Difficult pancreatic mass FNA: tips for success

Kenneth F. Binmoeller, MD, Vipulroy D. Rathod, MD

Pancreatic cancer is now the fourth leading cause of cancer-related deaths in the United States, and its incidence appears to be increasing. Cancer of the pancreas develops in approximately 30,000 people in the United States annually. The disease is associated with a high mortality rate and a median survival of approximately 4 months in untreated patients. Data from the National Cancer Database show the 5-year survival after surgery (pancreaticoduodenectomy) to be 3%.[1] However, if surgery achieves clear margins and negative lymph nodes, the 5-year survival approaches 25%. Unfortunately, most patients diagnosed with pancreatic cancer display clinical symptoms at an advanced stage of the disease when surgical cure is no longer possible. When unresectable, chemotherapy, radiation therapy, and a combination of the two may improve overall survival and quality of life.

EUS was developed in the early 1980s to overcome limitations to transabdominal US imaging of the pancreas caused by intervening gas, bone, and fat. The ability to position the transducer in direct proximity to the pancreas by means of the stomach and duodenum, combined with the use of high-frequency transducers, produces detailed high-resolution images of the pancreas that far surpasses that of CT or magnetic resonance imaging (MRI). A logical progression of diagnostic EUS was fine-needle aspiration (FNA). The echoendoscope itself serves as the vehicle to deliver the needle to the target site of puncture. The FNA needle is passed through the instrumentation channel of the echoendoscope and into the pancreatic target lesion under endosonographic guidance.

Current affiliation: Interventional Endoscopy Services, California Pacific Medical Center, San Francisco, California.

Reprint requests: Kenneth F. Binmoeller, MD, Interventional Endoscopy Services, California Pacific Medical Center, 2333 Buchanan St., 5th Floor, San Francisco, CA 94115.

doi:10.1067/mge.2002.127698

With the availability of EUS and EUS-guided FNA procedures in major medical centers around the world, earlier diagnosis and more accurate staging have improved the management of pancreatic cancer. This article will review EUS-guided FNA of the pancreas and tips to achieve successful results.

IS A TISSUE DIAGNOSIS ALWAYS NECESSARY?

Successful FNA begins with an appropriate indication. The indication needs to be determined on a case-by-case basis. As a rule, the FNA result should impact on management. However, a diagnosis of malignancy has obvious prognostic implications and FNA may be desired solely to document a diagnosis of malignancy.

Confronted with an unresectable mass on EUS, FNA is usually performed to document malignancy as a prerequisite for adjuvant chemotherapy or radiation therapy. When care is strictly supportive, FNA is not required. The need for FNA of a resectable mass is largely a question of the likelihood that the tumor represents adenocarcinoma. First-line treatment for adenocarcinoma is surgical and therefore FNA will not influence management. This changes when the differential includes tumors other than adenocarcinoma. A lymphoma or a small-cell metastasis to the pancreas, for example, would be treated by chemotherapy. Metastases to the pancreas, in particular, deserve special emphasis because they appear to be more common than previously appreciated. In one series, metastatic lesions comprised 11% of pancreatic masses referred for EUS-guided FNA.[2] From the standpoint of EUS imaging, a metastatic lesion cannot be differentiated from a primary one. FNA diagnosis of a neuroendocrine tumor may alter management to less invasive surgery, chemotherapy, or surveillance alone if the histologic features are sufficiently benign.[3]

FNA may be desirable before surgery for practical reasons. Patients may be reluctant to undergo a major operation without the certainty of a malignant diagnosis. Some surgeons prefer preoperative FNA to establish malignancy because it avoids the need for an intraoperative frozen section, which prolongs the operative procedure and may be inconclusive.

FNA is occasionally indicated to document the absence of malignancy when the pretest probability of malignancy is low. Chronic pancreatitis, for example, may manifest a pseudotumor. In the proper clinical setting a benign FNA may support conservative rather than surgical management.[4] Differentiation of an "inadequate" from a "negative" result is imperative when interpreting the FNA specimen. Direct consultation with the attending cytopathologist is recommended to verify that an adequately cellular FNA derived from the pancreas has been obtained.

