Focused Review Series: What Should We Know about EUS-FNA? Print ISSN 2234-2400 / On-line ISSN 2234-2443
Clin Endosc 2012;45:132-137 http://dx.doi.org/10.5946/ce.2012.45.2.132

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How Can We Get the Best Results with Endoscopic Ultrasound-Guided Fine Needle Aspiration?

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Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) has evolved to become an indispensable tool for tissue acquisition. While the overall diagnostic accuracy of EUS-FNA is greater than 90% for lung cancer staging, it is lower for pancreatic mass lesions. Several factors such as location of the tumor, disease characteristics and procedural techniques determine the outcomes of EUS-FNA. In this review we evaluate the various technical factors that are keys to attaining optimal procedural outcomes.

Key Words: Endoscopic ultrasound; Fine-needle cytology; Techniques

INTRODUCTION

Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) is used to acquire tissue from mucosal/submuocsal tumors, peri-intestinal structures including lymph nodes, pancreas, adrenal gland, gallbladder, bile duct, liver, kidney, lung, etc. Any suspicious lesion or organ that is in close proximity to the gut lumen and within reach of the linear array echoendoscope can be accessed with a needle. EUS-FNA with its very high diagnostic accuracy and excellent safety profile has become the modality of choice for establishing tissue diagnosis. But reported diagnostic accuracy of EUS-FNA varies in wide range. For example, EUS accuracy ranges from 78% to 94% for pancreatic tumor staging and from 64% to 82% for nodal staging in literature review.[1] This review will provide a perspective on technical aspects for obtaining the best results with EUS-FNA.

Several factors determine the outcome of EUS-FNA: the degree of technical difficulty, gauge of the needle, use of stylet or suction during FNA, presence of onsite cytopathologist, need for histology, and special maneuvers to procure better quality tissue. Accessories used to perform the FNA are expensive and studies have shown that the rate of needle dysfunction is between 10% and 15% and inadvertent puncture of the echoendocope is not an uncommon occurrence during FNA. Although there are no specific guidelines, incorporating an algorithmic approach in clinical practice is important to minimize costs and maximize clinical outcomes.

Received: June 4, 2012 **Revised:** June 14, 2012
Accepted: June 14, 2012

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ROUTE OF ACCESS

In general, any FNA prior to intubating the pylorus is technically easy to perform because the tip of the echoendoscope is relatively straight and there is no difficulty encountered during trans-esophageal or trans-gastric passage of the needle into the lesion. On the other hand, when the pylorus is intubated and a lesion is targeted via the trans-duodenal route, the tip of the echoendoscope is acutely angulated impeding free passage of the needle into the target lesion. This challenge can be easily overcome by advancing the echoendoscope to the second portion of the duodenum and then shortening it so that the tip of the scope remains straight. This enables free range of movement for the needle into the mass during the process of FNA. A disadvantage of this maneuver is that in a short scope position the echoendoscope is relatively unstable and tends to recoil into the stomach during the motion of

FNA. Having an assistant or technician to brace the scope during FNA passes can improve scope stability during tissue sampling. Sometimes anatomical distortion of the duodenum or a deep uncinate lesion can cause the needle trajectory to move away from the target and result in failure of the above maneuvers. In this scenario, accessing the lesion from the antrum or the lesser curvature of the stomach will be an easier, safer and effective option.

TYPE AND SIZE OF LESION

Even lesions as small as a few millimeters in size can be targeted by EUS-FNA. Once the lesion is identified and the decision is made to perform an FNA, the endosonographer should decide on the gauge of the needle. If a histological sample is required, consider use of the ProCore (Cook Endoscopy, Winston-Salem, NC, USA) needle or the 19-G needle. For cystic lesions, a 19-G needle along with suction is used to acquire fluid without the need for multiple punctures. It is also imperative to empty the cyst contents completely as the risk of infection appears higher in incompletely aspirated cysts. If there is a mass lesion or mural nodules associated with the cyst, these should be the primary target of FNA as the diagnostic yield is superior.

SIZE OF NEEDLE

FNA needles are available in three sizes: 25, 22, and 19 gauge. Several factors determine the choice of needles when performing an FNA: 1) which needle will provide better cellularity, 2) how much flexibility is needed to access a lesion, and 3) do I need histological (core) tissue? In four randomized trials that have attempted to identify the optimal needle for performing FNA, they compared the 22- and 25-G needles.[2-5] There was no significant difference in diagnostic accuracy according to needle size. But for FNA of pancreatic head/uncinate masses, there was a trend towards better performance with the 25-G needle.

