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Role of Repeated Endoscopic Ultrasound-Guided Fine Needle Aspiration for Inconclusive Initial Cytology Result

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For tissue diagnosis of suspected pancreatic cancer, endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) is the procedure of choice with high safety and accuracy profiles. However, about 10% of cytologic findings of EUS-FNA are inconclusive. In that situation, careful observation, surgical exploration, or alternative diagnostic tools such as bile duct brushing with endoscopic retrograde cholangiopancreatography or computed tomography-guided biopsy can be considered. However, some concerns and/or risks of these options render repeat EUS-FNA a reasonable choice. Repeated EUS-FNA may impose substantial clinical impact with low risk.

Key Words: Endosonography; Endoscopic ultrasound-guided fine needle aspiration; Pancreatic neoplasms

INTRODUCTION

Despite technical advancement of various imaging modalities, it is still impossible to differentiate benign and malignant pancreatic lesions by the images only. For tissue acquisition to differentiate pancreatic lesions, endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) is the procedure of choice with high accuracy and low complication rate. Pooled sensitivity and specificity of EUS-FNA in the diagnosis of etiology of solid pancreatic mass was 86.8% and 95.8%, respectively, in a meta-analysis.[1] Although EUS-FNA shows high diagnostic accuracy in patients with suspected pancreatic carcinoma, the rate of acquiring indeterminate cytologic findings is still up to 10.9%.[2] Endosonographer face difficulties when cytology result of EUS-FNA is inconclusive while malignancy is highly suspicious in clinical presentation.

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CYTOLOGIC EVALUATION OF EUS-FNA SAMPLE

Although EUS is minimally invasive, very safe and accurate technique for tissue diagnosis, sometimes endosonographers get nondiagnostic EUS-FNA results. After obtaining specimen by EUS-FNA, cytopathologist reads the sample and classifies them into inadequate, benign/reactive, atypical, suspicious, and/or malignant. Problems of EUS-FNA are inconclusive results and diagnostic errors including false positive and false negative. The reasons for those problems stem from the various situations such as failed puncture, successful puncture but obtained inadequate sample material, or successful puncture, obtained adequate sample material but cytology was negative for malignancy.

WHAT CAN WE DO IF INITIAL CYTOLOGY RESULT OF EUS-FNA IS INCONCLUSIVE?

There are several options. In the first place, clinical observation and follow-up with serial imaging is possible. But this results in high level of anxiety. One study showed that about 30% of patients with negative or nondiagnostic EUS-FNA result were finally able to be diagnosed as pancreatic cancer later.[3] In that situation, visible predictors of malignancy on the EUS were vascular invasion or lymphadenopathy.[3] When

pancreatic cancer is clinically suspected, careful short-term follow-up with EUS or other imaging modalities is very risky. Next, surgical exploration with blind pancreatic resection or chemoradiation therapy without definitive tissue diagnosis may be an option. But there may be some medicolegal problems.

As a consequence, when endosonographers get negative or nondiagnostic EUS-FNA result while pancreatic cancer is highly suspicious clinically, the most beneficial next step for the patient should be sought. Alternative diagnostic tools would be chosen to get tissue for diagnosis, such as bile duct brushing with endoscopic retrograde cholangiopancreatography (ERCP) or computed tomography (CT)-guided biopsy. However, ERCP with brushing is associated with postprocedural complications such as pancreatitis and CT-guided biopsy bears the risk of intraperitoneal spread. One study compared alternative methods which can be utilized for tissue sampling when pancreatic cancer is suspicious.[4] ERCP with brushing showed low sensitivity and surgical biopsy showed very high complication rate. CT or abdominal ultrasound-guided percutaneous approach showed high rate of failure compared with EUS-FNA. Considering that all of these options have some concerns and/or risks, retrial of EUS-FNA can also be a reasonable option.

RATIONALE OF REPEATING EUS-FNA

Components of EUS-FNA are lesion, equipment, endosonographer, and cytopathologist. If we can change one of the components of EUS-FNA, we can anticipate different results of repeated EUS-FNA.

Factors that can influence the result of EUS-FNA related with lesion are location, characteristics and size. As to location, pancreatic body and tail are not regarded as easy location compared to mediastinum. Pancreatic head and uncinate are even more difficult area.[5] Though we cannot change the location of the lesion, sometimes we can approach pancreatic head through the stomach, rather than the duodenum to get a better result. Characteristics of the lesion are also an important factor. If there is background pancreatitis, or extensive necrosis of the mass, it is difficult to get a good result from EUS-FNA.[6] We may try to target different area of the lesion to get a better result. Size of the lesion is also important. Accuracy of EUS-FNA increases as the size of the pancreatic mass increases.[7] However, one interesting study suggests that repeated EUS-FNA can improve diagnostic yield even in small pancreatic masses.[8] They evaluated the role of repeated EUS-FNA for small pancreatic mass with previous indeterminate and negative cytology. From January 2004 to October 2006, 47 EUS-FNA was done for pancreatic mass of less than 3 cm in size. Initial EUS-FNA results were 17 malignancies, 21 benign, and nine indeterminate. Repeated EUS-FNA for these nine indeterminate cases resulted in six malignancies, one benign, and two indeterminate. Again, EUS-FNA was done for these two indeterminate cases and one malignancy was proved. As a consequence, initial diagnostic accuracy of EUS-FNA 83% was increased up to 96% by repeated EUS-FNA.