IS EUS GUIDANCE THE BEST APPROACH?

Alternative methods to obtain a tissue diagnosis should be considered and reviewed with the patient before EUS-guided FNA. EUS guidance has several theoretical advantages over percutaneous CT-guided FNA. The superior resolution of EUS combined with real-time imaging should improve the accuracy of lesion targeting. More importantly, lesions that are too small to be detected by CT can be sampled. Seeding can occur with a percutaneous- or EUS-guided approach, but the risk should be lower with EUS guidance in view of the more direct access with short needle-to-tissue distance and absent violation of the peritoneal space. Seeding of the needle tract is inconsequential for transduodenal EUS-guided FNA because the duodenum becomes part of the resection specimen. Finally, the safety of FNA should be improved with the EUS-guided approach, especially lesions encased by vascular structures.

Tissue sampling by brush cytology of the bile and/or pancreatic ducts during ERCP is an alternative to FNA. Brush cytology has yielded disappointing results with accuracy rates generally below 50%. Lee et al.[5] examined brush cytology from 168 pancreaticobiliary strictures in 149 patients and found the diagnostic sensitivity to be 37%. More importantly, the role of ERCP for purely diagnostic objectives is rapidly vanishing with the advent of MRCP and the more widespread availability of EUS. Increasingly, ERCP with biliary stent placement is reserved for patients with an established diagnosis of unresectable malignancy.

RESULTS OF EUS-GUIDED FNA

Numerous studies have documented the high accuracy of EUS-guided FNA in diagnosing pancreatic malignancy and a favorable impact on management. The impact of EUS-guided FNA was studied by Chang et al.[6] in a series of 44 patients. EUS-guided FNA had a 95% accuracy rate for pancreatic lesions and 88% accuracy rate for lymph nodes. Three patients had enlarged celiac nodes on EUS that showed malignancy on FNA. Overall, FNA precluded surgery in 41%, avoiding the need for further diagnostic tests in 57%, and influenced clinical decisions in 68% of the patients, thus providing substantial cost savings.

In a recent study by Erickson and Garza[7] of 84 patients with pancreatic cancer who were evaluated by EUS-FNA, 34% of the lesions were not visualized with other modalities. Compared with patients who were evaluated with just CT with or without FNA, EUS-FNA diagnosis was significantly better for identifying and diagnosing pancreatic masses and associated lymph nodes. Surgical procedures for diagnosis decreased by 75% after the introduction of EUS-FNA at the authors' institution. Finally, compared with the pre-EUS CT era, survival was increased significantly by 3 months, which was attributed to the earlier diagnostic capability and greater sensitivity of EUS-FNA.

Gress et al.[8] specifically examined the role of EUS-FNA in patients with suspected pancreatic cancer after a negative CT-guided FNA or endoscopic retrograde cholangiopancreatography (ERCP) with brush cytology. In 102 such patients, 57 had positive cytology on EUS-FNA, 37 had negative cytology, and in 8 the examination was inconclusive. After a median follow-up of 24 months, all 57 patients with positive cytology on EUS-FNA had verification of the diagnosis of pancreatic cancer. There were 45 patients with negative or inconclusive cytology on EUS-FNA, 41 of whom had no evidence of a pancreatic malignancy at follow-up.

FACTORS INFLUENCING FNA RESULTS

FNA of the pancreas can be challenging for many reasons. First, accessing the mass can be difficult, especially when it is located in the uncinate process or the pancreatic isthmus. Second, FNA can be difficult because of the torque in the scope combined with angulation of the needle and its sheath. This increases the friction that must be overcome to advance the needle. Third, pancreatic tumors tend to be fibrotic and indurated, resisting penetration by the needle, but also preventing proper cell sampling once the needle is in the lesion. Puncturing the mass and moving the needle within the lesion can require considerable force. Multiple passes are generally required to obtain an adequate specimen from a pancreatic mass. Finally, the interpretation of the cytologic specimen can be challenging, especially when tumors are well differentiated.

