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Endoscopic Ultrasound Elastography for Solid Pancreatic Lesions: Ready to Replace Fine-needle Biopsy?

Solid pancreatic lesions (SPLs) have a broad etiology with pancreatic adenocarcinoma being the most dreaded and commonest. They often present a diagnostic challenge to both clinicians and histopathologists. Various imaging modalities such as computed tomography, magnetic resonance imaging, contrast-enhanced ultrasound, and endoscopic ultrasound (EUS) are commonly used for characterization of SPLs.[1] Although the improvement in resolution of various imaging modalities, the tissue acquisition and histological analysis are the most important and accurate investigation for the differential diagnosis of these lesions. Currently, EUS-guided fine-needle aspiration/biopsy (FNA/B) is the standard procedure for acquisition of tissue for histological diagnosis. However, the key limitation of this modality is its invasive nature as well as the potential of complications along with the low-negative predictive value (NPV), especially in lesions highly suspicious of malignancy clinically.[2] It is also a technically demanding procedure with low sensitivity in the background of chronic pancreatitis. This has led to a search for newer noninvasive diagnostic methods for SPLs that can accurately differentiate benign from malignant SPL's.

EUS elastography (EUS-E) is a newer advancement in the field of diagnostic EUS for noninvasive characterization of SPLs.[3] Elastography evaluates the tissue stiffness, and the principle behind testing tissue stiffness is that the normal pancreatic parenchyma, pancreatic cancers, and benign lesions have different levels of tissue stiffness. In general, the malignant lesions are stiffer than benign lesions, and this difference in tissue stiffness is exploited in EUS-E to differentiate between the two.[4] EUS-E expresses the tissue stiffness in qualitative or quantitative form. Qualitative EUS-E displays the tissue stiffness in the form of different colors, whereas, quantitative EUS-E measures the tissue stiffness as strain ratio (SR) or strain histogram.[4,5]

Several studies have reported data on both quantitative and qualitative EUS-E. In one of the first studies on qualitative EUS-E, Giovannini *et al*. reported the sensitivity, and specificity of EUS-E in the diagnosis of malignant pancreatic lesions being 100% and 67%, respectively.[6] Other studies on qualitative EUS-E have also reported similar results of high sensitivity but moderate specificity.[7,8] Quantitative EUS-E was developed to overcome the subjective limitations of qualitative EUS-E and was initially evaluated by Iglesias-Garcia *et al*.,[9] who reported diagnostic accuracy of 97.7% for malignant SPL with a cut-off SR of >6.04 for malignant lesions. Different studies have defined the different cut-off levels of SR with sensitivities varying from 67% to 98% and specificities between 45% and 71%.[10-12] Meta-analyses of studies evaluating EUS-E for pancreatic lesions have shown the sensitivity of 95% and specificity of 67%–69% for differentiating benign versus malignant SPLs.[13,14] In this news and views, we discuss two interesting studies that have further evaluated the role of EUS-E in SPLs.

Carrara *et al*.[15] evaluated the role of quantitative EUS-E (SR) and computer-aided fractal-based analysis of EUS-E images in the differentiation of SPLs. The "fractal" and "fractal geometry" are a mathematical tool for describing roughness of natural objects and fractal geometry has been used to evaluate the geometrical complexity of anatomical and imaging patterns observed in various lesions.[16-18] They studied 100 patients with 102 SPLs with 69 malignant and 33 benign lesions. EUS-E with measurement of SR was done 6 times on each patient: three SR measurements were done comparing the lesion to the healthy surrounding pancreatic parenchyma SR (pSR), and three SR measurements were done comparing the lesion with the healthy gastrointestinal tract wall SR (wSR). They also used fractal analysis-based technology for differentiating various SPLs where the elastographic images were analyzed using a computer program to determine the three-dimensional histogram fractal dimension. The software (NIH ImageJ, http://IMAGEJ.gov/ij) automatically splitted the Red, Green, Blue (RGB) histogram into its RGB channel components and gave their mean values. The final diagnoses were made by cytology, histology (EUS-sampling or resected specimens at surgery), or adequate follow-up time.

Both pSR and wSR were significantly higher in malignant as compared with benign SPLs (pSR: 24.5 vs. 6.4; $P < 0.001$; wSR: 56.6 vs. 15.3; $P < 0.001$). Pancreatic neuroendocrine tumor (NETs) had a significantly lower strain ratio (pSR) than malignant SPLs (7.1, 95% confidence interval [CI], 3.5–11.2; $P < 0.001$), but not significantly different from that of benign lesions (vs. 5.4; 95% CI, 2.1–8.8; $P = 0.441$). When the best cut-off levels of pSR and wSR at 9.10 and 16.2, respectively, were used, sensitivity/specificity/positive predictive value (PPV)/NPV/area under the curve were 88.4%/78.8%/89.7%/76.9%/86.7%,

and 91.3%/69.7%/86.5%/80%/85.7%, respectively. Moreover, a strategy of combining pSR and wSR values did not significantly improve the ability for diagnosis of malignancy.