Regarding equipment, ultrasound processor with better resolution can give us better view of targeting the lesion, but there is no study comparing the efficiency of ultrasound processor for EUS-FNA. There is suggestion that newly developed forward viewing echoendoscope may be helpful to puncture difficult lesions such as uncinate process or head of the pancreas.[9] There will be articles about EUS-FNA needles in this issue of *Clinical Endoscopy*.

EUS-FNA is a technically demanding procedure with a steep learning curve.[10] This means that the result of EUS-FNA may be very operator-dependent. According to guidelines for credentialing and granting privileges for EUS by American Society for Gastrointestinal Endoscopy, minimum of 150 supervised cases is recommended for competency of EUS. To perform EUS-FNA, at least 25 supervised EUS-FNA is recommended.[11] But a study showed that the rate of positive yield of EUS-FNA is increasing after 20, 30, 40 EUS-FNA procedures.[12] After looking at the learning curve of 300 consecutive EUS-FNA procedures, a study suggested that even after 45 EUS-FNAs during fellowship, more procedures are needed to gain proficiency and efficiency with EUS-FNA. These studies teach us that the yield of EUS-FNA depends on the experience of endosonographer.[13]

A well-trained cytopathologist is an essential element of successful EUS-FNA procedure and presence of on-site pathologist in the endoscopy suite and rapid on-site cytopathological examination are very helpful to get adequate specimen. On the other hand, an interesting study revealed that cytopathologists' expertise could impact the diagnostic accuracy of EUS-FNA result. In that study, local cytopathologists mailed the EUS-FNA slides of difficult cases to expert cytopathologists. Diagnostic sensitivity and accuracy were 72% and 75% for local cytopathologists, respectively, and 89% and 88% for expert cystopathologists, respectively.[14]

When EUS was repeated for a similar clinical indication at a tertiary-referral center, a significant clinical impact was observed in 63% of the patients.[15] Repeated EUS at the same center with various indications, also resulted in change of further management plan in 72% of the patients.[16] From those results, we might expect that repeated EUS-FNA by expert at another center or by the same endosonographer with different setting can give successful result as the cases of colonoscopy or ERCP maybe successfully performed on the previously failed procedure.

IMPACT OF REPEATED EUS-FNA

A study reported overall accuracy of second EUS-FNA as 84%.[6] Twenty four repeat EUS-FNA were done in the study center and second EUS-FNA proved malignancy in 46% of the cases. Eight out of 10 atypical/suspicious cases with initial EUS-FNA confirmed malignancy. Surprisingly, two out of 10 benign initial EUS-FNA cases changed diagnosis to malignancy and two malignancy cases were confirmed as benign. One out of two indeterminate cases was confirmed as malignancy. Another researcher performed repeat EUS-FNA 3 weeks later, when initial EUS-FNA result was indeterminate for solid pancreatic lesion. The result proved that 78% (7/9) of the patients with indeterminate cytology results had malignancy.[8] When EUS-FNA was performed in 62 cases of repeated EUS, 82% of patients (47/62) among them had inconclusive cytology with previous EUS-FNA, 73% cases (45/62) were prevented from undergoing further diagnostic work-up.[16] There is a retrospective study that evaluated repeated EUS-FNA performed in 15 cases including eight pancreatic mass and seven unknown intra-abdominal lymphadenopathy. Second EUS-FNA proved malignancy in 60% of the cases and overall accuracy of second EUS-FNA was 92.9%.[17] Mean while, there is a study of low diagnostic yield of repeat EUS-FNA. Twenty eight repeat EUS-FNA were done when pancreatic cancer was suspected but prior EUS-FNA results were non-diagnostic. Mean interval of two EUS-FNAs was 33 days. Malignancy was proved in 21.4% and overall diagnostic accuracy was 61%.[18]

CONCLUSIONS

Repeating EUS-FNA is a reasonable choice. Repeated EUS-FNA may impose substantial clinical impact with low risk. In clinical practice, repeated EUS-FNA is useful when the initial EUS-FNA result of a suspected tumor is nondiagnostic. Repeat EUS-FNA should be considered especially if predictors of malignancy, such as vascular invasion or lymphadenopathy, are visible on the EUS.

Conflicts of Interest

The author has no financial conflicts of interest.

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