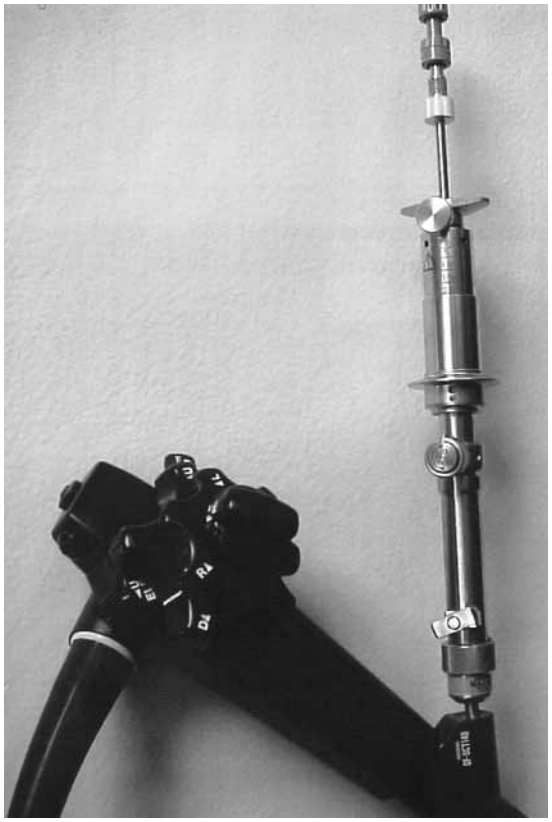

Figure 1. Automated spring-loaded Powershot needle (Olympus NA-11J-KB).

Location of the lesion

Lesions located in the uncinate process of the pancreas are the most difficult to puncture. To access a mass in the uncinate process, the echoendoscope must be advanced into the duodenal C-loop (second portion) in the "long" position. This exerts substantial angulation and torque on the FNA needle. The needle is not only more difficult to advance, but acquires a "bowed" shape. The altered shape can result in mistargeting. On real-time imaging the needle may "disappear" during advancement as it deviates from the desired plane of FNA.

Lesions in the pancreatic isthmus pose a similar challenge in that the echoendoscope is usually in the "long" position with the tip in the gastric antrum. A transgastric approach to FNA can be more difficult than the transduodenal owing to the laxity and redundancy of the gastric wall, as well as the capaciousness of the stomach. Lacking anchorage, the echoendoscope tends to displace during advancement of the FNA needle.

Lesions are easiest to sample when the scope is shortened and relatively straight. This is usually possible when sampling masses in the body or tail of the pancreas.

Consistency of the lesion

Pancreatic tumors incite a desmoplastic reaction and the resulting fibrosis may be difficult to penetrate. Failure to penetrate indurated lesions has been reported in 10% to 15% of attempted EUS-guided FNA procedures.[9] Even when penetration is possible, the cytologic yield is often scant or dry.

Difficult penetration of indurated pancreatic lesions can be overcome with an automated spring-loaded "Powershot" needle (Olympus NA-11J-KB) that enters the target lesion at high velocity (Fig. 1). Developed by Binmoeller et al.,[10] the automated device was designed to function analogous to spring-loaded biopsy needles used for percutaneous tissue sampling. In a preliminary study the Powershot needle successfully penetrated and biopsied indurated pancreatic masses that had failed FNA using a conventional manually operated needle.

Using an ex vivo porcine model, Muthusamy et al.[11] compared the Powershot needle with a standard manually operated needle (Olympus NA-10J-1). The effect of moving the needle to and fro within tissue and the use of suction were evaluated, and specimens were scored for contamination by gastric wall cells and the average cellular yield. The Powershot needle was associated with less contamination, but the cytologic yield was no greater than when using standard FNA technique.

Ardengh et al.[12] used the Powershot needle in 59 pancreatic lesions, including 42 solid masses. The sensitivity for the Powershot FNA in solid masses was 91% with a specificity of 90% and accuracy of 90.5% (personal communication). In a comparative study with two manually operated needles (Olympus NA-10J-1 and GIP needle) in 16 patients including 13 pancreatic masses, the Powershot needle was found to provide a higher tissue yield (87.5% vs. 62.5% for NA-10J-1 and 43.8% for GIP, not statistically significant) and a higher rate of core specimens (81.2% vs. 50% for NA-10J-1, not statistically significant).

