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# Endoscopic Ultrasound-Guided Fine Needle Aspiration in Cystic Pancreatic Lesions

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Incidental pancreatic cysts are being increasingly recognized recently with incremented concern about health and frequent health check-up. Endoscopic ultrasound (EUS) has emerged as the principal modality for imaging pancreas for various pancreatic diseases including pancreatic cyst. But imaging alone cannot accurately identify the exact nature of the pancreatic cyst. EUS-guided fine needle aspiration is a useful adjunctive procedure to differentiate pancreatic cystic lesions. Cystic fluid analysis with cytologic evaluation is important to diagnose etiology of pancreatic cystic lesions, helping the clinician to more accurately assess the presence or potential for malignancy.

**Key Words:** Endosonography; Pancreas; Cysts; Aspiration

## INTRODUCTION

The prevalence of pancreatic cystic neoplasms (PCNs) is around 2.5%.<sup>1,2</sup> Pancreatic cysts are increasingly discovered probably because of the ubiquitous presence of multi-detector computed tomography (CT) scans and their increased use to evaluate patients with abdominal complaints. Endoscopic ultrasound (EUS) plays a pivotal role in the evaluation of patients with pancreatic cysts but EUS and cross-sectional imaging alone have proven to be inaccurate in identifying the exact nature of the cysts. There is inadequate information on the natural history of pancreatic cysts but our knowledge base cannot be expanded without being able to determine the exact nature of the cyst noninvasively. Toward this end, EUS with fine needle aspiration (FNA) along with cyst fluid analysis has been advocated to improve the utility of EUS in the diagnosis of pancreatic cysts. The major concern for PCN is their potential for malignant transformation. Size >3 cm and/or the presence of mural nodules appear to be the best

indicators of malignant change in patients with the side branch form of intraductal papillary mucinous neoplasm (SB-IPMN) and mucinous cystic neoplasms (MCN).<sup>3</sup> EUS with cyst fluid aspiration and/or FNA can play a role in differentiating PCNs. This paper will review the role of EUS-FNA in the evaluation of PCNs.

## IMAGING OF PCN

Most PCNs are detected by CT. If the cysts are incidental (the patient has no symptoms referable to the pancreas), the great majority are determined to be neoplastic.<sup>4</sup> In one study, the majority of incidentally detected pancreatic cysts (58%) were mucinous and therefore had some malignant potential.<sup>4</sup> These data suggest that all incidentally found pancreatic cysts should undergo further evaluation.

There are characteristic imaging features of PCN. Serous cyst adenomas consist of multiple “micro cysts” with thin septae coursing through the lesion. They may have central (“starburst”) scarring or calcification. However, 20% have a dominant macrocystic or even solid component which can result in confusion with mucinous cysts.<sup>5,6</sup> MCNs are almost exclusively located in the tail of the pancreas and are either unilocular or have only a small number of discrete compartments. Rarely they will have peripheral (eggshell) calcification which is highly predictive of cancer.<sup>7</sup> MCN almost never communicate with the pancreatic ductal system. The cystic

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component of the side branch form of IPMN is essentially a dilated side branch(s) and by definition, is part of the pancreatic duct. Magnetic resonance imaging (MRI) is superior in imaging SB-IPMN by virtue of its ability to visualize the pancreatic ductal system. Secretin stimulated MRI/magnetic resonance cholangiopancreatography can be used to highlight the ductal anatomy<sup>8</sup> and is commonly used in pancreatic centers but its superiority to non-secretin studies in the evaluation of IPMN has not been proven. Identification of SB-IPMN with EUS can be made by visualizing a dilated side branch(s) with connection to the main pancreatic duct. Depending on the plane of imaging, they may appear as a chain of lakes-separate cysts that become confluent when scanning back and forth across the cyst.

The primary problem with imaging alone in the evaluation of pancreatic cysts is that there are no clearly differentiating features that allow a high degree of diagnostic accuracy. Studies have shown that imaging alone is inaccurate in differentiating each of the types of cystic neoplasms.<sup>9</sup> In a recent study from the group at the Academic Medical Center in Amsterdam, the accuracy in identifying the nature of a pancreatic cyst using EUS imaging alone was only 23% to 46% amongst a group of expert endosonographers.<sup>10</sup> This study used 4 criteria to differentiate cysts: 1) septations, 2) mural nodules, 3) a solid component, and 4) communication with the pancreatic duct. As a result of these discouraging reports, EUS-guided cyst aspiration and analysis along with cytology have been used to improve diagnostic accuracy; especially the differentiation between macrocystic serous cyst adenoma, SB-IPMN and MCN.

