Neoplasia in Chronic Pancreatitis: How to Maximize the Yield of Endoscopic Ultrasound-Guided Fine Needle Aspiration

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When performing endoscopic ultrasound-guided fine needle aspiration (EUS-FNA), identifying neoplasia in the setting of chronic pancreatitis can be technically challenging. The morphology of an ill-defined mass on sonography, presence of calcifications or intervening collaterals, reverberation from a biliary stent, low yield of tissue procurement, and interpretative errors in cytopathology can result in both false-negative and false-positive results. Although these challenges cannot be completely eliminated, elastography or contrast-enhanced imaging can aid in differentiating an inflammatory mass from a neoplasm. Also, performing more passes of FNA, procuring core biopsy material, performing rapid onsite evaluation, conducting ancillary pathology studies, and even repeating the procedure on a different day can aid in improving the diagnostic performance of EUS-FNA. This review provides a concise update and offers practical tips to improving the diagnostic yield of EUS-FNA when sampling solid pancreatic mass lesions in the setting of chronic pancreatitis.

Key Words: Endosonography; Biopsy; Biopsy, fine-needle; Pancreatitis, chronic; Pancreatic neoplasms

INTRODUCTION

The most common reasons for false-negative interpretation at endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) are inadequate sampling and incorrect targeting of lesions. This is encountered more frequently in patients with solid pancreatic masses in the setting of chronic pancreatitis. This review addresses this clinical conundrum and offers suggestions to mitigate these limitations.

WHAT IS THE BURDEN OF THE PROBLEM?

The sensitivity of EUS-FNA is only 54% to 74% when sampling solid pancreatic masses in the setting of chronic pancreatitis (Table 1). The presence of underlying chronic pancreatitis makes the morphological interpretation of neoplasms challenging. While a conglomerate of pancreatitis-induced lobulations may mimic a pancreatic mass (Fig. 1), the presence of acoustic shadowing from a calcified stone may undermine the visibility of a neoplasm (Fig. 2). Also, the coexistence of collateral vasculature in patients with severe chronic pancreatitis makes the process of FNA more challenging (Fig. 3). In one study, the median number of FNA passes required to establish a diagnosis of pancreatic cancer was five in patients with coexisting chronic pancreatitis versus only two in patients without chronic pancreatitis.

Some of the cytologic features that may mimic malignancy in chronic pancreatitis are occasional atypical cells that include enlarged, single cells with large nuclei; degenerative vacuoles; and occasional mitosis. Also, the marked desmoplasia of pancreatic adenocarcinoma might result in an inadequate, paucicellular specimen. Diagnosing well-differentiated adenocarcinomas can be particularly challenging as they tend to lack the typical hyperchromasia, display only minimal architectural disorder, and have only modestly increased nuclearto-cytoplasmic ratios.

The take-home message is that the major practical implication when performing EUS-FNA of solid pancreatic masses in the setting of chronic pancreatitis is that a tumor can be missed or wrongly classified. Also, more FNA passes may be required to establish a definitive diagnosis in these patients.
HOW CAN TECHNOLOGY IMPROVE NEOPLASIA DETECTION IN CHRONIC PANCREATITIS?

Elastography and contrast harmonic imaging are two recent technological developments in endosonography that enable better characterization of pancreatic masses. However, these technologies are not uniformly available worldwide, and the results have not been reproducible in all clinical investigations.

Elastography

Elasticity imaging has been reported to be useful for the differentiation of benign and malignant tissues, owing to the inherent differences in the hardness of tissues. Malignant tumors are usually stiffer than benign masses, and the strain information induced by small tissue deformations can be computed and displayed in real time. Real-time sonoelastography represents a technical improvement of grayscale ultrasound that allows the estimation of tissue strain during slight compressions induced by the transducer. The method works in real time, with the strain information being visually converted into a hue color scale and displayed as a transparent overlay superimposed on the grayscale ultrasound image. Consequently, soft tissues that are easy to compress are displayed in low hue values (green) and hard tissues that are difficult to strain are displayed in high hue values (blue). A multicenter trial that analyzed 121 focal pancreatic masses reported a κ value of 0.785 for pancreatic masses. EUS elastography was proven to have higher sensitivity and specificity than conventional grayscale EUS imaging (92.3% and 80%, respectively), for the differential diagnosis of focal pancreatic masses. Several investigators have performed multicenter trials that analyzed the use of EUS elastography to differentiate focal solid pancreatic masses.

