the color-coded elasticity score in real time, thereby allowing selection of the most suitable region for targeted EUS tissue sampling.[54] By avoiding necrotic (softer) areas, the diagnostic yield of tissue acquisition may be increased. A recent study[55] was conducted on 54 patients with solid pancreatic lesions, where a 25G EUS needle was inserted into the most suspicious part of the lesion according to EUS elastography. A positive diagnosis of adenocarcinoma was obtained in 85% of patients. The diagnostic accuracy, sensitivity, and specificity of the combination EUS-elastography/FNA was 94%, 93%, and 100%, respectively.

PRO: ADVANTAGES OF USING ELASTOGRAPHY

The use of EUS elastography should be encouraged because it provides valuable information complementary to B-mode imaging. It is performed in real time, is easy to use and learn, has no additional risks or costs, and increases the duration of the examination by only a few minutes. It has no known contraindications and does not require any specific preparation.[14] For EUS elastography of solid pancreatic lesions as well as for LNs, a high intra- and interobserver agreement has been described at least for experienced examiners.[8,14,56,57] A soft focal solid pancreatic lesion is almost never a PDAC, whereas stiff lesions might be malignant or benign. Elastography is, therefore, more reliable in excluding rather than confirming malignancy. On the other hand, elastography in combination with other endosonographic imaging tools such as contrast enhancement can be very helpful in confirming the malignant nature of a mass or of lymphadenopathy.[7,32-34,58] If multiparametric EUS imaging including elastography concordantly demonstrates features consistent with a malignant lesion, but EUS-guided sampling yields inadequate, inconclusive or even negative results, repeat sampling or decision for surgery is indicated.[15] Moreover, this may be particularly helpful if the region is not easily accessible by EUS needles, in patients with contraindications against fine-needle puncture and if multiple suspicious areas are present.[21,54,55,58,59] The use of elastography in pancreatic diseases and for characterization of LNs is recommended by the EFSUMB guidelines.[15,60] In 2015, clinical practice guidelines for elastography specific to the pancreas were published by the Japanese Society of Medical Ultrasonics.[61]

CONTRA: ARGUMENTS AGAINST USING ELASTOGRAPHY

In addition to the described published positive results of elastography, some of the authors never use elastography. Elastography is not an essential component of EUS because the majority of endosonographers are capable of producing excellent EUS outcomes without it. There are no data showing that elastography improves clinical outcomes when compared to EUS with or without EUS-guided tissue acquisition. In particular, there are no studies proving that elastography is truly superior in targeting cancer in suspicious lesions.

Most, if not all elastography studies are fundamentally flawed, because endosonographers cannot be

blinded to the standard B-mode EUS images when performing elastography. Hence, the incremental value of elastography over standard B-mode imaging is unclear. The accuracy of elastography for distinguishing malignant from benign lesions is usually in the range of 80%–90% – even in the hands of experts. This is clinically inacceptable for potential cancer because one cannot accept a 10%–20% chance of incorrect management. In addition, studies evaluating elastography likely overestimate its real accuracy, because studies never included only indeterminate masses. Studies usually included obvious cancers and likely clearly benign-appearing lesions. If these obviously benign or malignant lesions were excluded, the accuracy of elastography would likely drop closer to the range of 50%–60%, which is essentially the same as flipping a coin.

Finally, improvements in EUS histology needles have increased the accuracy of EUS-guided biopsy to over 95%. Therefore, in terms of mass lesions and nodes, the number of truly indeterminate cases is very low. One could go as far as to say that, in cases of suspected cancer, elastography is useless in patients in whom EUS-guided tissue sampling is performed, and is of questionable value when EUS-guided biopsy is negative (repeat biopsy is probably more useful than elastography).

There may be some future applications for elastography, but not in the management of suspected malignancy. There are some interesting data in benign conditions such as chronic pancreatitis, autoimmune pancreatitis, and liver fibrosis, although further work is required to reduce operator dependence and to corroborate the existing results in general clinical practice.

