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Endoscopic Ultrasound Elastography: An Emerging Clinical Tool

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Endoscopic ultrasound (EUS), a technology developed in the 1980s, has become well established in clinical practice throughout the world. EUS has proven to be beneficial in diagnosis and staging of a wide variety of pathologies throughout the gastrointestinal (GI) tract and has progressed throughout the years, with inclusion of tissue sampling and therapeutic procedures such as gallbladder (GB) or common bile duct (CBD) drainage, pseudocyst drainage and necrosis management. In terms of technology, the introduction of Doppler provided an ability to view vasculature. Moreover, in recent years, there has been an expansion in EUS technology, principally with ability to perform EUS Elastography (EUS-EG) and Contrast Enhanced EUS (CE-EUS).[1] Elastography (EG) is a noninvasive imaging modality of tissue evaluation that characterizes mechanical properties of tissues. Changes in tissue stiffness and/or elasticity have been theorized as a possible marker of either inflammation, fibrosis, or neoplastic infiltration.[2,13] EG has been studied for potential noninvasive diagnosis for several pathologies, even cancers, given the altered elasticity with increased tissue stiffness in different diseases.[10]

EUS-EG refers to the application of elastography within the imaging capability and platform of EUS. EUS-EG has been primarily deliberated as a novel approach to assess tissue in the pancreas, but more recently investigators are examining this approach to other areas in the GI tract and hepatobiliary system. Real time elastography (RTE) is the use of ultrasound along with the measuring of stress applied to the tissue being studied; comparing it to the strain/deformation it produces. RTE measures strain (compression causing tissue deformation) within the region being studied while being visualized with a color overlay on B-mode ultrasonography.[2] EUS-RTE allows estimation of the stiffness of tissues, which are approachable through the GI tract, and may allow early stage differentiation of

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benign and malignant tissues.[2-5] Tissue diagnosis, including EUS-guided fine needle aspiration/biopsy (EUS-FNA/FNB) is the gold standard for the diagnosis of malignancies (in the GI tract, including pancreatic cancer). While some groups have attempted to describe EUS-EG as having the potential to provide a "virtual biopsy",[59] in reality, most agree that such technologies may at best act as an adjunct to biopsy and tissue diagnosis.[2-5]

The present article is intended to provide endoscopists a comprehensive review of this novel technology, while appraising the literature on it, and contemplating its potential uses in clinical practice.

[I]. How is EUS-EG Performed?

There are two different modalities of EUS-EG: qualitative and quantitative.

Qualitative Elastography

Qualitative elastography is an objective measurement of the compression of tissues using a B-mode ultrasound image as an indicator of stiffness.[1,10] This modality detects the deformations from compression on a B-mode ultrasound image on regions of interest (ROI).[1,10,12] Prior to evaluating the ROI, a sufficient basis of either reference tissue (normal tissue) surround the ROI is imperative. Dietrich et al. suggest the most accurate images were achieved when the target lesion was about 25-50% of the ROI.[2] In this mode of imaging, it is also imperative to avoid large blood vessels, so as to minimize flow related motion artifact.[1,10,12] In qualitative measurement, elasticity (stiffness) can be measured in a number scale that corresponds with a color scheme. Stiff tissue on elastography is seen as a darker blue; intermediate tissue as green; medium tissue (less hard than intermediate) as yellow; and soft tissue as red.[1,10,12] The elastographic pattern is performed and reviewed as a color pattern that overlays a classic B-mode ultrasound picture.[1,10,12]

Quantitative Elastography

Strain Ratio (SR)

In addition to qualitative data, SR can be calculated by measuring mean strain of the reference area/lesion divided by the mean strain in total ROI. This ratio depends on the important assumption that strain is evenly distributed throughout the entire ROI.[2] Two different regions (Region-1 and Region-2) are chosen for qualitative analysis. Region-1 includes the largest amount of target lesion possible with the smallest amount of surrounding normal parenchyma. Region-2 includes the softer (higher density of red) areas of ROI that do not include the target lesion.[1,10] The strain of the ROI is then compared to a region of normal surrounding tissue (reference) that receives similar stress.[2] SR quantifies the difference of strain in the areas within the same ROI.[2]

Histogram Analysis

In a strain histogram (SH), a diverse distribution of different strain patterns obtained qualitatively can be statistically analyzed and measured for quantitative evaluation,[2] allowing depiction of range and overall pattern of strain through much of the ROI. The SH represents elasticity measured qualitatively from 0 (hardest) until 255 (softest) along the X-axis,[1] and the important parameters being mean strain, standard deviation of the mean, percentage of blue area, and complexity of blue area. The shape of the SH is described by a distribution of numbers that reflects the homogeneity of the color pattern studied in an elastography image.[2,6-9]

