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Methods to Increase the Diagnostic Efficiency of Endoscopic Ultrasound-Guided Fine-Needle Aspiration for Pancreatic Solid Lesions: an update review

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Abstract

Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) is a means to procure adequate specimen for histological and cytologic analysis. The ideal EUS-FNA is undoubtedly to be safe, accurate, and with a high sample adequacy rate and low adverse events rate. In recent years, many guidelines and trials about EUS-FNA have been published. The purpose of this article is to introduce the updated influence of some main factors on the diagnostic efficiency of EUS-FNA as well as a rare but serious complication named needle tract seeding.

INTRODUCTION

Pancreatic cancer is one of the worst situations of pancreatic solid lesions. The incidence of pancreatic cancer is increasing year by year.[1] And the 5-year survival rate is no more than 10%.[2] As a result of the low early diagnosis rate, about 80% of patients are diagnosed when pancreatic cancer has reached the unresectable stage.[3] Therefore, a reliable and widely applicable early assessment of pancreatic cancer is extremely important for personalized therapies.[4] Decades after the endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) was designed in the early 1990s by Vilmann *et al*[5], it has already been considered as a recommended method when the diagnosis is unclear for patients with suspected pancreatic cancer after the pancreatic protocol CT scan.[6–8]

According to the latest research, genetic testing technology such as whole-exome sequencing and nuclear DNA content assessment could also be used in EUS-FNA.[9] . In recent years, many guidelines and trials about EUS-FNA have been published. [10,11] In the past few years, endoscopic ultrasound-guided fine-needle biopsy (EUS-FNB) has become a useful tool. The newer FNB needles are equally effective in pancreatic lesions and non-pancreatic lesions, such as subepithelial lesions and abdominal lymph node lesions, which can improve the sample adequacy rate and diagnostic accuracy.[12,13] But the evidence relating to this is limited and more multiple large sample studies and randomized clinical trials are stilled warranted to improve the diagnosis efficiency of EUS-FNA.[14]

MASS SIZE

With the development of pancreatic cancer diagnosis technology, early detection of small pancreatic solid lesions is increasingly common. In the past, it was believed that there was no relationship between lesion size and EUS-FNA diagnostic yield.[15,16] But previous related researches were conducted with rapid on-site evaluation (ROSE), in which the procedure would be repeated until confirming the representative cells from the target lesion. Nevertheless, according to a retrospective cohort study by Crinò *et al*, the adequacy, accuracy, and sensitivity of EUS-FNA for pancreatic solid lesions without ROSE are related to the size of the mass.[17] This finding indicates that endoscopists have to be more cautious when facing the diagnosis of small pancreatic solid lesions without ROSE, especially for patients with lesions less than 20mm.[6]

NEEDLE SIZE

According to the latest guidelines in UK, Japan, and China, there is still uncertainty about the optimal needle size of EUS-FNA for pancreatic solid lesions supported by high-level evidence. Generally, in terms of needle choice, a 19-gauge needle is used for interventional surgery. A 22-gauge needle is customarily applied in histologic

evaluation, while a 25-gauge needle has been widely used in cytologic assessment with the ROSE.[18,19]

In recent years, due to their manageability and safety, 22-gauge and 25-gauge needles have gained increasing popularity in clinical trials.[20] According to a meta-analysis including 7 trials with 689 patients and 732 Lesions from 2007 to 2014, there was no significant difference between a 22-gauge needle and a 25-gauge needle on cytologic evaluation in terms of diagnostic sensitivity, specificity, sample adequacy, and adverse events.[21] Besides, a retrospective study of 153 patients with pancreatic ductal adenocarcinoma (PDAC) shows that both 22-gauge and 25-gauge needles provided equally adequate specimens for immunohistochemical (IHC) analysis.[22]