Size of the lesion

Small lesions (<2 cm) not only require greater targeting accuracy, but may defy FNA because of the tendency of the needle to displace the target during advancement. Sampling of small lymph nodes is especially challenging because they are embedded in loose connective tissue (Fig. 2). The Powershot needle can improve the success of FNA by advancing the needle into the target lesion under high velocity. Targeting is more accurate because the needle remains straight and "spears" the target lesion before it can displace.

Site of FNA

The optimal site for FNA of pancreatic tumor is difficult to define. Pancreatic head tumors are often necrotic in the center, and therefore EUS-guided FNA from the edge of the lesion may provide the more representative tissue. However, the periphery may yield fibrotic tissue because of a desmoplastic reaction induced by a centrally located carcinoma. A wide sampling of the mass at the periphery and center is therefore the best approach.

Needle size

Intuitively, larger needles should acquire more tissue, thereby improving diagnostic accuracy. However, comparative studies have failed to show an improvement in diagnostic accuracy by using larger needles. In fact, many studies have shown larger needles to provide inferior accuracy rates compared with thinner ones.[13] The main reason for this is the difference in the interpretation of specimens for cytology and histology. Standard FNA needles of 22 or 23 gauge provide a cytologic sample, whereas larger needles of 18 or 19 gauge provide a tissue core for histology. Histology preserves tissue architecture but can miss subtle features of malignancy that may only be seen on cytology. In a study of EUS-guided FNA of the pancreas with an 18-gauge needle, Binmoeller et al.[14] found histology to have a lower sensitivity than cytology in detecting malignancy.

A 19-gauge true-cut biopsy needle (Wilson-Cook "Quick-Core," Winston-Salem, N.C.) has recently been commercialized. As of the time of the writing of this manuscript there are no published clinical data on the results of pancreatic biopsy using this needle. The use of larger needles for EUS-guided FNA has technical drawbacks. The increased diameter of the needle makes penetration of indurated pancreatic lesions more difficult. Increased diameter also results in increased needle stiffness. A stiff needle will be more difficult to pass through the echoendoscope, especially with the tip is angulated. A stiff needle will also restrict the flexibility of the bending section of the echoendoscope.

Types of needles

Commercially available manually operated needles have been found to be grossly equivalent in performance and diagnostic yield. Erickson et al.[15] reported no difference between the GIP and Wilson-Cook needles in the number of passes needed for EUS-FNA diagnosis of pancreatic lesions. Similarly, Fritscher-Ravens et al.[16] found no significant differences between the Wilson-Cook and GIP needle. The Wilson-Cook Echotip needles have gained popularity in the United States because of their disposability.

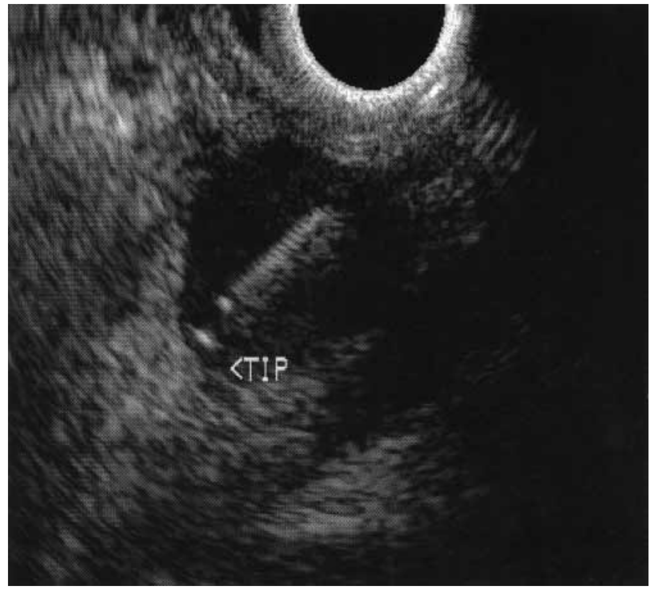

Figure 2. EUS-guided FNA of a celiac lymph node.

The ability to lock the penetration depth of this needle is attractive in that it avoids overshooting of the target lesion when forceful advancement is required.