[II]. EUS-EG of the Pancreas

EUS allows high-resolution imaging of the pancreas aiding in accurate diagnosis (and staging) of chronic, cystic, inflammatory and neoplastic pancreatic disorders. However, EUS cannot reliably differentiate between cancer and focal pancreatitis, with only B-mode imaging,[12] and this is a potential area where EUS-EG may add worth. This was first evaluated by Hiroka et al.[13] The normal parenchyma of the pancreas appears homogenously green on EUS-EG (soft tissue), a well-defined reproducible characteristic.[12]

a. Solid Masses

The imaging of pancreatic lesions has been historically performed using abdominal ultrasound, CT, MRI, and PET scan.[14] The aggressiveness and morbidity of pancreatic cancer (PC) have made it imperative to discover alternative methods to assist with the diagnosis. EUS-FNA/FNB is most commonly used diagnostic modality, with a high

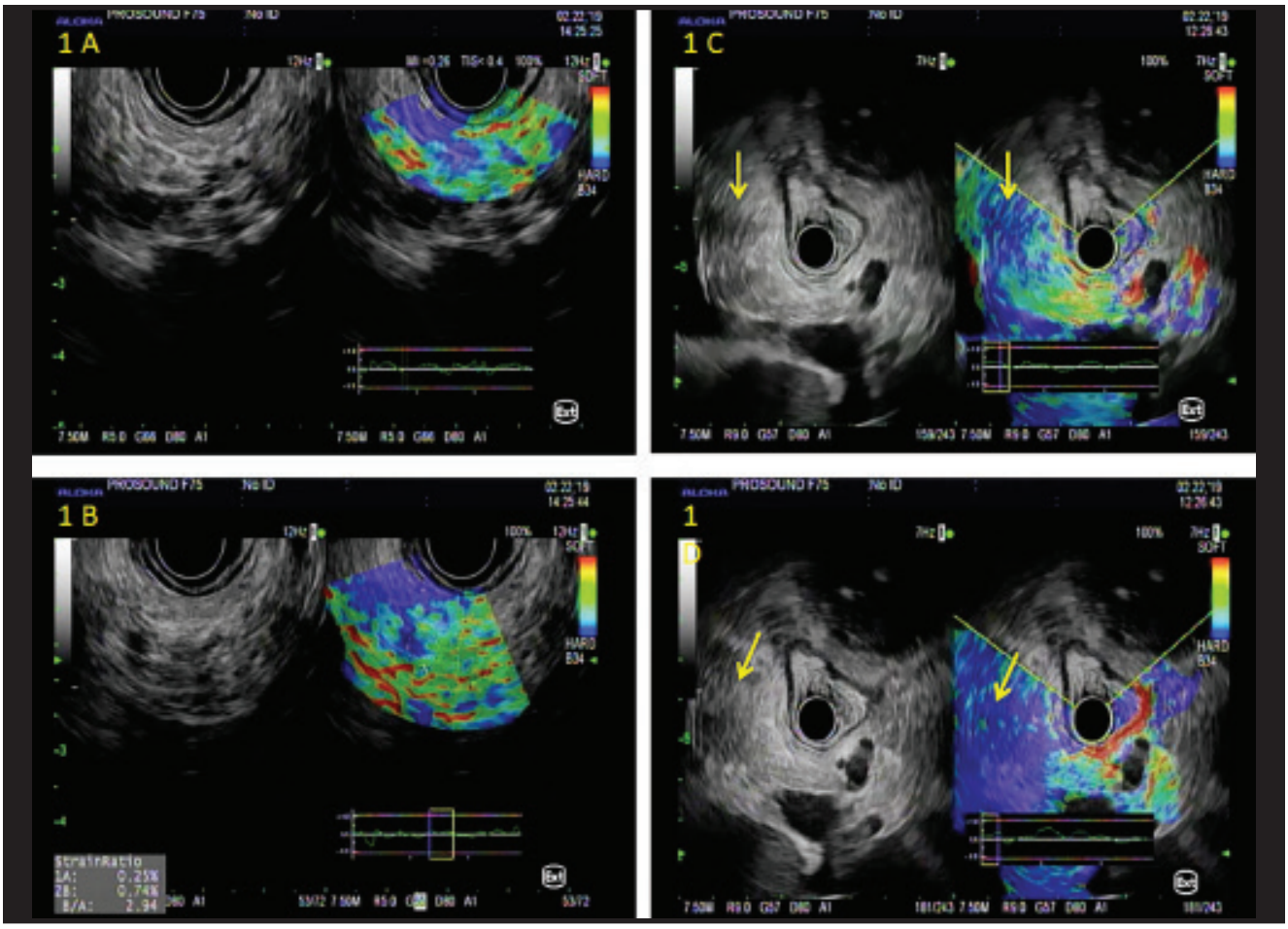

Figure 1. EUS-EG on a patient with suspected early CP, demonstrating predominantly intermediate (green) and stiff (blue) patterns on qualitative exam (1A) and SR of 2.94 on quantitative evaluation (1B), Patient with recent attack of acute pancreatitis referred for EUS demonstrating predominantly stiff (blue) pattern in proximal body and neck (yellow arrow), while intermediate (green) pattern in distal body and tail (1C and 1D).

specificity but a lower sensitivity, and EUS-EG had been proposed as an alternative or adjunct method to detect masses and even predict malignant potential. This was conceived because of the belief of increased stiffness (decreased elasticity) with malignant pancreatic lesions.[15]

