The Future of EUS-guided Tissue Acquisition: Toward Personalized Medicine

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Introduction

Major advances in endoscopic techniques to diagnose and manage pancreatic diseases have fundamentally changed the approach to these difficult clinical challenges. The diagnosis of benign and malignant pancreatic diseases is much more readily obtained through a combination of cross-sectional imaging and endoscopic procedures (Table 1). ERCP (endoscopic retrograde cholangio-pancreatography) and EUS (endoscopic ultrasound) are the most important endoscopic tools for imaging and accessing the pancreas.

In this review we will examine the major recent advances in the diagnosis of malignant diseases of the pancreas using ERCP and EUS.

The role of EUS in the diagnosis of pancreatic malignancy

With the increasing accuracy of CT and MRI for the detection and diagnosis of pancreatic malignancy, the need for diagnostic ERCP has decreased. In addition, the added capabilities provided by EUS have also decreased the need for ERCP. EUS is a powerful diagnostic tool in the detection of pancreatic malignancy by detecting focal mass lesions arising from the pancreatic parenchyma. Although EUS is very sensitive in the detection of pancreatic malignancy, the finding of a focal hypoechoic mass is not specific for malignancy and often EUS-guided FNA is required (2). There are several associated findings of typical pancreatic cancer. Since the pancreatic malignancy arises from the pancreatic parenchyma, the malignant mass often obstructs the pancreatic duct. Proximal to the site of obstruction, a diffusely dilated pancreatic duct will be seen. Surrounding the obstructed pancreatic duct will be changes in the pancreatic parenchyma. As a result of the obstruction, the parenchyma often becomes edematous and hypoechoic by EUS. Occasionally, a dilated side branch duct is seen and may simulate the presence of a cyst. Chronic pancreatitis may simulate the findings of pancreatic malignancy with the presence of a focal mass, dilated pancreatic duct, and abnormal parenchyma. However, the finding of pancreatic calcifications provides strong evidence for a benign process. The presence of alcoholic pancreatic disease may interfere with the diagnosis of pancreatic malignancy (3).

The aspiration of a pancreatic mass can provide tissue for the diagnosis of a malignancy. Traditionally, computed tomography (CT) and trans-abdominal ultrasonography (US) have been used to guide the aspiration of
a pancreatic mass. However, open MRI techniques are now being employed for pancreatic FNA (4). Recently, endoscopic ultrasound (EUS) has been introduced as an alternative to CT/US guidance for biopsies because of superior imaging of the pancreas achieved by EUS (5).

The most common technique for tissue acquisition from a pancreatic mass is fine needle aspiration (FNA). The use of a small gauge needle for aspiration cytology of the pancreas has increased the safety and ease of FNA compared to the traditional core tissue biopsy using large gauge needles (6,7). The tissue obtained during FNA is evaluated with cytological techniques whereas core tissue specimens are processed for histology (8).

The request for a tissue diagnosis of a pancreatic lesion may originate from a number of specialists caring for a patient. The primary care physician may request a tissue diagnosis in order to aid the patient and family in decision-making. The oncologist often requires a tissue diagnosis in order to provide chemotherapy. The surgeon may need a diagnosis for surgical planning. Lastly, the patient may request a biopsy in order to increase the certainty of a diagnosis.

The most common indication for obtaining tissue from a pancreatic lesion is the need for the documentation of a malignancy in a patient with a malignant-appearing pancreatic mass. In patients who are not operative candidates, a large pancreatic mass can be accessed with either CT scanning or EUS. A tissue diagnosis is particularly important in patients who will be treated with chemotherapy. The cytological analysis of aspirated pancreatic tissue can readily differentiate between adenocarcinoma, islet cell malignancies, metastasis to the pancreas, and inflammatory lesions. A ‘tissue’ diagnosis in patients with a pancreatic mass is an important factor in the planning of surgery. For example, the surgical approach to islet cell tumors is often quite different than adenocarcinomas. A more compelling indication for a pancreatic mass ‘biopsy’ is the finding of an atypical pancreatic mass on imaging. The differential diagnosis of an atypical pancreatic mass is often quite wide and includes adenocarcinoma, islet cell tumor, pancreatic metastasis, focal chronic pancreatitis, and cystadenomas (9). The surgical approach as well as the overall management of the patient will often be altered depending on the results of the pancreatic ‘biopsy’. For example, the management of a serous cystadenoma is quite different than an islet cell tumor.

EUS-Guided FNA of the pancreas has been performed over the past 5-10 years. Using the guidance of the high frequency ultrasound transducer on the tip of the echoendoscope, a small gauge needle is passed through the wall of the gastrointestinal tract and into the pancreatic mass (Figure 2). A number of different sizes of needles are used, ranging from 25 to 19 gauge needles. Peri-pancreatic lymph nodes can also be targeted for FNA. The accuracy of EUS-FNA for lymph nodes is similar to EUS-FNA of pancreatic masses. It has been recommended that for optimal results, a pancreatic mass should be sampled with 7 aspirations and lymph nodes should be sampled with 5 aspirations (10). If an on-site cytologist is present, the number of aspirations can be reduced to whatever is necessary in order to obtain diagnostic tissue (11). Liver metastasis can also be aspirated by EUS and the tissue used as the basis for the diagnosis of the primary pancreatic lesion.