Suction

Active suction during FNA can increase the cytologic yield, but with a potential increase in artifact and blood contamination. A study by Wallace et al.[17] found that suction did not improve the overall diagnostic yield of lymph node FNA. However, the yield and accuracy of lymph node FNA without suction were very high in this study.

Anecdotal experience suggests that suction improves the yield of pancreatic FNA. It is unknown whether wall suction or a high-powered mechanical suction pump can provide better cellularity than manual aspiration with a syringe.

Operator experience

Successful EUS-FNA requires a thorough knowledge of normal and abnormal anatomy and experience with techniques of FNA. As with other interventional endoscopic procedures, there is a "learning curve" that may impact results of FNA. In a multicenter study of Wiersema et al.[9] the accuracy of EUS-FNA improved with operator experience from 80% to 92% ($p < 0.001$). In another study the only variable that was found to be a significant predictor of EUS-FNA accuracy in the multivariable model was operator experience.[18]

On-site cytopathology

Cytologic samples can be rapidly stained and examined, thereby providing immediate assessment of adequacy, and in many cases a provisional diagnosis can be made at the time of the procedure. Furthermore, involvement by an on-site pathologist optimizes clinical correlation and ensures that specimens are optimally handled. In some cases samples are required for ancillary investigations, such as microbiology, flow cytometry, or molecular studies.

The presence of an expert on-site cytopathologist has been found to significantly impact FNA success rates. In a prospective assessment of 109 FNA procedures, Erickson et al.[15] showed that the absence of a cytopathologist resulted in poor diagnostic accuracy as well as increased procedure time, number of needles used, and overall examination costs. Among a variety of factors studied, the differentiation of the primary tumor was the strongest predictor for the number of passes required to establish a diagnosis of malignancy. Well-differentiated adenocarcinomas required a significantly higher number of aspirations than moderately or poorly differentiated ones. Overall, pancreatic masses required 5 to 6 passes compared with 2 to 3 passes for lymph nodes or hepatic metastases. Interestingly, the number of needle passes has not been found to predict a cellular, diagnostic specimen, suggesting that increasing the number of passes alone does not improve accuracy.[18]

PRACTICAL TIPS TO IMPROVE FNA RESULTS

Sample suspicious lymph nodes or ascites first. Lymph nodes and ascites are more easily targeted and sampled than pancreatic lesions. Metastatic spread to celiac or mediastinal lymph nodes or the presence of malignant ascites establishes unresectability (M-1 stage disease).[19]

Select the optimal site for the first pass. The first FNA pass provides the best specimen. If a diagnosis of malignancy can be established with the first pass by an on-site cytopathologist, further FNA passes are not required, saving time and expense. With additional FNA passes the needle becomes progressively blunt and deformed.

Perform FNA with the echoendoscope maximally straightened. Performing FNA with the echoendoscope in the short and straightened position will minimize deformity and friction that can cause mistargeting. Angulation may also occur at the handling end (keep the shaft attachment to the handle as straight as possible).

Straighten the needle before FNA. Inspect the shape of the needle before FNA. If the needle is bowed or deformed, manually regroom the needle until it advances in a straight axis from the outer sheath.

Communicate with the cytopathologist. Communicating clinical background information and imaging findings to the cytopathologist can facilitate the interpretation of the FNA specimen. Reviewing slides with the cytopathologist provides valuable feedback to improve FNA technique.