Qualitative Analysis

In 2006, Giovannini et al. studied the use of EUS-EG in the qualitative analysis of 24 solid pancreatic lesions, and using color patterns of the image, they were scored with blue lesions being malignant.[16] The authors described a 5-point scoring system for description of a solid pancreatic mass: 1 = normal pancreatic tissue with mainly predominantly (mostly homogenously) green color pattern; 2 = little degree of fibrosis with increased heterogeneity, but still in the soft tissue range, which meant green with some shade of yellow and red; 3 = concerning for an early PDAC, with presence of blue with minimal heterogeneity; 4 = presence of neuroendocrine tumor or possible metastases, with area of green surrounded by a larger area of blue (less elastic tissue); 5 = advanced PDAC, with predominantly blue elastographic image, and some heterogeneity suggesting tissue necrosis.[16] In this study, although limited by size, the sensitivity and specificity for predicting malignancy was 100% and 67% respectively[16].

Giovannini et al. published in 2009 a follow up multicenter study where 121 pancreatic lesions were analyzed with qualitative EUS-EG,[18] using the same scoring system as above, and attributed 1-2 as benign, 3 as indeterminate and 4-5 as

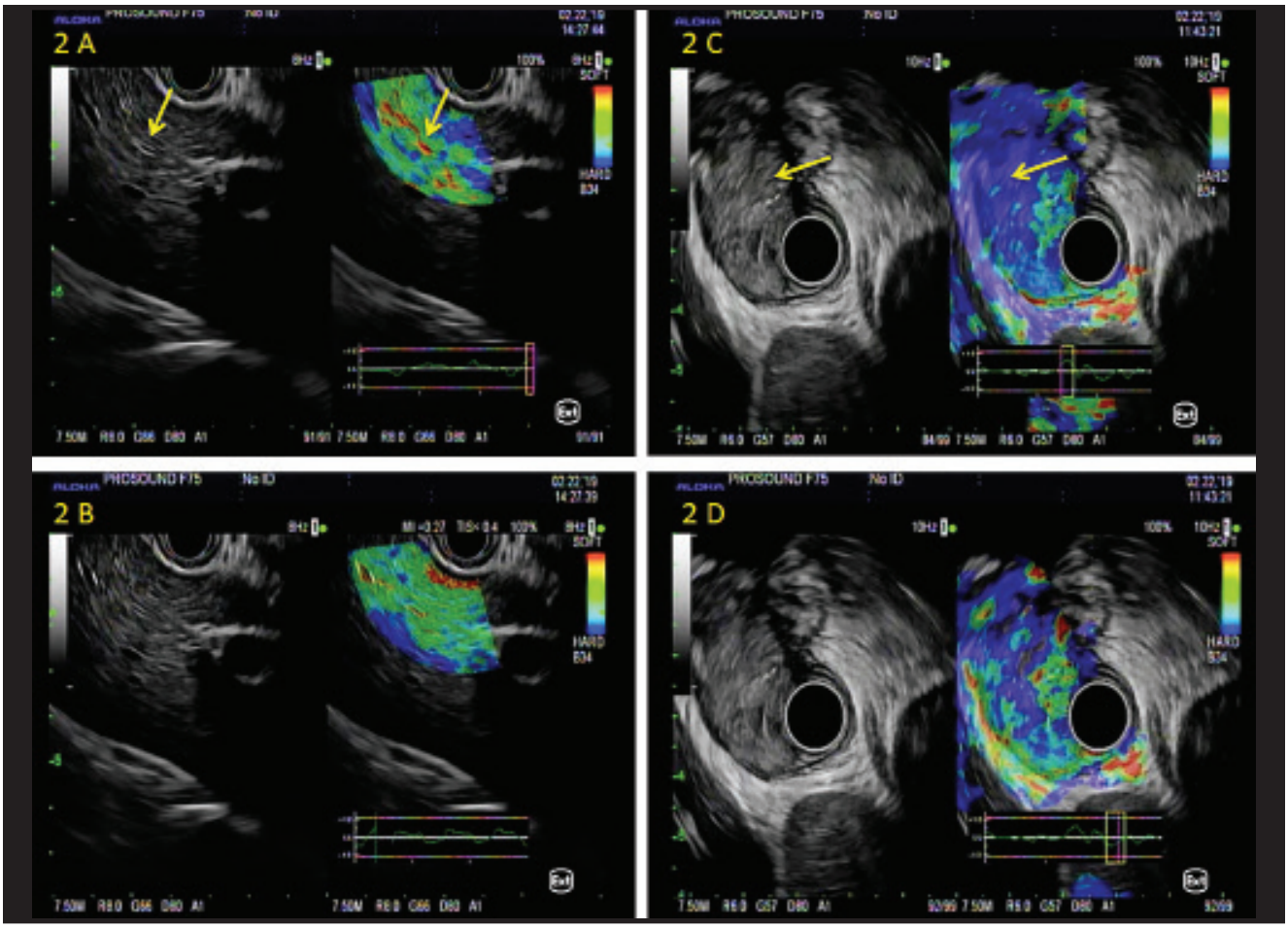

Figure 2. EUS-EG of liver, demonstrating soft (red) pattern of blood vessels (yellow arrow), while the remainder of liver parenchyma is intermediate (green) pattern (2A and 2B). Patient with esophageal mass, with EUS-EG evaluation demonstrating predominantly hard/stiff (blue) pattern (2C and 2D), fine needle biopsy of which demonstrated adenocarcinoma.