## EUS-FNA FOR PANCREATIC CYSTIC FLUID ASPIRATION

Difficulties in establishing an accurate diagnosis with imaging alone have prompted investigators to pursue adjunctive measures. The idea of using analysis of cyst aspirates to diagnose PCN dates back to 1991.<sup>11</sup> The Massachusetts General Hospital surgical group is credited with advancing the clinical application of this concept<sup>12</sup> and Brugge<sup>13</sup> then applied EUS-FNA techniques to obtain cyst fluid noninvasively.

The technique of cyst aspiration is relatively straightforward. In most hospital laboratories, 1 to 2 mL of fluid is needed to perform carcinoembryonic antigen (CEA) analysis. As a result, the cyst should be 1 to 2 cm in size to obtain sufficient fluid for CEA analysis. Recently, it has been possible to perform CEA on as little as 500  $\mu$ L of fluid (RedPath Integrated Pathology, Pittsburgh, PA, USA). Because the fluid may be quite viscous, a 19 or 22 gauge needle is preferred. A single pass is made and the cyst is completely drained. Intravenous antibiotics are recommended during the procedure with oral anti-

biotics given for 3 to 5 days afterwards. It is recommended that the fluid be sent for CEA, amylase and/or lipase, and cytology. Some investigators will also send it for an extracellular mucin stain or viscosity measurement.

The rationale for analyzing for amylase or lipase is to aid in determining if there is ductal communication. This can help to differentiate a MCN from IMPN. The cooperative pancreatic cyst study group then reported that cyst fluid analysis for CEA was the best test to differentiate a mucinous from a nonmucinous cyst.<sup>14</sup> However, the sensitivity and specificity for CEA is 73% and 84%, respectively, and 25% of mucinous cysts will have a CEA level less than 192 ng/mL.<sup>14</sup>

It may be possible to improve the analysis of cyst fluid by combining CEA and molecular analysis (DNA quantity, K-ras mutations and allelic imbalance mutations). Sawhney et al.<sup>15</sup> reported a 100% sensitivity of discrimination between mucinous and nonmucinous cysts using a combination of CEA and molecular analysis. It has also been reported that combining an extracellular mucin stain with CEA analysis can provide an accurate discrimination between mucinous and nonmucinous cyst.<sup>16</sup>

Problems with EUS-guided cyst aspiration were delineated in a paper by de Jong.<sup>17</sup> One hundred forty-three consecutive patients with indeterminate pancreatic cysts underwent EUS-guided cyst aspiration and the fluid was sent for CEA, CA19-9, amylase and cytology. Only 90% could be punctured (cyst in inaccessible location or too small). Of the remaining 128 patients, only 31% had adequate cellularity for analysis and there was sufficient fluid for CEA in only 68 (49%). Complications were encountered in 2.4%.

Fluid specimens from pancreatic cysts seldom yield cells because few viable cells are shed from the lining. The lining epithelium can be patchy which also contributes to the difficulty in obtaining adequate samples. The lining of serous cyst adenomas is a glycogen-rich cuboidal epithelium whereas mucinous cysts have a mucin containing columnar epithelium (MCN is differentiated from IPMN by having ovarian-type stroma). A cytology brush within a 19 gauge needle has been developed in an attempt to improve cytologic yield during EUS-guided cyst aspiration (EchoBrush; Cook Endoscopy, Winston-Salem, NC, USA). The needle is passed into the cyst and then the brush is advanced against the inner wall of the cyst. The 1st report of using the cytology brush for pancreatic cyst cytology came from Al-Haddad et al.<sup>18</sup> They studied 10 patients with pancreatic cysts and compared the cellular yield for standard FNA compared to brush cytology of the cyst wall. In 7 of 10 patients, the cellular yield and detection of diagnostic cells was superior for the EchoBrush. Two complications were encountered-1 major and 1 minor bleed. Sendino et al.<sup>19</sup> reported results in 30 patients with pancreatic

cysts evaluated with the EchoBrush (Cook Endoscopy). In 8/30 patients (27%) the brush cytology failed for technical reasons. However, the brush cytology provided a specific diagnosis in 20/22 (91%) patients in which the technique succeeded. The brush technique was superior to fluid aspiration (73% vs. 36%;  $p=0.08$ ). Three patients experienced complications (10%): 1 self limited pancreatitis, 1 self limited bleed, and 1 retroperitoneal bleed resulting in patient death at 30 days.