The chief advantage of EUS-guided FNA is the ability to target, small, intra-pancreatic masses. Nearly 25% of EUS targets of FNA in the pancreas cannot be seen with CT. Similarly, EUS can also target low grade malignancies such as neuroendocrine tumors and metastatic lesions to the pancreas (9) (Figure 5). These types of targets were not previously accessible by CT guidance. EUS can also target lesions suspected with the findings of ERCP, such as a focal stricture. FNA of cystic malignancies does not yield the accuracy commonly associated with the FNA of solid lesions (Figure 6). However, FNA-cytology of intra-ductal papillary mucinous tumors
(IPMT) can yield diagnostic material, particularly when solid lesions associated with the cystic lesion are targeted. The greatest impact on patient care is the ability to avoid unnecessary surgery in non-operative candidates (12). In 60% of patients, there was a change in patient management based on the results of the EUS FNA. Most commonly the results of EUS and FNA result in a higher stage of malignancy. With the increased use of CT scanning findings such as pancreatic enlargement, the importance of EUS-guided FNA has increased (13). EUS-FNA was particularly accurate at identifying pancreatic malignancy in those patients presenting with obstructive jaundice. However, falsely negative pancreatic FNA remains a problem mostly as a result of contamination from the GI tract (14).

Pancreatic masses can be readily staged with the findings of EUS (15). Stages T1-2 pancreatic malignancies are intra-pancreatic lesions without evidence of extra-pancreatic extension. Stage T3 pancreatic cancer has focally involved local structures such as the duodenum and bile duct. T4 lesions have invaded the portal vein and its branches, making surgical resection difficult. Metastatic lesions in the liver, peritoneum, and lymph nodes can also be detected aspirated for cytology (16).

Peripancreatic lymph nodes are readily imaged and staged with EUS. Since the ultrasound appearance of lymph nodes is not specific for malignancy, fine needle aspiration is commonly performed. The specificity of cytology is very high when malignant cytologic material is found. The sensitivity is in the range of 60-70%. The finding of malignant lymph nodes remote from the site of malignancy may have a significant impact on the decision making for resection.

EUS is not primarily used for detection of metastatic disease. Although is EUS is highly sensitive for the presence of metastatic lesions within the left lobe of the liver, the right lobe of liver is incompletely examined with EUS. Fine needle aspiration is commonly performed of lesions in the liver that are suspicious for metastatic lesions. The sensitivity and specificity are very high, approaching more than 90%. There are few complications from fine needle aspiration of lymph nodes and liver lesions.

EUS can also be used for the diagnosis of cystic neoplasms of the pancreas (17) (Table 2). Using the high resolution imaging of endoscopic ultrasound, the morphologic features of various cystadenomas have recently been defined. Figure 4 However, the detailed imaging features of cystic neoplasms by EUS do not appear to be sufficiently accurate to differentiate between benign and malignant cystadenomas unless there is evidence of a solid mass or invasive tumor. Fine needle aspiration under EUS guidance can be performed on small lesions within the pancreas.

Cyst fluid, aspirated using EUS guidance, can be analyzed through the use of cytology and a variety of tumor markers. However, the low cellular content of cyst fluid has hampered the use of the cytologic analysis of cyst fluid. Small, cuboidal cells in cytologic specimens are diagnostic of serous cystadenomas. In contrast, mucinous cystic neoplasms may have epithelial cells with evidence of mucin secretion or atypica. Only inflammatory cells should be present in the fluid aspirated from pseudocysts.

A variety of cyst fluid tumor markers have been studied to help differentiate between the major types of cystic neoplasms. Several studies suggest that carcinoembryonic antigen (CEA) or CA 72-4 are useful for identifying mucinous lesions (18). These carbohydrate antigens are secreted by the epithelium lining mucinous lesions and are present in high concentrations. Cyst fluid concentrations of CEA and CA 72-4 are very low in serous cystadenomas. Unfortunately, there is considerable overlap in cyst fluid concentration of CEA in benign and malignant mucinous cystic lesions and pseudocysts (19). Nevertheless, the aspiration of cyst fluid for CEA
analysis has been demonstrated to be a cost effective approach (20).

Intra-ductal papillary mucinous neoplasms can be imaged with endoscopic retrograde cholangio-pancreatography (ERCP) or EUS. The endoscopic appearance of mucin extrusion from a widely patent ampulla is diagnostic of an intraductal papillary mucinous neoplasm. Contrast retrograde pancreatography will demonstrate the characteristic findings of mucinous filling defects within the duct, diffuse ductal dilation, and cystic dilation of side branches. EUS may assist in the detection of malignancy arising from intraductal papillary mucinous neoplasms by demonstrating wall invasion and guiding fine needle aspiration (21).

In summary, the endoscopic procedures, ERCP and EUS, have had a major impact on the management of patients with pancreatic malignancy. The early diagnosis may improve the patient management and length of survival from these aggressive malignancies.

References

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