

# New diagnostic techniques for the differential diagnosis of pancreatic mass: Elastography helps me 100%

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## INTRODUCTION

The introduction of endoscopic ultrasound (EUS) in the clinical practice has provided an important advancement in the management of solid pancreatic lesions, mainly in the diagnosis and staging of pancreatic cancer.<sup>[1]</sup> However, an accurate diagnosis and classification cannot always be determined using only conventional B-mode EUS imaging. In this setting, EUS-guided tissue acquisition is crucial for providing definitive diagnosis. Although diagnostic accuracy of EUS-guided tissue acquisition can be considered to be very high, with sensitivities between 80% and 85% and specificities approaching 100%,<sup>[2-4]</sup> it is technically demanding for both an endosonographer and a pathologist. Furthermore, cytohistological assessment can be falsely negative. Finally, EUS-guided tissue acquisition can be associated with small but not insignificant morbidity rates.<sup>[5]</sup> Hence, new methods are warranted to permit more accurate but still noninvasive characterization of these pancreatic lesions and to limit the need for EUS-guided tissue sampling and guided biopsies of areas to cases with the highest suspicion of malignant lesions where tissue sampling is still necessary.

One of these methods surfacing in recent years is EUS-guided elastography.<sup>[6]</sup>

Elastography is a real-time method, based on ultrasound technology, which allows evaluation of tissue stiffness. This is highly relevant since certain pathologies, such as cancer, can induce alterations in tissue stiffness, which is distinct from alterations that derive from inflammatory processes. Currently, elastographic evaluation, based on the strain technique, is available for the use under EUS guidance,<sup>[7]</sup> with the pancreas and different pancreatic pathologies, being one of the biggest and most important indications for this methodology.

## ROLE OF ENDOSCOPIC ULTRASOUND-GUIDED ELASTOGRAPHY IN SOLID PANCREATIC LESIONS

According to the current knowledge, solid malignant pancreatic tumors are generally stiffer than surrounding tissues. This is the basis for the role of elastography in the characterization of these types of lesions.

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Based on qualitative elastographic evaluation, up to 4 well-defined patterns have been described that characterize solid pancreatic lesions and contribute to its classification: a homogeneous green pattern present commonly in the normal pancreas; a heterogeneous, predominantly green pattern with slight yellow and red lines present only in inflammatory pancreatic masses; a heterogeneous, predominantly blue pattern with small green areas and red lines and a geographic appearance present mainly in pancreatic malignant tumors (including pancreatic adenocarcinoma); and a homogeneous blue pattern present only in pancreatic neuroendocrine malignant lesions. Giovannini *et al.*, using this qualitative evaluation, reported that the sensitivity and specificity for malignancy were 100% and 67%, respectively.<sup>[8]</sup> In a subsequent multicenter trial, Giovannini *et al.* reported EUS elastography findings in 121 cases with pancreatic masses.<sup>[9]</sup> The sensitivity, specificity, positive predictive value, and negative predictive value of the differentiation between benign and malignant pancreatic masses were 92.3%, 80.0%, 93.3%, and 77.4%, respectively, with an overall accuracy of 89.2%. The interobserver agreement from the evaluation of 30 cases yielded a kappa score of 0.785 for the detection of malignancy. Iglesias-Garcia *et al.*, in 130 patients with solid pancreatic masses and 20 controls, reported that sensitivity, specificity, positive and negative predictive values, and overall accuracy of EUS elastography for detecting malignancy were 100%, 85.5%, 90.7%, 100%, and 94.0%, respectively. All of the patients were evaluated by two endosonographers who made the same interpretation in 121/130 cases and 20/20 controls, yielding a kappa value of 0.772.<sup>[10]</sup> Importantly, interobserver agreement can be considered adequate. An additional study focused on the evaluation of this interobserver agreement concluded that EUS-guided elastography is reproducible for the evaluation of solid pancreatic lesions, even among endoscopists with limited or no experience.<sup>[11]</sup> However, not all studies presented the same level of accuracy. Janssen *et al.* reported a similar sensitivity (93.8%) but a significant lower specificity (65.4%), underlining the difficulties encountered in evaluating advanced chronic pancreatitis (CP).<sup>[12]</sup> In the study by Hirche *et al.*, they could only perform an adequate elastographic evaluation in 56% of the patients. The authors faced difficulties in certain clinical situations where an adequate elastography evaluation may be difficult, including difficulties in including an entire lesion and enough surrounding tissues in the analyzed region of interest in large (>35 mm) lesions, in the lesions

distant from the transducer, and in the presence of fluid (vessels, cysts, *etc.*).<sup>[13]</sup> However, these technical problems have been resolved with the latest generation of elastography software.