| Investigator                        | No. of patients | Sensitivity of EUS-FNA without CP, % | Sensitivity of EUS-FNA with CP, % | p-value |
|-------------------------------------|-----------------|---------------------------------------|----------------------------------|---------|
| Fritscher-Ravens et al. (2002)      | 200 (74 with CP)| 89.3                                  | 53.5                             | -       |
| Varadarajulu et al. (2005)          | 300 (75 with CP)| 91.3                                  | 73.9                             | 0.02    |

EUS-FNA, endoscopic ultrasound-guided fine needle aspiration; CP, chronic pancreatitis coexisting with solid pancreatic masses.

Fig. 1. (A) A hypoechoic mass simulating a neoplasm is observed on linear endosonography. (B) However, a careful examination reveals the mass to be a conglomeration of lobules secondary to chronic pancreatitis.

Fig. 2. Hyperechoic shadowing by a pancreatic duct stone obscures an underlying pancreatic adenocarcinoma.

Fig. 3. The presence of collateral vasculature makes tissue acquisition more challenging in chronic pancreatitis.
Cancer in Chronic Pancreatitis

Table 2. Sensitivity and Specificity of Endoscopic Ultrasound Elastography for the Differential Diagnosis of Focal Pancreatic Masses (Includes Only Studies with >50 Patients)

| Reference                    | No. of patients | Sensitivity, % | Specificity, % |
|------------------------------|-----------------|----------------|---------------|
| Hirche et al. (2008)         | 70              | 41.0           | 53.0          |
| Giovannini et al. (2009)     | 121             | 92.3           | 80.0          |
| Iglesias-Garcia et al. (2009) | 130             | 100            | 85.5          |
| Iglesias-Garcia et al. (2010) | 86              | 100            | 92.9          |
| Săftoiu et al. (2010)        | 54              | 84.8           | 76.2          |
| Schrader et al. (2012)       | 86              | 100            | 100           |
| Săftoiu et al. (2011)        | 258             | 93.4           | 66.0          |

Several studies have evaluated the role of elastography in solid pancreatic masses but with disparate results (Table 2). The take-home message is that preliminary data suggest that elastography and, in particular, contrast-enhanced EUS improves the ability to differentiate neoplasms from chronic pancreatitis. However, the management decision by surgeons is based on tissue characteristics and not on sonographic characteristics. No study has shown that, when using contrast-enhanced EUS, performing a biopsy at a particular spot within a mass definitively yields malignant cells. Unless this critical question can be addressed, the real-life utility of contrast-enhanced EUS remains debatable.

WHAT TECHNIQUES AND STRATEGIES WILL IMPROVE THE DIAGNOSTIC YIELD OF EUS-FNA?

For a cytopathologist, rendering a diagnosis on hypocellular samples is one of the more common causes for delivering a false diagnosis. Therefore, several practical measures must be undertaken to enhance the diagnostic yield of EUS-FNA when sampling solid pancreatic masses in the setting of chronic pancreatitis.

Rapid onsite evaluation

Several studies have shown that the presence of an onsite cytopathologist improves the diagnostic yield, decreases the number of unsatisfactory samples, and minimizes the number of passes required to establish a diagnosis. In addition, two recent meta-analyses on EUS-FNA of pancreatic masses showed that the presence of an onsite cytopathologist was associated with a diagnostic sensitivity of 88% to 95% compared with ≤80% in the absence of a cytopathologist. Therefore, in challenging cases, the presence of an onsite cytopathologist is critical to achieve good clinical outcomes.

Number of FNA passes

The marked desmoplasia of pancreatic adenocarcinoma might result in an inadequate specimen, which is commonly encountered in the setting of chronic pancreatitis. Also, diag-
nosing well-differentiated cancers can be challenging as they tend to lack the typical hyperchromasia, display minimal architectural disorder, and have only modestly increased nuclear-to-cytoplasmic ratios. Therefore, the number of passes required to establish a diagnosis of malignancy is significantly greater in the presence of coexisting chronic pancreatitis (two passes). This is particularly relevant when rapid onsite evaluation (ROSE) is not possible. These authors and other experts recommend performing a minimum of seven passes by using the "fanning" technique.21,22

**FNA technique**

Current evidence does not support the routine use of a suction or a stylet during EUS-FNA as they tend to increase the bloodiness of the specimen.23 However, if the FNA pass yields only minimal tissue or a dry tap, then suction may be used, particularly in severe chronic pancreatitis in which the desmoplastic stroma traps the cancer cells, yielding only a scant aspirate. Also, the use of a large-caliber 19 G needle may be considered if the tissue yield is minimal or if core biopsy is desired. A core biopsy yields tissue fragments with an intact histological architecture that is sometimes required, particularly in patients with well-differentiated pancreatic adenocarcinoma, when cytology is inconclusive.