Elasticity of tissues is influenced by several pathophysiological processes, the most important being fibrosis and necrosis. Both mechanisms are not unique to malignant tissue transformation, but may also occur in inflammatory lesions, for example, in chronic (pseudo-tumoral) pancreatitis, autoimmune pancreatitis,[23,40,62] and sarcoidosis.[63] Chronic pancreatitis is a risk factor for pancreatic malignancy, and the diagnosis of malignancy arising on a background of chronic pancreatitis is an important and difficult clinical scenario but one in which the utility of elastography is reduced. Therefore, despite its high sensitivity to diagnose malignancy, the clinical value of EUS elastography is hampered by low specificity that for characterization of solid pancreatic lesions in one large prospective study was as low as 22%.[17] Used alone, it would miss few malignancies, but would result in unnecessary resections in 30%–35% of cases in its current form. For this reason, EUS elastography cannot replace histology or cytology at the expense of additional examination time. The fact that the strain applied is unknown and we cannot obtain absolute values for elasticity, represent some of the main limitations of EUS elastography. Information from qualitative and semi-quantitative elastography depends on the ROI selected. The lack of standardization of technique hampers the generalizability of the technique. For measurement of strain ratio, there is no agreement within the literature on the position of the second (comparative) ROI,[6,7,9] which can significantly influence the results of measurement.[64] Positioning the second ROI within the gastrointestinal wall, as suggested in one of the first publications,[5] may be hampered by the "slip artifact."[9] In conclusion, the use of SR is for research purposes only.

Modification of presets, diameter of the lesion, as well as the elasticity of the lesion surrounding tissue may influence the results of elastography significantly.[65-68] Qualitative elastography using scoring systems is prone to subjective assessment, and cutoff values for strain ratio differ a lot between studies. Moreover, compression by the transducer can artificially increase the strain,[3,14] and in some anatomical positions, compression induced by physiological pulsations of the heart and large arterial vessels is not sufficient to create stable elastography images. Finally, the length and specifications of training in elastography have not yet been established.[14]

CONCLUSIONS

Elastography is complementary and not alternative to tissue sampling, and it was never intended to replace EUS-guided tissue sampling. Elastography may be used as an additional noninvasive technique to help characterize lesions in the proximity of the gastrointestinal tract, guiding fine-needle punctures and helping to decide on further clinical management. In a pancreatic soft lesion, elastography has a very high negative predictive value to exclude ductal adenocarcinoma of the pancreas. Qualitative as well as semi-quantitative EUS elastography are complementary tools for differentiating malignant and inflammatory pancreatic masses and LNs. Newer techniques (in

particular EUS-based shear-wave elastography) or the combination with other modalities such as contrast enhanced EUS, can further increase the value of elastography in the near future.