One of the limitations to EUS-FNA is that certain lesions such as stromal cell tumors and lymphomas may be difficult to diagnose without histological samples as preservation of tissue architecture and morphology is essential for accurate pathological assessment.[6] In order to overcome this limitation, a 19-G Trucut needle biopsy (EUS-TNB) was developed to procure histological tissue.[6] The overall diagnostic accuracy of EUS-TNB is reported to be 75% to 84% at various sites in the body,[7,8] and 61% to 67.5% for pancreatic masses.[8,9] A major limitation of TNB is that the rigidity induced by its 19-G caliber and the mechanical friction of the firing mechanism produced by a torqued echoendoscope limits its use for evaluating pancreatic head and duodenal lesions.[8,9] Recently, a new 19-G fine needle biopsy (EUS-FNB) device was developed with ProCore (Cook Endoscopy) reverse bevel technology for histological sampling. In a large prospective cohort study, histologic samples were obtained successfully with a diagnostic accuracy of more than 90%.[10] However, when EUS-FNB was performed via transduodenal route with this needle, some technical difficulties were still persisted. The same FNB device is now available in a 22-G platform to facilitate easy transduodenal sampling. A recent randomized trial compared the 22-G FNB device (ProCore needle) and 22-G FNA needle for sampling of pancreatic mass lesion.[11] While there was no difference in the diagnostic accuracy, the quality of histological core procured by the 22-G FNB device was not significantly different from that obtained using a standard FNA needle, 80% vs. 67%.

The role of the standard 19-G FNA needle for yielding histological samples was evaluated prospectively in a recent study.[12] Of 120 patients, the procedure was technically successful in 98.9% (*n*=119) and adequate histological sample was obtained in 97.5% (*n*=116). A limitation of this study was that patients with pancreatic head/uncinate masses were excluded. As the standard 19-G needle is too stiff to navigate the transduodenal route, a flexible 19-G needle (Flex 19 G Expect; Boston Scientific, Natick, MA, USA) made of nitinol has been recently introduced. In a pilot study of 50 patients, the flexible 19-G needle could be used successfully for both diagnostic (*n*=38) and therapeutic (*n*=12) indications with no documented technical failures.[13] Of the 38 diagnostic cases, 32 were pancreatic head/uncinate masses and 6 were submucosal lesions. EUS-FNA (cytology positive) was successful in 92.1% and a histological core tissue was procured in 94.7% patients.

PRESENCE OF THE STYLET

The presence of a stylet in the FNA assembly is to prevent the tip of the needle from being clogged with gut wall tissue before entering the target lesion. Of the three randomized trials[14-16] that evaluated the role of a stylet during EUS-FNA, in all three trials, the use of a stylet did not improve the diagnostic yield for malignancy but increased the bloodiness of the specimen. Based on this data, we recommend removal of the stylet when performing FNA.

APPLICATION OF SUCTION

According to randomized trials that evaluated the role of suction during EUS-FNA,[17] the use of suction did not improve the diagnostic yield and the specimens were reported

to be more bloody. In our opinion, if the aspirate obtained is scant, such as with FNA of a solid mass in the setting of chronic pancreatitis, then suction can be used to procure a better sample. In all other instances, FNA of solid mass lesions can be undertaken without suction.

NUMBER OF PASSES

The goal of performing FNA is to obtain a positive diagnosis in the quickest possible time with the least number of passes. The number of passes to be made depends on the presence or absence of on-site cytopathologist for assessment of specimen adequacy, establishment of on-site diagnosis, and to guide the need for further sampling. In the absence of an on-site cytopathologist, adequate passes should be performed to avoid the need for repeat procedures. Studies have shown that with solid pancreatic mass lesions, seven passes provided a sensitivity and specificity of 83% and 100%, respectively, and five passes on lymph nodes yielded sensitivity and specificity of 77% and 100%, respectively.[18] FNA of liver and lymph nodes require less needle passes when compared to pancreatic mass lesions.[19] In this study, the authors recommended 5 to 6 passes for pancreatic mass lesions and 2 to 3 passes for lymph nodes. In lieu of established guidelines, one should perform at least 5 to 7 passes on pancreatic mass lesions and 3 to 5 passes on lymph nodes when an on-site cytopathologist is not available. It would be ideal if the endosonographer is proficient in staining the slides and assessing them for specimen adequacy so as to determine the number of passes to perform. A dedicated pass must always be performed for cellblock whenever possible to increase the diagnostic yield.