As for the 19-gauge needle, it has advantages over the 22-gauge and 25-gauge needle in terms of the size and quality of the tissue samples obtained without ROSE.[23] However, as a result of its stiffness and difficulty in use, the 19-gauge needle often fails when performed *via* the transduodenal approach in a bent position, essentially in the pancreatic head or uncinate process tumors.[23] To overcome this problem, a flexible 19-gauge needle with nitinol shaft (19 G Flex) was introduced. However, according to a randomized study by Laquière *et al*[24], the 19 G Flex needle was inferior to a standard 22-gauge needle in diagnosing pancreatic head cancer and was still difficult to use in the transduodenal approach. Intermediate size needles (20-G or 21-G) are on the way.[25,26]

SUCTION, SLOW-PULL OR NON-SUCTION

Suction is commonly used to obtain adequate samples, but it may damage cellular structures and contaminate the sample with blood, clouding cytologic interpretation.[27] Compared with dry suction, wet suction can have better sample adequacy and higher diagnostic accuracy without increasing blood pollution.[28,29] In addition, slow-pull and non-suction sampling are techniques that procure samples of good quality with only slight blood contamination. According to a prospective randomized trial by Cheng *et al*[30,31] and a multicenter randomized trial by Saxena P *et al*[32] , both suction and slow-

pull sampling need 2 passes on average and show equivalent sensitivity, specificity, and accuracy. And the combination of the two techniques shows better sampling results than each alone. This study also indicates a conclusion in contrast to Alizadeh *et al*[33] that suction does not increase blood contamination of the sample compared with slow-pull sampling in pancreatic solid lesions.

WITH OR WITHOUT STYLET

The use of a stylet during EUS-FNA prolongs the procedure time with an increased risk of unintentional needle stick injury due to the repeat passes in the reinsertion of the stylet.[34] However, a longer operation time does not mean better diagnostic efficiency. As indicated by prospective studies and meta-analyses, the use of a stylet during EUS-FNA confers no significant difference concerning technical success, the mean number of needle passes, needle malfunction, complication, adequate sample rate, cellularity, contamination rate, bloodiness, cytological diagnostic accuracy, and histological diagnostic accuracy.[35–38]

RAPID ON-SITE EVALUATION

In the past, it was believed that ROSE could help with the diagnostic accuracy of pancreatic EUS-FNA and a lower number of needle passes and inadequate samples.[39] However, recent comprehensive data on the impact of ROSE have been conflicting. In a multicenter randomized controlled trial and a meta-analysis, no statistical difference was demonstrated in diagnostic accuracy, adequate rate, procedure time, and the average number of needle pass between EUS-FNA with and without ROSE.[40,41] But a study that considered pancreatic, submucosal upper gastrointestinal tract and adjacent lesions indicated that ROSE does improve the adequate rate and diagnostic accuracy of EUS-FNA, especially in pancreatic solid lesions.[42] The variety of conclusions among different studies may lie in other factors such as the difficulty in implementing blind methods, the encouragement to additional passes when malignant cells are not detected, and the experience of endoscopists and cytopathologists.[43] Therefore, ROSE

alone may not be a predominant factor. But it could be considered as an essential part during the learning period and in hospitals with the diagnostic accuracy rate lower than 90%.[44]

CONTRAST-ENHANCED HARMONIC ENDOSCOPIC ULTRASOUND AND ELASTOGRAPHY

Contrast-enhanced harmonic endoscopic ultrasound (CEH-EUS) and elastography has been widely used to assist in the diagnosis of pancreatic indeterminate lesions.[45] It can correctly distinguish false negative diagnosis of EUS-FNA, thus improving the diagnosis rate of pancreatic diseases and EUS-FNA.[46,47] CEH-EUS-guided fine-needle aspiration (CEH-EUS-FNA) avoids fibrosis, necrotic areas, and blood vessels in pancreatic lesions, and can locate the sampling site more accurately.[48] Compared with the standard EUS-FNA, it can reduce the number of punctures when obtaining equivalent sufficient samples, thus reducing the incidence of adverse events related to EUS-FNA , such as bleeding, perforation, infection, pancreatitis, etc.[46,49] Elastography strain imaging is accessible through EUS, wherein it gauges tissue distortion by the application of a predetermined pressure. The combined utilization of CEH-EUS or elastography appears to enhance the diagnostic capability of EUS.[50] But a meta-analysis suggested more studies assessing the combined utilization were needed.[51]