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Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Bamber J, Cosgrove D, Dietrich CF, *et al*. EFSUMB guidelines and recommendations on the clinical use of ultrasound elastography. Part 1: Basic principles and technology. *Ultraschall Med* 2013;34:169-84.
2. Giovannini M, Hookey LC, Bories E, *et al*. Endoscopic ultrasound elastography: The first step towards virtual biopsy? Preliminary results in 49 patients. *Endoscopy* 2006;38:344-8.
3. Cui XW, Chang JM, Kan QC, *et al*. Endoscopic ultrasound elastography: Current status and future perspectives. *World J Gastroenterol* 2015;21:13212-24.
4. Costache MI, Dumitrescu D, Săftoiu A. Technique of qualitative and semi-quantitative EUS elastography in pancreatic examination. *Endosc Ultrasound* 2017;6:S111-4.
5. Iglesias-Garcia J, Larino-Noia J, Abdulkader I, *et al*. Quantitative endoscopic ultrasound elastography: An accurate method for the differentiation of solid pancreatic masses. *Gastroenterology* 2010;139:1172-80.
6. Dietrich CF, Bibby E, Jenssen C, *et al*. EUS elastography: How to do it? *Endosc Ultrasound* 2018;7:20-8.
7. Carrara S, Di Leo M, Grizzi F, *et al*. EUS elastography (strain ratio) and fractal-based quantitative analysis for the diagnosis of solid pancreatic lesions. *Gastrointest Endosc* 2018;87:1464-73.
8. Săftoiu A, Vilmann P, Gorunescu F, *et al*. Accuracy of endoscopic ultrasound elastography used for differential diagnosis of focal pancreatic masses: A multicenter study. *Endoscopy* 2011;43:596-603.
9. Dietrich CF, Barr RG, Farrokh A, *et al*. Strain elastography-How to do It? *Ultrasound Int Open* 2017;3:E137-49.
10. Săftoiu A, Vilmann P, Gorunescu F, *et al*. Neural network analysis of dynamic sequences of EUS elastography used for the differential diagnosis of chronic pancreatitis and pancreatic cancer. *Gastrointest Endosc* 2008;68:1086-94.
11. Ohno E, Hirooka Y, Kawashima H, *et al*. Feasibility of EUS-guided shear-wave measurement: A preliminary clinical study. *Endosc Ultrasound* 2019;8:215-6.
12. Yamashita Y, Tanioka K, Kawaji Y, *et al*. Utility of elastography with endoscopic ultrasonography shear-wave measurement for diagnosing chronic pancreatitis. *Gut Liver* 2019. doi: 10.5009/gnl19170. [Epub ahead of print].
13. Ohno E, Hirooka Y, Kawashima H, *et al*. Feasibility and usefulness of endoscopic ultrasonography-guided shear-wave measurement for assessment of autoimmune pancreatitis activity: A prospective exploratory study. *J Med Ultrason* (2001) 2019;46:425-33.
14. Iglesias-García J, Lariño-Noia J, Domínguez-Muñoz JE. New imaging techniques: Endoscopic ultrasound-guided elastography. *Gastrointest Endosc Clin N Am* 2017;27:551-67.
15. Săftoiu A, Gilja OH, Sidhu PS, *et al*. The EFSUMB guidelines and recommendations for the clinical practice of elastography in non-hepatic applications: Update 2018. *Ultraschall Med* 2019;40:425-53.
16. Janssen J, Schlörer E, Greiner L. EUS elastography of the pancreas: Feasibility and pattern description of the normal pancreas, chronic pancreatitis, and focal pancreatic lesions. *Gastrointest Endosc* 2007;65:971-8.
17. Dawwas MF, Taha H, Leeds JS, *et al*. Diagnostic accuracy of quantitative EUS elastography for discriminating malignant from benign solid pancreatic masses: A prospective, single-center study. *Gastrointest Endosc* 2012;76:953-61.
18. Itokawa F, Itoi T, Sofuni A, *et al*. EUS elastography combined with the strain ratio of tissue elasticity for diagnosis of solid pancreatic masses. *J Gastroenterol* 2011;46:843-53.