malignant. This EUS-EG was then compared to final pathology obtained using EUS-FNA or surgical pathology. The sensitivity and specificity of EUS-EG to differentiate between malignant and benign masses were 92.3% and 80.6% respectively, and positive (PPV) and negative predictive values (NPV) were 93.3% and 78.1% respectively, with a global accuracy of 89.2%. The study had 7 false negatives, which authors attributed to lesions with necrotic tissue and/or high vascularity, which would be read as softer tissue on EG images. The authors, however, acknowledged inter-observer variability of images leading to difficulties with interpretation.[18] Similarly, Iglesias-Garcia et al. used qualitative EUS-EG to analyze 20 controls (with a homogenous green pattern) and 130 pancreatic lesions, which included 78 malignant lesions (77 PDAC, 1 metastatic), 42 inflammatory mass (CP) and 10 neuroendocrine tumor (3 insulinoma, 1 glucagonoma, 5 non-functioning).[17] For the diagnosis of malignancy, EUS-EG was found to have a sensitivity of 100 % and specificity of 85.5%, with PPV of 90.7% and NPV of 100%, and overall accuracy of 94%. In this study, the elastographic images were evaluated by a single endosonographer, who was blinded to the pathology, and a second operator re-evaluated the same images, blind to both clinical information and histopathological diagnosis.[17] The authors noted that with patients of CP, inflammation could be particularly difficult to image and may be confused with malignancy, and hence emphasized on need for histopathological diagnosis for an accurate and proper diagnosis.[17]

Jannsen et al. studied qualitative EUS-EG to evaluate normal pancreas (n=20), CP (n=20), focal pancreatic lesions (n=33), and elastographic patterns were classified in terms of homogeneity and color.[19] Elastographic homogeneity was classified into three types: 1 = homogenous; 2 = inclusive of 2 or 3 colors; 3 = "honeycomb" pattern, while elastographic color patterns were represented with letters A = blue; B = green/yellow; C = red.[19] To discern between benign pancreatic lesion and malignancy, the authors achieved a sensitivity of 93.8%, however, compared to other studies, a lower specificity and accuracy of 65.4% and 73.5% respectively. The authors also noted an overlap in their elastographic images between CP and pancreatic neoplasm,[19] as well as low PPV for pancreatic neoplasms. This led authors to conclude that advanced CP is difficult to differentiate from hard pancreatic masses on EUS-EG,[19] and hence emphasized EUS-EG cannot be a standalone diagnostic indicator, and it must be used as complement or supplement tissue diagnosis.[19] Hirche et al. reported challenges in evaluating a ROI lesion greater than 35 mm in diameter with EUS-EG, lesions with increased distance from the transducer, and due to presence of fluid,[20] and hence low sensitivity and specificity of 41% and 53% along with an accuracy of 45%.[20]

Quantitative Analysis

Iglesias-Garcia et al. in 2010 evaluated 86 patients with pancreatic masses using EUS-EG to analyze their SR,[21] which was found to higher with patients with malignant lesions when compared to inflammatory masses, and both had higher SR than normal pancreas.[21] The authors inferred that quantitative EUS-EG with SR was more accurate than qualitative EUS-EG, with a sensitivity and specificity of 100% and 92.9%. Through the years, multiple other studies have evaluated the SR for differentiation of malignant lesions, and cut-off values have varied from 3.7 to 24, resulting in sensitivity ranging between 67-98% and specificities between 45-71%.[22-27]

In 2008, Saftoiu et al., in a prospective study, evaluated the hue-histogram quantitative EUS-EG[28] (22 controls with normal pancreas, 11 CP, 32 PDAC, 3 NET). Each EUS-EG image collection was reported as a numerical value in the form of a vector value (a number from 1 to 256). A frame of 10 images was given a value, and the mean of 10 frames was defined as the mean value.[28] With a defined cutoff value of 175, the authors achieved a sensitivity of 91.4%, specificity of 87.9% with an accuracy of 89.7% to differentiate between benign and malignant masses, with PPV 88.9%, and NPV 88.9%. A major limitation of this study was inclusion of normal pancreas, which could have been used as a reference point for normal EUS-EG characteristics.[28] When the authors analyzed the data for diagnosis of focal masses excluding normal pancreas, the sensitivity remained similar at 93.8%; however, the specificity dropped down to 63.6% with an accuracy of 86.1%, which raises doubt on the ability of EUS-EG to differentiate between benign and malignant masses.[28] In a subsequent multi-centric study, the same authors evaluated hue histogram quantitative EUS-EG on 258 patients (211 PDAC and 47 CP).[7] Using the same methodology and cut-off, the analysis yielded a sensitivity, specificity, and accuracy of 93.4%, 68.9%, and 85.4% respectively, with NPV 68.9% and PPV 92.5%.[7]