NEEDLE TRACT SEEDING

Apart from common complications such as pancreatitis and bleeding, a rare but serious complication has also begun to receive increasing attention since 2003. It was firstly reported by Hirooka *et al* about the cancer recurrence due to needle tract seeding after EUS-FNA for a patient with a pancreatic tumor.[52] Since then, relevant studies have been published continuously, discussing the impact of tumor cell seeding by needle tract on short-term prognosis.[53] According to several retrospective studies, although pre-operative EUS-FNA has not been proved associated with overall survival or an increased rate of gastric and peritoneal cancer recurrence, its potential worse long-

term prognosis is still non-negligible.[54–57] Furthermore, this phenomenon is unique to tumors in the pancreatic body and tail, considering that the needle tract is not included in surgical resection of these tumors.[58–65] Therefore, if possible, paying more attention to the imaging findings of the needle tract in the postoperative follow-up or including the needle tract during the surgical resection may improve the long-term prognosis.[66] And an appropriate risk information about needle tract seeding before EUS-FNA should be necessary.[65]

ABOUT EUS-FNB AND MACROSCOPIC ON-SITE EVALUATION

EUS-FNB has become the first choice requiring multiple immunohistochemical staining to assist in the diagnosis of diseases such as autoimmune pancreatitis and pancreatic metastasis.[67] At present, the relevant research mainly focuses on the research and development of puncture needles of different needle types and shapes. The most common ProCore® biopsy needle improves the adequacy of the tissue specimen, and the Acquire® biopsy needle improves the quality of the tissue specimen due to its tip stability and more controllable puncture site.[19,67]However, a study demonstrated that 22G Acquire® needle achieved better accuracy than 20G needle due to more tissue of pancreatic masses for histologic assay.[68]

Trial from Yousri M reported that both FNA and FNB are safe and effective for accurately diagnosing pancreatic and non-pancreatic abnormalities. In comparison to tissue examination alone, FNB demonstrates higher sensitivity and diagnostic accuracy when diagnosing pancreatic lesions. Additionally, FNB can provide a higher quality histological specimen with reduced contamination from blood[69].AND a other randomized controlled trial suggested EUS-FNB without ROSE showed great diagnostic accuracy in solid pancreatic lesions, and ROSE might not be recommended with new FNB needles used.[70]Although newer FNB needles have the advantage of being self-assisting in diagnosing diseases, standard FNA needles are still very competitive because their high flexibility allows them to puncture difficult target sites and allow for ROSE.[25] Then a meta-analysis found evidence to suggest that EUS-FNB

with ROSE was not significantly better than EUS-FNB with newer end-cutting needles. However, there may still be a potential role for ROSE when reverse bevel needles were utilized[71]. However, ROSE necessitates the presence and expertise of a pathologist, incurs supplementary expenses, and is not accessible in many medical centers. The macroscopic on-site evaluation (MOSE) by an endoscopist was introduced as an alternative to ROSE, and the two study found MOSE is a complementary technology that reduces the necessary number of needle for sample acquisition and improving diagnostic accuracy in some clinical condition.[71,72]

DISCUSSION

EUS-FNA plays a pivotal role in the diagnosis and evaluation of pancreatic solid lesions. Although there are still no globally accepted guidelines for the application of EUS-FNA in pancreatic solid lesions, relevant and clinically meaningful studies on techniques is booming. The ideal EUS-FNA is undoubtedly to be safe, accurate, and with a high sample adequacy rate and low adverse events rate. More studies are even exploring its use in cancer diagnosis beyond the digestive system.[73–75]