**Ancillary studies**

In challenging cases, in addition to procuring tissue in cell blocks, the specimen needs to be fixed in alcohol for better delineation of the nuclear morphology. Also, several biomarkers are increasingly available to distinguish reactive ductal epithelium from neoplastic cells. Therefore, additional (sufficient) tissue must be procured in cell blocks to facilitate the performance of ancillary studies. Several biomarkers are increasingly available to distinguish reactive ductal from neoplastic cells.

**Repeat EUS-FNA**

If the suspicion for malignancy remains very high, the patient is a good surgical candidate, and the lesion appears resectable, then the best option is surgery. As the degree of suspicion for malignancy decreases, the health status of the patient is marginal and the resectability is intermediate; thus, repeat EUS-FNA is probably the best course of action. Three studies have shown that a repeat EUS-FNA yields a correct diagnosis in 61% to 84% of patients.27-29 Therefore, when seven or more FNA passes have been performed and the diagnosis is uncertain, performing a repeat EUS-FNA may be the best course of action. In the opinion of these authors, after performing seven FNA passes, one reaches a point of "diminishing return" and persisting with more FNAs is unlikely to be of clinical benefit.

The take-home message is that given the presence of increased collaterals and poor visualization of the mass, it is important to be "efficient" when performing FNA of pancreatic masses, particularly in the setting of chronic pancreatitis. Performing the fanning maneuver during FNA, conducting ROSE, performing adequate number of FNA passes, and procuring additional specimen for ancillary studies are critical steps that must be followed. If none of these prove useful, repeating the procedure at another time is important before subjecting the patient to more invasive evaluations.

**CONCLUSIONS**

Diagnosing neoplasia in chronic pancreatitis can be challenging. Use of contrast harmonic imaging and modifying different steps in the technique of FNA as outlined in this review will likely improve technical outcomes.

**Conflicts of Interest**

The authors have no financial conflicts of interest.

**REFERENCES**

1. Fritscher-Ravens A, Brand L, Knöfel WT, et al. Comparison of endoscopic ultrasound-guided fine needle aspiration for focal pancreatic lesions in patients with normal parenchyma and chronic pancreatitis. Am J Gastroenterol 2002;97:2768-2775.
2. Varadarajulu S, Tamhane A, Eloubeidi MA. Yield of EUS-guided FNA of pancreatic masses in the presence or the absence of chronic pancreatitis. Gastrointest Endosc 2005;62:728-736.
3. Kulesza P, Eloubeidi A. Endoscopic ultrasound-guided fine-needle aspiration: sampling, pitfalls, and quality management. Clin Gastroenterol Hepatol 2007;5:1248-1254.
4. Frey H. Realtime elastography. A new ultrasound procedure for the reconstruction of tissue elasticity. Radiologe 2003;43:850-855.
5. Saftoiu A, Yilmaz P. Endoscopic ultrasound elastography: a new imaging technique for the visualization of tissue elasticity distribution. J Gastrointestin Liver Dis 2006;15:161-165.
6. Dietrich CF, Saftoiu A, Jensen C. Real time elastography endoscopic ultrasound (RTE-EUS), a comprehensive review. Eur J Radiol 2014;83:405-414.
7. 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;15:1587-1593.
8. Hirche TO, Iggere A, Barreiros AP, et al. Indications and limitations of endoscopic ultrasound elastography for evaluation of focal pancreatic lesions. Endoscopy 2008;40:910-917.
9. Iglesias-Garcia J, Larino-Noia J, Abdulkader I, Forteza J, Dominguez-Munoz JE. EUS elastography for the characterization of solid pancreatic masses. Gastrointest Endosc 2009;70:1101-1108.
10. Iglesias-Garcia J, Larino-Noia J, Abdulkader I, Forteza J, Dominguez-Munoz JE. Quantitative endoscopic ultrasound elastography: an accurate method for the differentiation of solid pancreatic masses. Gastroenterology 2010;139:1172-1180.
11. Saftoiu A, Iordache SA, Gheonea DI, et al. Combined contrast-enhanced power Doppler and real-time sonoelastography performed during EUS, used in the differential diagnosis of focal pancreatic masses (with videos). Gastrointest Endosc 2010;72:739-747.
12. Schrader H, Wiese M, Ellrichmann M, et al. Diagnostic value of quantitative EUS elastography for malignant pancreatic tumors: relationship with pancreatic fibrosis. Ultraschall Med 2012;33:E196-E201.