PRESENCE OF STENTS

Presence of stents in the biliary tree can cause foreign body reaction and there is concern about the impact of stents on the diagnostic accuracy of EUS-FNA. Three studies[20-22] have addressed this question and all three concluded that the presence or absence of stents do not impact the diagnostic accuracy of EUS-FNA (Table 1). There was also no difference in diagnostic yield irrespective of whether the stent was plastic or metal.[21,22]

TECHNIQUE OF EUS-FNA

The sensitivity of FNA for pancreatic mass lesions diminishes as the size of the lesion increases to over 4 cm.[23] This is due to necrosis of the tumor mass, which is likely to be more pronounced in the center of the lesion. To overcome this limitation, two studies have suggested that aspiration of lesions at the periphery or in multiple areas improve the diagnostic accuracy.[24,25] In the "fanning" technique of FNA, the needle is positioned at four different areas within the mass and then moved back and forth multiple times in each area to procure tissue. Aspiration is usually initiated at the left margin of the tumor mass and then "fanned" until the right margin is targeted. The trajectory of the needle is altered using either the "up/down" endoscope dial and/or the elevator. In a recent randomized trial of 54 patients with solid pancreatic mass lesions, the fanning technique established a significantly higher first pass diagnosis in 85.7% of patients compared to only 57.7% with the standard technique.[26] Also, the median number of passes required to establish a definitive diagnosis was significantly less with the fanning technique of FNA.

It appears, therefore, that the fanning technique is superior to the standard approach for EUS-FNA of pancreatic masses as a diagnosis can be established with fewer passes. However, slight modifications should be made when using the 19-G needle as multiple to and fro motions during a single pass renders the lesion and the sample more bloody making cytological interpretation difficult.

RAPID ON-SITE CYTOPATHOLOGY EVALUATION

Presence of a cytopathologist or cytotechnician during EUS-FNA improves diagnostic yield, decreases unsatisfactory samples, reduce the need for additional passes, and consequently the procedural time.[27-30] In a recent study[29] of 182 patients with pancreatic masses who underwent EUS-FNA, with (n=95) or without (n=87) an on-site cytopathologist, the presence of an on-site cytopathologist was associated with a significantly lower number of inadequate samples (1% vs. 12.6%) and a higher diagnostic sensitivity (96.2% vs. 78.2%). In the absence of an on-site cytopathologist, one can adopt the

Table 1. Studies Showing Endoscopic Ultrasound-Guided Fine Needle Aspiration Performance in the Presence of Biliary Endoprosthesis

Author	No. of patients	Comparators	Diagnostic accuracy
Fisher et al.[20]	268	Stent vs. No stent	92.4% vs. 88.5%
Ranney et al.[21]	241	Stent vs. No stent	95% vs. 93%
		Plastic vs. Metal	95% vs. 95%
Siddiqui et al.[22]	677	Plastic vs. Metal stent	97.1% vs. 97 %

following steps to improve FNA outcomes: 1) using the fanning technique to procure better quality sample, 2) performing 5 to 7 passes on pancreatic mass lesions and 3 to 5 passes on lymph nodes, 3) making a dedicated pass for cell-block analysis, and 4) using the pro-core needle or the 19 G needle to acquire histological core tissue if needed.

INDETERMINATE SAMPLE

Sometimes an FNA can be non-diagnostic even in expert hands. This is more commonly encountered when: 1) sampling a pancreatic mass in the background of chronic pancreatitis, 2) if the lesion is in the uncinate process of the pancreas, it may be difficult to visualize the lesion and/or obtain tissue, and 3) when cytology is indeterminate.[31] At present there is no universal protocol on how to manage patients with a high clinical suspicion for pancreatic cancer, but have negative cytology by EUS-FNA. The three options are: 1) clinical observation with repeat EUS-FNA in 3 months, 2) surgical exploration, or 3) computed tomography (CT)-guided biopsy. CT-guided biopsy is less favorable due to risk of tumor seeding. If the suspicion of malignancy is high, the patient is a good operative candidate, and, the lesion appears resectable, then the best option is surgery. On the other hand, if the index of clinical suspicion for malignancy is low, the health status of the patient is marginal, and, the resectability appears borderline, then repeat EUS-FNA is the best course of action. In three studies,[32-34] a repeat EUS-FNA yielded a correct diagnosis in 61% to 84% of patients. Also, despite limited data, combining fluorescence in situ hybridization and K-ras/p53 analysis may improve the diagnostic yield.[35,36]