Fractal analysis showed a significant statistical difference (P = 0.0087) between the mean surface fractal dimension of malignant (D = 2.66 ± 0.01) versus NET (D = 2.73 ± 0.03) lesions, and a statistical difference for all three channels red, green, and blue (P < 0.0001). Statistically significant differences were also found between mean surface fractal dimensions of uninvolved tissues surrounding malignant lesions (D = 2.658 ± 0.01) versus NETs (D = 2.745 ± 0.034, P = 0.0019) and NETs versus inflammatory lesions (D = 2.654 ± 0.02, P = 0.0473). The authors concluded that enhancing EUS images with an elastographic quantitative score (pSR and wSR) and combining EUS-E with fractal analysis and RGB color-based computer-aided image analysis can aid in better characterization of SPL's.

In another study by Ignee *et al*.,[19] the authors evaluated the role of qualitative EUS-E in the differential diagnosis of small solid SPLs ≤15 mm in size. In this study, patients above 18 years of age with SPL's seen over 10 years were retrospectively included from 13 international centers. Lesion stiffness relative to the surrounding pancreatic parenchyma, as qualitatively assessed and documented at the time of EUS-E, was retrospectively compared with the final diagnosis obtained by FNA/biopsy or surgical resection. A total of 218 patients (97 males; age 60 ± 15 [range 21–92 years]) with SPL of mean size 11 ± 3 mm were retrospectively analyzed. The color-coded measurement over the region of interest in the surrounding pancreatic tissue was compared to the elastography measurement over the lesion, and the lesion was classified as soft or stiff. The lesions with less or same stiffness as the surrounding pancreatic parenchyma were classified as soft, and those stiffer than parenchyma as stiff lesions.

On elastography, 50% of lesions were stiff lesions and 50% were soft lesions. High stiffness of the lesion had a sensitivity of 84% (95% CI 73%–91%), specificity of 67% (58%–74%), PPV of 56% (50%–62%), and NPV of 89% (83%–93%) for the diagnosis of any malignancy. For the diagnosis of pancreatic ductal adenocarcinoma, the sensitivity, specificity, PPV, and NPV were 96% (87%–100%), 64% (56%–71%), 45% (40%–50%), and 98% (93%–100%), respectively. They concluded that the ductal adenocarcinoma is very unlikely in patients with small SPL in the presence of soft EUS-E pattern (NPV of 98%).

Commentary

Despite the advancements in clinical, endoscopic and histological fields, the differential diagnosis of SPLs remains a challenge. The advent of EUS has revolutionized the evaluation of SPLs by providing high-resolution images, and subsequent addition of FNA/B has improved the diagnostic ability of EUS. However, EUS FNA has low-negative predictive value in the evaluation of malignancy and presence of fibrosis/necrosis decreases the diagnostic yield of EUS FNA. EUS-E is newer imaging that attempts to improve on this limitation of EUS FNA. It is a noninvasive imaging palpation modality that attempts to characterize the lesions as soft or hard. Malignant SPLs are generally harder than adjacent pancreatic tissue, and this difference can be easily made out on EUS-E. Various studies have explored the potential of EUS-E in differentiating between benign and malignant lesions and have yielded encouraging results.[6-10] Despite these encouraging results, EUS-E is currently not ready to replace EUS FNA/B because of false positives and false negatives. Hence, there have been numerous attempts to improve on the specificity of EUS-E like the use of quantitative EUS-E or addition of software-based evaluation of EUS-E images like fractal analysis. The study by Carrara *et al*.,[15] has been able to give cut-off values for Olympus EU-ME2 processor (pSR [>9.10] and wSR [>16.2] as clinically relevant values to discriminate between malignant and benign SPLs). Moreover, they have shown that fractal analysis improved on the diagnostic ability of EUS-E. Elastography and fractal geometry analyses evaluate different features of the same lesion with EUS-E quantifying tissue stiffness and fractal analysis estimating the roughness of a lesion or its underlying nonlinear dynamical behaviors.

So how do these two new studies on EUS-E impact our clinical practice? These studies again highlight the limitations of EUS-E, i.e., inability to replace EUS FNA/B as a diagnostic gold standard. However, over the last one decade, there has been considerable advancement in EUS-E and analysis software, and the combination of techniques such as stiffness and roughness will definitely improve on the discriminating ability of EUS-E. Despite these advancements, currently, it seems tissue is the issue, and EUS-E cannot replace FNA/B. EUS-E cannot be useful in all patients but in certain clinical situations like a patient of SPL with negative EUS FNA and pSR and wSR showing high SRs would require the repetition of FNA/FNB or close clinical follow-up.

EUS-E is still in its early childhood, and with time to come and further advancement in the technology more

evidence is likely to grow regarding this new emerging and promising modality.

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