The needle size research of EUS-FNA has always been a popular topic. According to a network meta-analysis involving 27 randomized controlled trials and 2711 patients, there was no significant difference in diagnostic accuracy and sample adequacy among 19-gauge, 22-gauge, and 25-gauge needles.[76] This means that endoscopists could choose the needle size based solely on the purpose of the operation, for instance, interventional surgery, histological evaluation, and cytologic assessment. It is also important to note that although the 19-gauge needle shows advantages in terms of the quantity and quality of tissue samples obtained without ROSE, it cannot be denied that it does not perform well *via* the trans-duodenal approach in a bent approach.[23] The modification of a 19-gauge needle, such as material and shape, to make it flexible and easier to use seems warranted.

Conflicts in the studies of ROSE may be due to the difficulty of performing the blind method, the recommendation of additional punctures when no malignant cells are

detected, and the difference in the experience of endoscopists and cytopathologists.[43] This prevents ROSE itself from being considered as a major factor affecting the diagnostic accuracy of EUS-FNA, at least without sufficient evidence. What is almost certain, however, is that ROSE plays a role in the effect of mass size on the accuracy of EUS-FNA. Thus, in hospitals without ROSE, endoscopists should be more cautious in patients with small pancreatic solid lesions.[17]

According to the prospective randomized trial by Cheng *et al*, there was no statistically significant difference between slow-pull and suction EUS-FNA techniques in safety, accuracy, and bloodiness.[30] Several slow-pull and suction techniques, for instance, wet suction, have also been modified to enhance tissue acquisition or reduce tissue damage.[77] However, sufficient evidence to prove one technique superior to another is still in need.

As mentioned above, it would be reasonable not to use a stylet during the EUS-FNA process, which may make the operation easier, reduce labor intensity, and more time and cost-effective without affecting the quality of the results.

In recent years, although the incidence of needle tract seeding is low, due to its serious consequences, this complication has received more and more attention from endoscopists. It may also be precisely because of its low incidence that the results of its impact on the overall survival rate were not obtained in the relevant original researches and meta-analysis.[54–57] In order to fully clarify the clinical characteristics of the EUS-FNA posterior needle tract seeding, further prospective studies are warranted. But in the current clinical practice, it is still recommended to pay attention to the phenomenon of needle tract seeding and appropriate risk information should be necessary.

Organoids offer a comprehensive depiction of the intricate diversity inherent in tumors, covering their genetic constitution, transcriptional landscape, metabolic dynamics, cytological intricacies, and histological characteristics. And organoids serve as a synthesized representation of multiple tumoral features in vivo, thereby serving as a pivotal conduit between fundamental tumor research and clinical applications, like

drug screening.[78] With the exploration and development of new technologies, tissues obtained by EUS can also be used for organoid culture.[79]

Mostly, tumor organoids are cultured from surgically resected samples, the inherent difficulty in obtaining viable specimens from advanced-stage tumors, like pancreatic cancer, poses a significant impediment to this approach. In contrast, EUS-FNA emerges as a versatile methodology, applicable across all disease stages, encompassing preoperative, perioperative, post-therapeutic, and recurrent phases. This methodological flexibility positions EUS-FNA as unconstrained by disease staging, thereby facilitating the establishment of dynamic organoid that faithfully mirror the temporal progression of the disease.[80] In contrast to traditional methods, these specimens after ROSE can be used immediately in the laboratory to generate organoid cultures. And samples can be taken as the disease progresses, not just after the lesion needs to be surgically removed.

In conclusion, short-term outcomes of the factors introduced above are relatively explicit for the improvement of EUS-FNA. Multiple large sample studies and prospective randomized trials are still warranted to discuss cytopathologic support, modification in techniques, materials, and long-term consequences.

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