13. 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.

14. Reddy NK, Ioncică AM, Săftoiu A, Vilmann P, Bhutani MS. Contrast-enhanced endoscopic ultrasonography. World J Gastroenterol 2011;17: 42-48.

15. Săftoiu A, Dietrich CE, Vilmann P. Contrast-enhanced harmonic endoscopic ultrasound. Endoscopy 2012;44:612-617.

16. Claudon M, Cosgrove D, Albrecht T, et al. Guidelines and good clinical practice recommendations for contrast enhanced ultrasound (CEUS): update 2008. Ultraschall Med 2008;29:28-44.

17. Dietrich CE, Ignee A, Braden B, Barreiros AP, Ott M, Hocke M. Improved differentiation of pancreatic tumors using contrast-enhanced endoscopic ultrasound. Clin Gastroenterol Hepatol 2008;6:590-597.

18. Hocke M, Schulze E, Gottschalk P, Topalidis T, Dietrich CE. Contrast-enhanced endoscopic ultrasound in discrimination between focal pancreatitis and pancreatic cancer. World J Gastroenterol 2006;12:246-250.

19. Săftoiu A, Iordache SA, Gheonea DI, et al. Combined contrast-enhanced power Doppler and real-time sonoelastography performed during EUS, used in the differential diagnosis of focal pancreatic masses (with videos). Gastrointest Endosc 2010;72:739-747.

20. Gong TT, Hu DM, Zhu Q. Contrast-enhanced EUS for differential diagnosis of pancreatic mass lesions: a meta-analysis. Gastrointest Endosc 2012;76:301-309.

21. Matsubara H, Itoh A, Kawashima H, et al. Dynamic quantitative evaluation of contrast-enhanced endoscopic ultrasonography in the diagnosis of pancreatic diseases. Pancreas 2011;40:1073-1079.

22. Hewitt MJ, McPhail MJ, Possamai L, Dhar A, Vlavianos P, Monahan KJ. EUS-guided FNA for diagnosis of solid pancreatic neoplasms: a meta-analysis. Gastrointest Endosc 2012;75:319-331.

23. Hébert-Magee S, Bae S, Varadarajulu S, et al. The presence of a cytopathologist increases the diagnostic accuracy of endoscopic ultrasound-guided fine needle aspiration cytology for pancreatic adenocarcinoma: a meta-analysis. Cytopathology 2013;24:159-171.

24. Jhala NC, Jhala D, Elloum I, et al. Endoscopic ultrasound-guided fine-needle aspiration biopsy: a powerful tool to obtain samples from small lesions. Cancer 2004;102:239-246.

25. LeBlanc JK, Ciaccia D, Al-Assi MT, et al. Optimal number of EUS-guided fine needle passes needed to obtain a correct diagnosis. Gastrointest Endosc 2004;59:675-681.

26. Varadarajulu S, Fockens P, Hawes RH. Best practices in endoscopic ultrasound-guided fine needle aspiration. Clin Gastroenterol Hepatol 2012;10:697-703.

27. Eloubeidi MA, Varadarajulu S, Desai S, Wilcox CM. Value of repeat endoscopic ultrasound-guided fine needle aspiration for suspected pancreatic cancer. J Gastroenterol Hepatol 2008;23:567-570.

28. DeWitt J, McGreevy K, Sherman S, LeBlanc J. Utility of a repeated EUS at a tertiary-referral center. Gastrointest Endosc 2008;67:610-619.

29. Nicaud M, Hau W, Collins D, Wagh MS, Chauhan S, Draganski PV. The utility of repeat endoscopic ultrasound-guided fine needle aspiration for suspected pancreatic cancer. Gastroenterol Res Pract 2010;2010:268290.