EUS-EG using SR was compared to contrast-enhanced EUS (CE-EUS) for diagnosis of 62 consecutive solid pancreas lesions.[29] The authors concluded that the overall accuracy for determination of malignancy using combination of EUS-EG and CE-EUS was comparable to EUS-guided tissue acquisition (91.9% vs. 91.5%), which was not higher than EUS-EG (98.4%) or CE-EUS (85.5%) when used alone. Thus combining the two modalities does not offer additional diagnostic advantage. A meta-analysis from 2012 evaluating 13 studies with 1042 patients with solid pancreas masses found a pooled sensitivity and specificity of 95% and 69% respectively, for EUS-EG for differentiating benign from malignant lesions.[36] A subsequent meta-analysis from 2017 on 19 studies with 1687 patients echoed the previous overall results, but did not find any statistical difference between qualitative and quantitative EUS-EG for accurate diagnosis of malignant pancreatic lesions.[14] The authors proposed both qualitative and quantitative EUS-EG as valuable complementary techniques to EUS-FNA for accurate differentiation of solid pancreas lesions.[14]

(continued on page 18)

(continued from page 16)

Similar results were reported from a recent multi-centric study on small solid pancreatic masses, where EUS-EG determined the lesions to be less/equally stiff as surrounding parenchyma (soft lesions) or stiffer (hard lesions).[62] The authors noted that EUS-EG can rule out malignancy with high level of certainty if the lesion appears soft, while stiff lesions can be benign or malignant.[62]

b. Chronic Pancreatitis (CP)

The diagnosis of CP is challenging because of the histopathologic diversity and variable clinical presentation. EUS is utilized as a diagnostic modality for early CP in clinical practice, by evaluation of parenchymal and ductal features, as defined by Rosemont criteria (RC);[58] however, it has limitations, which include a lack of heterogeneity for a number and/or a threshold for diagnosis. Furthermore, Rosemont criteria have poor reproducibility and insufficient histopathological correlation.

A study on consecutive 191 patients with epigastric pain or known CP using EUS-EG with SR and comparison with standard EUS-RC, suggested a strong direct linear correlation between the number of EUS-RC and the SR ($r=0.813$; $P<0.0001$, ROC area 0.949).[57] The authors estimated EUS-EG accuracy of 91.1% for diagnosing CP (with cut-off SR of 2.25).[57] In a subsequent study, 96 patients with known CP, pre-classified as 4 stages of RC (normal, indeterminate for CP, suggestive of CP, and consistent with CP) were subjected to EUS-EG.[55] The 'mean-value' of each group, which negatively correlated with pancreatic fibrosis was calculated using histogram analysis, and found to be 90.1 ± 19.3, 73.2 ± 10.6, 63.7 ± 14.2, and 56.1 ± 13.6, respectively. The 'mean-values' were significantly different between different stages, and there was a significant negative correlation between 'mean-value' and number of EUS-RC features ($r_s = -0.59$, $p < 0.001$). Regression analysis demonstrated that hyperechoic foci with shadowing and lobularity with honeycombing were most important diagnostic variables. While the authors hence provided an objective diagnostic apparatus for potential use as an adjunct to qualitative RC,[55] the limitations of the study were evident, including lack of reproducibility of EUS-EG images and image influence by ROI size/position, and amount of strain applied.

CP also results in pancreatic exocrine insufficiency (PEI), resultant from tissue fibrosis and loss of acinar cells, the measurement of which includes inefficient/inadequate testing including 72-hour quantification of fecal fat, C-mixed triglyceride breath test (infrequently available), fecal elastase/chymotrypsin (measure secretion and not digestion). Dominguez-Munoz et al. have attempted to utilize EUS-EG as a tool to quantify fibrosis, as a surrogate for PEI in patients with CP.[56] In this single center prospective study, 115 patients (22 undetermined, 49 suggestive, 44 consistent with CP) were included, 35 of which had pre-determined PEI using C-MTG (^{13}C-mixed triglyceride) breath test. EUS-EG was performed by EUS experts blinded to PEI results, and SR was calculated. The authors observed higher SR in patients with PEI, compared to those with normal breath test (4.89 vs. 2.99), and the probability of PEI increased linearly with SR (4.2% with SR < 2.5, and 92.8% with SR > 5.5). The authors proposed adding EUS-EG with SR as an adjunct in EUS evaluation of CP, to act as surrogate for pancreatic fibrosis and likelihood of PEI. However, reproducibility of EUS-EG results remains a major limitation in this study also, in addition to use of C-MTG breath test for estimation of PEI, as opposed to a more reliable test (coefficient of fat absorption, CFA quantification).