Table 2. Practical Tips for Obtaining Best Results with Endoscopic Ultrasound-Guided Fine Needle Aspiration (EUS-FNA)

1. Recognize the challenge early and plan accordingly.
2. Use less of the elevator and more of the up/down dial for the technique of FNA.
3. In the duodenum, ensure that the echoendoscope is as straight as possible.
4. Avoid using the stylet.
5. No suction unless a dry aspirate with a "good pass."
6. Adopt the 'fanning' technique.
7. Presence of an on-site cytopathologist for rapid diagnosis.
8. If on-site cytopathology is not available, 5-7 passes are required for pancreatic mass lesions and 3-5 for lymph nodes.
9. Ensure a dedicated pass is made for cellblock.
10. Ensure one stab for cystic lesions with aspiration to dryness under antibiotic cover.
11. Have a clinical management strategy for indeterminate FNA.
12. Consider 19 -G/ProCore needle for obtaining core specimens.
13. Learn to interpret cytopathology slides for specimen adequacy.
14. Reduce complications by taking utmost care with intubation, using antibiotics for cyst aspirations, excluding intervening vasculature and the pancreatic duct along the needle path.

NEEDLE DYSFUNCTION

In a retrospective study of 548 EUS-FNA procedures performed over an 8 months period at a high volume center, the rate of needle failure was estimated at 11.4%.[37] More technical failures were encountered with the use of 19-G needles than 22/25-G needles (22.9% vs. 10.6%). Of the 61 therapeutic interventions performed with the 19-G needle, there were more technical failures with transduodenal vs. other routes, 50% vs. 10%. Of the 487 diagnostic FNAs performed using 22/25-G needles, more technical failures were encountered with transduodenal vs. other routes, 24.3% vs. 4.2%. This data indicates that that the 19-G needle is associated with more technical failures when performing transduodenal passes.

COMPLICATIONS

All three needles have an excellent safety profile with the risks of pancreatitis, bleeding and perforation being less than 1%. Taking additional precautions when performing the procedure would help to avoid complications. The risk of perforation is high when: 1) Intubating the cricopharyngeal sphincter particularly in the elderly patients. Forceful pushing of the echoendoscope, when resistance is encountered, should be avoided. If required, the echoendoscope is exchanged for a gastroscope to evaluate the anatomy and then a guidewire should be placed in the stomach to facilitate scope exchange. 2) The echoendosope should never be forced across an obstructive lesion, particularly in the esophagus. Scanning is undertaken at the level of the stricture and if further assessment is required the stricture should be dilated followed by intubation with the echoendoscope. 3) Care must be taken when advancing the scope from the duodenal bulb to the 2nd portion of the duodenum. Attention is needed to ease the tip of the echoendoscope with the aid of the up/down dial.

While performing FNA, intervening vasculature should be excluded from the path of the needle to reduce the risk of bleeding. Prior to the procedure anticoagulants should be stopped for 5 days and clopidogrel for 7 days. Close liaison with cardiologist, referring physician and the endosonographer is necessary for safe outcomes. Whilst performing FNA of the pancreas, the pancreatic duct should not be punctured to reduce the risk of pancreatitis. The use of antibiotics in cystic lesions is required to reduce the risk of infection. We ad-

minister one dose of intravenous antibiotic (ciprofloxacin) prior to the procedure and then continue oral antibiotics for three days. Overall, with good practices (Table 2), EUS-FNA has an excellent safety profile, as highlighted in a recent meta-analysis.[38]

CONCLUSIONS

EUS-FNA is a very safe and effective procedure. The outcomes are incumbent upon a team approach with close coordination between the endosonographer, nurses, and the cytopathologist. Simple technical steps coupled with attention to finer details is required to achieve the best results.

Conflicts of Interest

The authors have no financial conflicts of interest.

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