REFERENCES

1. Stephens J, Kuhn J, O'Brien J, Preskitt J, Derrick H, Fisher T, et al. Surgical morbidity, mortality, and long-term survival in patients with peripancreatic cancer following pancreaticoduodenectomy. Am J Surg 1997;174:600-4.
2. Fritscher-Ravens A, Sriram PV, Krause C, Atay Z, Jaeckle S, Thonke F, et al. Detection of pancreatic metastases by EUS-guided fine-needle aspiration. Gastrointest Endosc 2001;53: 65-70.
3. Rathod VD, Binmoeller KF, Thul R, Brand B, Seitz U, Bohnacker S, et al. The role of EUS-guided fine needle aspiration-biopsy (FNAB) in the diagnosis of neuroendocrine tumors. Gut 1997;41:25-26E.
4. Hollerbach S, Klamann A, Topalidis T, Schmiegel WH. Endoscopic ultrasonography (EUS) and fine-needle aspiration (FNA) cytology for diagnosis of chronic pancreatitis. Endoscopy 2001;33:824-31.
5. Lee JG, Leung JW, Baillie J, Layfield LJ, Cotton PB. Benign, dysplastic, or malignant—making sense of endoscopic bile duct brush cytology: results in 149 consecutive patients. Am J Gastroenterol 1995;90:722-6.
6. Chang KJ, Nguyen P, Erickson RA, Durbin TE, Katz KD. The clinical utility of endoscopic ultrasound-guided fine-needle aspiration in the diagnosis and staging of pancreatic carcinoma. Gastrointest Endosc 1997;45:387-93.
7. Erickson RA, Garza AA. Impact of endoscopic ultrasound on the management and outcome of pancreatic carcinoma. Am J Gastroenterol 2000;95:2248-54.
8. Gress V, Gottlieb K, Sherman S, Lehman G. Endoscopic ultrasonography-guided fine-needle aspiration biopsy of suspected pancreatic cancer. Ann Intern Med 2001;134:459-84.
9. Wiersema MJ, Vilmann P, Giovannini M, Chang KJ, Wiersema LM. Endosonography-guided fine-needle aspiration biopsy: diagnostic accuracy and complication assessment. Gastroenterology 1997;112:1087-95.
10. Binmoeller KF, Jabusch HC, Seifert H, Soehendra N. Endosonography-guided fine-needle biopsy of indurated pancreatic lesions using an automated biopsy device. Endoscopy 1997;29:384-8.
11. Muthusamy R, Jafri SF, Ghafari S, Hosobuchi C, Chang KJ, Nguyen P. Techniques for optimal cytologic yield using the Olympus KB-22 "shotgun" needle in endoscopic ultrasound (EUS) guided fine needle aspiration (FNA): an ex-vivo model [abstract]. Gastrointest Endosc 2001;53:AB120.
12. Ardengh JC, Paulo GA, Ferrari AP. Comparative study of 3 systems for endoscopic ultrasound guided fine needle aspiration (EUS-FNA) [abstract]. Gastrointest Endosc 2001;53: AB168.
13. Glenthoj A, Sehested M, Torp-Pedersen S. Ultrasonically guided histological and cytological fine needle biopsies of the pancreas. Reliability and reproducibility of diagnoses. Gut 1990;31:930-3.
14. Binmoeller KF, Thul R, Rathod V, Henke P, Brand B, Jabusch HC, et al. Endoscopic ultrasound-guided, 18-gauge, fine needle aspiration biopsy of the pancreas using a 2.8 mm channel convex array echoendoscope. Gastrointest Endosc 1998;47: 121-7.

15. Erickson RA, Sayage-Rabie L, Beissner RS. Factors predicting the number of EUS-guided fine-needle passes for diagnosis of pancreatic malignancies. Gastrointest Endosc 2000;51: 184-90.
16. Fritscher-Ravens A, Topalidis T, Bobrowski C, Krause C, Thonke E, Jackle S, et al. Endoscopic ultrasound-guided fine-needle aspiration in focal pancreatic lesions: a prospective intraindividual comparison of two needle assemblies. Endoscopy 2001;33:484-90.
17. Wallace MB, Silvestri GA, Sahai AV, Hawes RH, Hoffman BJ, Durkalski V, et al. Endoscopic ultrasound-guided fine needle aspiration for staging patients with carcinoma of the lung. Ann Thorac Surg 2001;72:1861-7.
18. Harewood GC, Wiersema LM, Hailing AC, Keeney GL, Salamao DR, Wiersema MJ. Influence of EUS training and pathology interpretation on accuracy of EUS-guided fine needle aspiration of pancreatic masses. Gastrointest Endosc 2002;55:669-73.
19. Delcore R, Rodriguez FJ, Forster J, Hermreck AS, Thomas JH. Significance of lymph node metastases in patients with pancreatic cancer undergoing curative resection. Am J Surg 1996;172:463-9.