[III]. EUS-EG of Lymph Nodes

EUS can accurately image several groups of lymph nodes (LNs); however, EUS imaging alone cannot differentiate benign from the malignant ones. Attempts have been made to predict malignant potential, using EUS features like round shape, hypoechoic intensity, >10 mm size, and sharp margins, but have been suboptimal, with low specificity. Endoscopists have to ultimately resort to FNA of the LN for accurate diagnosis, which may have difficulties and complications. EUS-EG has been tried for the detection of malignant LNs in a wide variety of malignancies (GI tract and hepatobiliary system).

Giovannini et al.[16] from France evaluated 31 LNs from 25 patients (3 cervical, 17 mediastinal, 5 celiac, 6 aortocaval) using qualitative EUS-EG (blue=malignant, green=benign) to predict

Table 1. List of Studies that Evaluated EUS-EG for Pancreatic Solid Masses

Year/Author	# of EUS (# of patients)	% of Malignant Masses	Reference Point for Diagnosis	EUS-EG Method for Diagnosis	Sensitivity	Specificity	Cut off
2006 Giovannini et al.[16]	24 (24)	75	EUS-FNA, surgical pathology	Qualitative/color pattern	100%	67%	Blue predominance
2007 Janssen et al.[19]	33 (33)	81.8	EUS-FNA, surgical pathology,	Qualitative/color pattern	93.8%	65.4%	Blue predominance
2008 Saftoiu et al.[28]	43 (43)	74	EUS-FNA, surgical pathology, follow up	Hue histogram (quantitative)	91.4%	87.9	175 mean value
2009 Giovannini et al.[18]	121 (121)	76	EUS-FNA, surgical pathology	Qualitative/color pattern	92%	80%	Blue predominance
2009 Iglesias-Garcia et al.[17]	130 (130)	67.7	EUS-FNA, surgical pathology, follow up	Qualitative/color pattern	100%	85%	Blue predominance
2010 Iglesias-Garcia et al.[21]	86 (86)	67.4	EUS-FNA, surgical pathology, follow up	Qualitative/color pattern or strain ratio (quantitative)	100%	92%	SR cut off 6.04 or Blue predominance
2010 Saftoiu et al.[30]	54 (54)	61.1	EUS-FNA, surgical pathology, follow up	Hue histogram (quantitative)	84%	76.2%	175
2011 Itokawa et al.[52]	86 (86)	93	EUS-FNA, surgical pathology	Qualitative/color pattern	98.6%	64.3%	Blue predominance
2011 Saftoiu et al.[7]	258 (258)	81.8	EUS-FNA, surgical pathology, follow up	Hue histogram (quantitative)	93%	66%	170
2012 Dawwas et al.[22]	111 (104)	83.8	EUS-FNA, surgical pathology, follow up	Strain ration (quantitative)	95.7%	16.7% (with cutoff 6.04)	6.04
2012 Figueiredo et al.[23]	47 (47)	72	EUS-FNA, surgical pathology, follow up	Strain ration (quantitative)	90%	75%	8
2012 Hocke et al.[32]	58 (58)	32.8	EUS-FNA, surgical pathology, follow up	Qualitative/color pattern	94.7%	33.4%	Blue predominance
2014 Havre et al.[24]	48 (39)	37.5	EUS-FNA, surgical pathology, follow up	Qualitative/color pattern or strain ratio (quantitative)	67%	71%	4.4 or Blue predominance
2015 Kongkam et al.[25]	38 (38)	76.3	Surgical histopathological and cytological diagnosis	Strain ration (quantitative)	86.2%	66.7%	3.17
2015 Opacic et al.[33]	105 (105)	55.2	EUS-FNA, surgical pathology, follow up	Hue histogram (quantitative)	100%	46%	86
2016 Mayerle et al.[26]	91 (91)	74.7	EUS-FNA, surgical pathology, follow up	Strain ration (quantitative)	96% 77%	43% 65%	SR 10 (SR 24.82)
2017 Chantarojanasiri[54]	136 (136)	69.9	EUS-FNA, surgical pathology	Qualitative/color pattern	67.4%	70.7%	Blue predominance
2017 Iglesias-Garcia et al.[29]	62 (62)	74.2	EUS-FNA, surgical pathology, follow up	Strain ration (quantitative)	100%	92%	10
2017 Okasha et al.[35]	172 (172)	71.5	EUS-FNA, surgical pathology	Qualitative/color pattern or strain ratio	92%	77%	7.8 or Blue predominance

malignant potential, and reported sensitivity of 100%, specificity of 50% when compared to EUS-FNA or surgical pathology, thus opening an avenue for further research in this area.[16] Subsequently, they pooled their data with other European centers (101 LNs),[18] with reported sensitivity of 91.8%, specificity 82.5%, PPV 88.8%, NPV 86.8% and overall accuracy of 88.1% for qualitative EUS-EG prediction of malignant LNs.[18] Subsequently, Saftiou et al. evaluated quantitative EUS-EG on 42 LNs and noted slightly improved sensitivity (95.8% vs. 91.7%) and accuracy (95.2% vs. 92.9%) and at-par specificity with qualitative EUS-EG; they proposed use of EUS-EG as an adjunct to tissue diagnosis of LNs.[40] A similar study on 66 LNs noted that 31/37 benign LNs had largely homogenous pattern, and 23/29 malignant LNs had predominantly hard pattern, yielding high overall accuracy with good inter-observer agreement for prediction of malignant LNs.[39] A meta-analysis on 431 LNs in 368 patients suggested sensitivity of 88% and specificity of 85% for EUS-EG differentiation of benign and malignant LNs, further endorsing its potential for use as an adjunct screening method.