19. Xie J, Liu H, Liu WS, *et al*. Quantitative shear wave elastography for noninvasive assessment of solid pancreatic masses. *Clin Hemorheol Microcirc* 2020;74:179-87.
20. Dietrich CF, Ferraioli G, Sirli R, *et al*. General advice in ultrasound based elastography of pediatric patients. *Med Ultrason* 2019;21:315-26.
21. Dietrich CF, Hocke M. Elastography of the pancreas, current view. *Clin Endosc* 2019;52:533-40.
22. Koya T, Kawashima H, Ohno E, *et al*. Increased hardness of the underlying pancreas correlates with the presence of intraductal papillary-mucinous neoplasm in a limited number of cases. *J Med Ultrason* (2001) 2019;46:441-7.
23. Ohno E, Hirooka Y, Kawashima H, *et al*. Feasibility and usefulness of endoscopic ultrasonography-guided shear-wave measurement for assessment of autoimmune pancreatitis activity: A prospective exploratory study. *J Med Ultrason* (2001) 2019;46:425-33.
24. D'Onofrio M, Tremolada G, de Robertis R, *et al*. Prevent pancreatic fistula after pancreatoduodenectomy: Possible role of ultrasound elastography. *Dig Surg* 2018;35:164-70.
25. Ying L, Lin X, Xie ZL, *et al*. Clinical utility of endoscopic ultrasound elastography for identification of malignant pancreatic masses: A meta-analysis. J Gastroenterol Hepatol 2013;28:1434-43.
26. Mei M, Ni J, Liu D, *et al*. EUS elastography for diagnosis of solid pancreatic masses: A meta-analysis. *Gastrointest Endosc* 2013;77:578-89.
27. Hu DM, Gong TT, Zhu Q. Endoscopic ultrasound elastography for differential diagnosis of pancreatic masses: A meta-analysis. Dig Dis Sci 2013;58:1125-31.
28. Pei Q, Zou X, Zhang X, *et al*. Diagnostic value of EUS elastography in differentiation of benign and malignant solid pancreatic masses: A meta-analysis. *Pancreatology* 2012;12:402-8.
29. Li X, Xu W, Shi J, *et al*. Endoscopic ultrasound elastography for differentiating between pancreatic adenocarcinoma and inflammatory masses: A meta-analysis. *World J Gastroenterol* 2013;19:6284-91.
30. Zhang B, Zhu F, Li P, *et al*. Endoscopic ultrasound elastography in the diagnosis of pancreatic masses: A meta-analysis. *Pancreatology* 2018;18:833-40.
31. Ignee A, Jenssen C, Arcidiacono PG, *et al*. Endoscopic ultrasound elastography of small solid pancreatic lesions: A multicenter study. *Endoscopy* 2018;50:1071-9.
32. Iglesias-Garcia J, Lindkvist B, Lariño-Noia J, *et al*. Differential diagnosis of solid pancreatic masses: Contrast-enhanced harmonic (CEH-EUS), quantitative-elastography (QE-EUS), or both? *United European Gastroenterol J* 2017;5:236-46.
33. Chantarojanasiri T, Hirooka Y, Kawashima H, *et al*. Endoscopic ultrasound in diagnosis of solid pancreatic lesions: Elastography or contrast-enhanced harmonic alone versus the combination. *Endosc Int Open* 2017;5:E1136-43.
34. Iordache S, Costache MI, Popescu CF, *et al*. Clinical impact of EUS elastography followed by contrast-enhanced EUS in patients with focal pancreatic masses and negative EUS-guided FNA. *Med Ultrason* 2016;18:18-24.
35. Smetana GW, Macpherson DS. The case against routine preoperative laboratory testing. *Med Clin North Am* 2003;87:7-40.
36. Dominguez-Muñoz JE, Iglesias-Garcia J, Castiñeira Alvariño M, *et al*. EUS elastography to predict pancreatic exocrine insufficiency in patients with chronic pancreatitis. *Gastrointest Endosc* 2015;81:136-42.
37. Kuwahara T, Hirooka Y, Kawashima H, *et al*. Quantitative diagnosis of chronic pancreatitis using EUS elastography. *J Gastroenterol* 2017;52:868-74.
38. Itoh Y, Itoh A, Kawashima H, *et al*. Quantitative analysis of diagnosing pancreatic fibrosis using EUS-elastography (comparison with surgical specimens). *J Gastroenterol* 2014;49:1183-92.