Quantitative EUS-guided elastography has also shown to be an accurate tool, based on the determination of strain ratio, hue histogram, and/or strain histogram. Iglesias-Garcia *et al.* reported their results on the strain ratio on 86 patients. This methodology even increased the accuracy of qualitative elastography, yielding an overall diagnostic accuracy for malignancy of 97.7% when presenting strain ratio level >6.04 or mass elasticity <0.05%. In addition, EUS-guided elastography could differentiate pancreatic cancers from inflammatory masses (100% sensitivity and 96% specificity) and pancreatic cancers from neuroendocrine tumors (100% sensitivity and 88% specificity).<sup>[14]</sup> Using the same method, another prospective study evaluated 109 patients. With the qualitative technique, all pancreatic cancers presented intense blue coloration; however, the inflammatory masses showed mixed colorations (green, yellow, and low-intensity blue). With the quantitative technique, the mean strain was  $39.1 \pm 20.5$  for pancreatic cancer and  $23.7 \pm 12.6$  for inflammatory masses ( $P < 0.05$ ).<sup>[15]</sup> Several studies have been conducted with the aim to determine the accuracy of the strain ratio for detecting malignancy in solid pancreatic tumors. Different cutoff values have been defined from 3.7 to 24, with diagnostic sensitivities ranging from 67% to 98% and specificities between 45% and 71%.<sup>[16-22]</sup> This issue highlights that standardization of the techniques is needed. Another quantification method is based on hue histograms. Săftoiu *et al.* reported a sensitivity, specificity, positive and negative predictive values, and accuracy of 91.4%, 87.9%, 88.9%, 90.6%, and 89.7%, respectively, using 175 as the cutoff for the mean of the hue histogram.<sup>[23]</sup> Recently, a multicenter study involving 258 patients (211 with pancreatic adenocarcinoma and 47 with CP) and using the same methodology showed that sensitivity, specificity, positive and negative predictive values, and accuracy were 93.4%, 66.0%, 92.5%, 68.9%, and 85.4%, respectively, using the same cutoff value (175) for the mean of the hue histogram (38, 39). Schrader *et al.* investigated quantitative elastography based on the mean of the hue histogram in 86 patients with malignant pancreatic masses and 28 controls without pancreatic disease. A 100% sensitivity and specificity for malignancy detection was obtained through the

quantitative measurement of the blue color.<sup>[24]</sup> No differences in terms of diagnostic accuracy have been documented between strain ratio and strain histogram. Iglesias-Garcia *et al.* reported that a strain ratio >10 and a mean strain histogram value <50 were the optimal cutoff values for the classification of lesions as malignant with an overall accuracy of 98%.<sup>[25]</sup>

Finally, several meta-analyses have been performed to determine the role of EUS-guided elastography in the differential diagnosis of solid pancreatic masses. Two meta-analyses evaluated the role on the differentiation of malignant pancreatic tumors from inflammatory pancreatic masses, showing a sensitivity of 95% and a specificity ranging from 67% to 69%.<sup>[26,27]</sup> The third meta-analysis included seven studies and 752 patients, with a global sensitivity of 97% and a specificity of 76%. This meta-analysis highlighted the difficulties of differentiating adenocarcinoma and neuroendocrine tumors, due to the similar hardness of both tumors.<sup>[28]</sup> The fourth meta-analysis found that the use of a color pattern for elastographic interpretation was associated with a sensitivity of 99% and a specificity between 69% and 76%.<sup>[29]</sup> Using hue histograms, the sensitivity was 92% and the specificity was slighter lower at 86%.

## SUMMARY

In clinical practice, differential diagnosis of solid pancreatic lesions remains a major clinical challenge and is crucial for optimizing the management of these patients. EUS can be considered the best method for diagnostics and characterization. In this setting, EUS-guided elastography provides very useful and valuable information on the malignant potential of lesions and should be included in the diagnostic algorithm. However, in many occasions, there is still the need for tissue confirmation for the final diagnosis.

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