Knabe et al. utilized EUS-EG in LN staging in esophageal cancer patients.[42] The authors evaluated 40 LNs, 21 of which were confirmed malignant by cytology/surgical histopathology, and observed that EUS-EG evaluation of LNs yielded a sensitivity of 100%, specificity of 64.1% and PPV of 75%. As a secondary step the investigators employed computer based analysis of elastographic images, which increased specificity to 86.7%, with a slight drop on sensitivity to 88.9%.[42] The authors hence proposed a potential role for EUS-EG in clinical staging of malignancies. Likewise, SR (with cut-off at 7.5) has been reported to have better sensitivity (83%) and specificity (96%) than conventional EUS characteristics for determining malignant nodal disease in esophago-gastric cancer, with an overall accuracy of 90%.[44] Similarly, analysis of 55 LNs in 75 patients with biliary malignancies (40 cholangiocarcinoma, 35 galbladder cancer) suggested sensitivity of 96% and specificity of 89% with EUS-EG for malignant nodal disease.[45]

However, in a contrasting report, Larsen et al. compared EUS, qualitative EUS-EG and quantitative EUS-EG to histology, to determine the most accurate method of loco-regional staging.[43] In 56 patients with upper GI cancers planned for surgery, regional LNs were evaluated with EUS, and qualitative and quantitative EUS-EG before EUS-FNA/B was performed. The sensitivity of EUS for differentiating malignant from benign LNs was 86%, compared to 55-59% with EUS-EG.[43] These divergent results do not support that qualitative or quantitative EUS-EG being better than conventional EUS for differentiation of malignant LNs.[43]

Based on the available literature, it may be prudent to screen LNs using EUS-EG and then perform EUS-FNA/B on those that are predominantly hard and blue on EUS-EG patterns or with high SR. Even with obvious merits including no/minimal change in time of procedure or cost, and avoidance of complications associated with attempted FNA/B of small LNs, wide adoption of this as a protocol is hindered by lack of standardization for diagnosis and the small number of supportive studies.

[IV]. EUS-EG of the Liver and Biliary Tract

Data on use of EUS-EG in liver are limited to a single study in 2009 reporting EUS-EG for solid hepatic masses.[63] Additionally, this qualitative technique was utilized to evaluate the bile duct in 41 patients (20 with IBD/PSC and 21 controls),[49] where the investigators noted a stiff/intermediate elastography score in 16 patients (compared to 4 controls), while 17 controls and 4 patients had a soft score, and proposed using this technology as non-invasive screen for PSC in IBD patients.[49] However, no further developments happened in these areas.

While liver biopsy is the gold standard to determine degree of fibrosis in patients with chronic liver disease, similar assessment with Elastography (Fibroscan™) is an established non-invasive office-based approach, practiced widely.[47] More recently, a study from Boston reports computation of liver fibrosis index (LFI) by utilizing EUS-EG images, and noted significantly increased mean LFI in patients with cirrhosis, when compared to those wit fatty liver (3.2 vs. 1.7, p=s) and normal liver (3.2 vs. 0.8, p=s). Similarly, significant increase was noted in fatty liver group compared to normal

(continued on page 22)

(continued from page 20)

liver (1.7 vs. 0.8, p=s)[46]. While this single center, single endoscopist study demonstrates that LFI can be reliably computed from EUS-EG images, and correlates with abdominal imaging, but small number of cirrhosis patients (n=8) is a major hindrance to its widespread adoption. Nevertheless, this approach may have potential advantages over trans-abdominal elastography approach; including better signal penetration through thin gastric wall, compared to skin and subcutaneous fatty layer in obese patients, and deserves to be investigated further.

[V]. EUS-EG of the GI Tract

EUS is widely utilized to view the layers of GI tract, to identify and characterize any thickenings or lesions, to evaluate depth of lesions as well as differentiate between T1a and T1b lesions to determine their best management strategy. Limited literature is available for EUS-EG in various subepithelial lesions, rectal lesions and in IBD patients, as discussed here.

a. Subepithelial Lesions (SELs)

Very sparse data exists on use of EUS-EG for evaluation of SELs. A small study of 25 patients with gastric SELs evaluated with EUS-EG using Giovannini elastic score, and higher elastic score were found in patients with GIST (stiffer lesions) than pancreas rests, leiomyomas, schwannomas, all with low/medium elastic scores (soft/mixed lesions).[52]