39. Iglesias-Garcia J, Domínguez-Muñoz JE, Castiñeira-Alvariño M, *et al*. Quantitative elastography associated with endoscopic ultrasound for the diagnosis of chronic pancreatitis. *Endoscopy* 2013;45:781-8.
40. Dietrich CF, Hirche TO, Ott M, *et al*. Real-time tissue elastography in the diagnosis of autoimmune pancreatitis. *Endoscopy* 2009;41:718-20.
41. Fröhlich E, Jenssen C, Schuler A, *et al*. Contrast-enhanced ultrasound for characterisation of focal liver lesions, practical advice. *Z Gastroenterol* 2015;53:1099-107.
42. Xu W, Shi J, Zeng X, *et al*. EUS elastography for the differentiation of benign and malignant lymph nodes: A meta-analysis. *Gastrointest Endosc* 2011;74:1001-9.
43. Knabe M, Günter E, Ell C, *et al*. Can EUS elastography improve lymph node staging in esophageal cancer? *Surg Endosc* 2013;27:1196-202.
44. Paterson S, Duthie F, Stanley AJ. Endoscopic ultrasound-guided elastography in the nodal staging of oesophageal cancer. *World J Gastroenterol* 2012;18:889-95.
45. Sazuka T, Akai T, Uesato M, *et al*. Assessment for diagnosis of lymph node metastasis in esophageal cancer using endoscopic ultrasound elastography. *Esophagus* 2016;13:254-63.
46. Dumonceau JM, Deprez PH, Jenssen C, *et al*. Indications, results, and clinical impact of endoscopic ultrasound (EUS)-guided sampling in gastroenterology: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline-Updated January 2017. *Endoscopy* 2017;49:695-714.
47. Fusaroli P, Jenssen C, Hocke M, *et al*. EFSUMB Guidelines on Interventional Ultrasound (INVUS), Part V. Ultraschall Med 2016;37:77-99.
48. Jenssen C, Hocke M, Fusaroli P, *et al*. EFSUMB guidelines on interventional ultrasound (INVUS), Part IV-EUS-guided interventions: General aspects and EUS-guided sampling (Long Version). *Ultraschall Med* 2016;37:E33-76.
49. Fusaroli P, Jenssen C, Hocke M, *et al*. EFSUMB guidelines on interventional ultrasound (INVUS), Part V-EUS-guided therapeutic interventions (short version). *Ultraschall Med* 2016;37:412-20.
50. Ignee A, Jenssen C, Hocke M, *et al*. Contrast-enhanced (endoscopic) ultrasound and endoscopic ultrasound elastography in gastrointestinal stromal tumors. *Endosc Ultrasound* 2017;6:55-60.
51. Tsuji Y, Kusano C, Gotoda T, *et al*. Diagnostic potential of endoscopic ultrasonography-elastography for gastric submucosal tumors: A pilot study. *Dig Endosc* 2016;28:173-8.
52. Kim SH, Yoo IK, Kwon CI, *et al*. Utility of EUS elastography in the diagnosis of gastric subepithelial tumors: A pilot study (with video). *Gastrointest Endosc* 2020;91:172-700.
53. Lisotti A, Serrani M, Caletti G, *et al*. EUS liver assessment using contrast agents and elastography. *Endosc Ultrasound* 2018;7:252-6.
54. Jafri M, Sachdev AH, Khanna L, *et al*. The role of real time endoscopic ultrasound guided elastography for targeting EUS-FNA of suspicious pancreatic masses: A review of the literature and a single center experience. *JOP* 2016;17:516-24.
55. Facciorusso A, Martina M, Buccino RV, *et al*. Diagnostic accuracy of fine-needle aspiration of solid pancreatic lesions guided by endoscopic ultrasound elastography. *Ann Gastroenterol* 2018;31:513-8.
56. Soares JB, Iglesias-Garcia J, Gonçalves B, *et al*. Interobserver agreement of contrast-enhanced harmonic endoscopic ultrasonography in the evaluation of solid pancreatic lesions. *Endosc Int Open* 2015;3:E205-9.
57. Giovannini M, Thomas B, Erwan B, *et al*. Endoscopic ultrasound elastography for evaluation of lymph nodes and pancreatic masses: A multicenter study. *World J Gastroenterol* 2009;15:1587-93.
58. Dietrich CF, Săftoiu A, Jenssen C. Real time elastography endoscopic ultrasound (RTE-EUS), a comprehensive review. *Eur J Radiol* 2014;83:405-14.
59. Dietrich CF, Arcidiacono PG, Braden B, *et al*. What should be known prior to performing EUS? *Endosc Ultrasound* 2019;8:3-16.
60. Cosgrove D, Piscaglia F, Bamber J, *et al*. EFSUMB guidelines and recommendations on the clinical use of ultrasound elastography. Part 2: Clinical applications. *Ultraschall Med* 2013;34:238-53.
61. Hirooka Y, Kuwahara T, Irisawa A, *et al*. JSUM ultrasound elastography practice guidelines: Pancreas. *J Med Ultrason* (2001) 2015;42:151-74.
62. Dong Y, D'Onofrio M, Hocke M, *et al*. Autoimmune pancreatitis: Imaging features. *Endosc Ultrasound* 2018;7:196-203.
63. Tana C, Schiavone C, Ticinesi A, *et al*. Ultrasound imaging of abdominal sarcoidosis: State of the art. *World J Clin Cases* 2019;7:809-18.
64. Havre RF, Waage JR, Gilja OH, *et al*. Real-time elastography: Strain ratio measurements are influenced by the position of the reference area. *Ultraschall Med* 2012;33:559-68.
65. Carlsen JF, Pedersen MR, Ewertsen C, *et al*. A comparative study of strain and shear-wave elastography in an elasticity phantom. *AJR Am J Roentgenol* 2015;204:W236-42.
66. Carlsen JF, Ewertsen C, Săftoiu A, *et al*. Accuracy of visual scoring and semi-quantification of ultrasound strain elastography-a phantom study. PLoS One 2014;9:e88699.
67. Havre RF, Elde E, Gilja OH, *et al*. Freehand real-time elastography: Impact of scanning parameters on image quality and *in vitro* intra-and interobserver validations. *Ultrasound Med Biol* 2008;34:1638-50.
68. Dietrich CF, Jenssen C. Modern ultrasound imaging of pancreatic tumors. Ultrasonography 2020;39:105-113.