The results may suggest that benign SELs have homogenous strain pattern, representing low/intermediate elasticity/stiffness, while lipomas are generally homogenous soft. For detection of malignant SELs, conventional EUS features include size >30-40 mm, presence of ulcer or irregular contour, heterogenous appearance, or presence of LN involvement, and on EUS-EG they appear to have a heterogenous pattern with predominantly stiff pattern.[12,52]

b. Trans-rectal EUS-EG

Transrectal EUS-EG (TRUS-EG) has been evaluated for diagnosis of benign and malignant rectal tumors and fecal incontinence. Waage et al. evaluated 69 patients with TRUS-EG and reported sensitivity 91%, specificity 87% and accuracy 90% for detection of malignant rectal tumors, with best SR cut-off value of 1.25 as evaluated with ROC analysis.[54]

c. IBD

As a pilot effort, Rustemovic et al. evaluated the use of TRUS-EG for the diagnosis and characterization of IBD (and phenotype).[53] 55 IBD patients (30 CD, 25 UC) and 28 non-IBD controls were subjected to TRUS-EG and significant difference in rectal wall thickness and SR was noted between CD patients (even in patients without rectal involvement) and controls. Similarly, difference in rectal wall thickness was also found in patients with active UC, compared to quiescent UC. Interestingly, significant difference in rectal wall thickness and SR was also found between CD and UC patients, especially patients with active CD having much higher SR than active UC.[53] The authors felt a potential for EUS-EG as a modality to differentiate between UC and CD, and also to evaluate tissues for diseases with transmural inflammation.

[VI]. Future Directions in use of EUS-EG

a. Combination of EUS-EG and CE-EUS

Contrast enhanced endoscopic ultrasound (CE-EUS) is another emerging clinical modality, which may assist in diagnosis of solid masses. CE-EUS is reported to have a high specificity and sensitivity for the diagnosis of PDAC.[29] Multiple retrospective studies evaluating CE-EUS and EUS-EG have postulated a potential benefit of combining the two modalities for diagnosis of solid lesions, but have agreed to need for further evidence.[23,30,32,34] The study by Iglesias-Garcia et al., which defined the accepted SR and strain histogram numbers used by future studies, analyzed 62 solid pancreatic lesions with CE-EUS, SR EUS-EG and strain histogram EUS-EG, and reported better numbers with EUS-EG than CE-EUS.[29]

b. EUS-EG and EUS-FNA/B

EUS-FNA/B is well accepted as gold standard for tissue diagnosis of PDAC, but may have potential for false negatives, and hence many authors suggest benefits of EUS-EG as adjunct, especially in cases when malignancy is strongly suspected, but negative or indeterminate EUS-FNA/B results.[59] In a study of 28 solid pancreatic

lesions, EUS-FNA alone versus combination of results of FNA and SR provided sensitivity of 90% versus 95.2% and NPV 80% versus 83.3%, thus suggesting that negative results of both EUS-FNA and SR together were more reliable to exclude malignant solid pancreatic lesions.[25] The European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) guidelines now advocate for EUS-EG as a diagnostic aid, rather than first line for diagnosis.[60]

[VII]. Challenges with EUS-EG

While we have highlighted the literature on EUS-EG in various fields of study, EUS-EG is yet not mainstream in North America given several limitations in its technology, wide gaps in literature and lack of widespread commercial availability. The foremost amongst its technical limitations is lack of standardization in EUS-EG procedure, particularly in quantitative assessments of stiffness, which hinders its usage in clinical practice, even at centers that it is available. Equally importantly, this technique is also inundated by the fact that it is highly operator dependent, and the results are based on subjective analysis of relative stiffness compared to surrounding tissue.[1,2,10,12,17,18] Evaluation is also highly dependent on choosing ROI, which can lead to selection bias at the very outset.[1,18] In addition to strong operator dependence, what is even more bothersome is limited reproducibility of these findings. The subjectivity of tissue compression is also another well-known limitation of EUS-EG. Motion artifact due to cardiac and respiratory movements can cause increased difficulty in obtaining an accurate image.[2,10] To add to technical struggle, excessive compression of parenchyma can potentially lead to inaccurate strain measurement, making the results inconsistent. Also, imposing structures, which include the heart and other major vessels, must be avoided in order to obtain accurate images as well. Furthermore, in EUS-EG, the applied stress value is an unknown factor; therefore, the operator can never get an absolute elasticity value (through the calculation with Young's modulus). Finally, EUS-EG does require technical skill and extensive training in order to produce high quality image, and the length of training to be proficient in EUS-EG is not yet defined. With all these technical limitations, its not surprising that EUS-EG has had a restricted scope of growth.

[VIII]. Conclusions

From the multiple studies evaluating EUS-EG, it can be safely concluded that EUS-EG cannot replace tissue diagnosis, but there are several conceivable merits that value its candidacy as an able adjunct to clinical diagnosis. While EUS-EG may not have sensitivity, specificity and accuracy of the highest order to definitively diagnose a malignancy, but in combination with EUS-FNA/B it may provide an improved negative predictive value to safely exclude one. Clinicians who practice EUS-EG see in this technology a great potential for an additive study to supplement the histopathologic diagnosis, and those who do not practice it may feel overwhelmed by its technological limitations and operator learning curve. As the saying goes, "New technology is not good or evil in and of itself. It's all about how people choose to use it". It remains to be seen how EUS-EG is adopted from this point on. ■

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