A recent report presents better results in obtaining cytology by performing cyst wall puncture (CWP).<sup>20</sup> The technique reported was to advance a 22 gauge needle into the cyst and aspirate all the fluid contents. Then, without withdrawing the needle, the needle tip is moved back and forth across the residual hypoechoic cyst wall. If the cyst wall was not visualized, the needle was moved 2 to 3 mm from the needle tip location where the aspiration was completed. Using this technique, the authors reported obtaining material adequate for cytologic assessment in 81% of cysts (60/66). Thirty percent of cysts with CEA <192 ng/mL were proven to be mucinous by cytology. In 67% of cases where the cyst fluid volume was insufficient for CEA analysis, cytology demonstrated mucinous epithelium. Finally, 4 malignant cysts were diagnosed independently using this CWP technique. The complication rate was 1.45% (1 episode of pancreatitis which was graded as mild and self-limited).

An alternative or adjunct to cyst wall cytology might be to directly examine the cyst wall. There have been recent reports of using a small confocal microscopy probe (Mauna Kea Technologies, Paris, France). The Cellvizio system is a probe based confocal microscopy system and a very small probe has been developed which can be passed down a 19 gauge needle. Like any other optical biopsy system, the diagnosis depends on interpretation of images.

Konda et al.<sup>21</sup> reported use of this technology on 18 patients; 12 of whom had pancreatic cysts. 6 of 18 procedures encountered technical problems with catheter loading. Imaging succeeded in 17/18 patients and in 10/17, the images were considered to be high quality. Two patients encountered serious complications of pancreatitis requiring hospitalization. This preliminary study demonstrated feasibility. Future studies will need to address safety issues and determine if a specific diagnosis can be made easily and safely.

There have also been reports using the optical catheter used in the Spyglass system (Boston Scientific, Natick, MA, USA) to directly visualize the cyst lining. The optical fiber is passed down a 19 gauge needle after puncturing the cyst. Aparicio et al.<sup>22</sup> reported successful visualization of the cyst lining in 2 patients. Both patients also underwent forceps biopsies thru the 19 gauge needle. Direct visualization of both cysts revealed smooth lining and biopsies revealed a mucin-

nous cystadenoma in both cases. There were no immediate complications in either case but one developed severe pancreatitis 1 month after the procedure.

## EUS-FNA FOR CYST WALL MASS

Identification of masses or nodules emanating from the cyst wall can indicate the presence of cancer or high grade dysplasia.<sup>3</sup> However, it is important to make a differentiation between a mural nodule and an aggregate of mucin. This distinction was studied by Zhong et al.<sup>23</sup> who reviewed pathology, EUS and CT examinations from 57 patients who had undergone surgical resection of mucinous cysts. Cancer or high grade dysplasia was found in 23% of cysts with mural nodules versus 3% without nodules ( $p=0.02$ ). Mucin balls accounted for 65% of the intracystic lesions detected by EUS and were characterized by being round, having smooth edges and being anechoic in the center with an echogenic rim. Mural nodules could be distinguished by repositioning the patient or cyst aspiration. EUS had sensitivity of 75% for the detection of mural nodules compared to 24% for CT.

Aspiration of cyst contents is indicated if identification of the cyst cannot be made with imaging alone. However, if there is an associated mass or mural nodule, then the mass itself should be targeted for cytologic examination. While mucinous cysts are the most common indication, cystic degeneration of neuroendocrine tumors and adenocarcinoma as well as solid pseudopapillary neoplasm and acinar-cell cystadenocarcinoma represent cystic neoplasms of the pancreas that present with a solid component. In these cases, EUS-FNA can be very useful to establish a histologic diagnosis. Any of the 3 gauges of needles (25, 22, or 19) could be used. In the instance of a mass, one should target the mass and avoid the cyst to avoid infection. Multiple punctures into a cyst is the main risk factor for infection. In the case of a mural nodule, it is best if the cyst fluid can be removed 1st leaving a solid mass to target. Our practice is to combine fluid aspiration (performed 1st) and then the needle is re-directed to the mass. We prefer to have the 1st pass stained and interpreted before considering a 2nd pass to minimize the number of passes needed to establish the diagnosis and decrease the rate of complications.

There has been concern in performing EUS-FNA of a cyst in the body or tail of the pancreas if malignant transformation is suspected. Our Japanese colleagues have been most vocal in expressing concerns about the potential of needle tract seeding of cancer cells.<sup>24,25</sup> A resectable cystic mass in the body of the pancreas should be considered for surgical resection without FNA in most circumstances.

## CONCLUSIONS

Pancreatic cysts are being increasingly recognized and when detected incidentally, they are likely neoplastic and should undergo further evaluation which should include EUS. Imaging alone cannot accurately identify the exact nature of the cyst. EUS-FNA is a useful adjunctive procedure in many cases of indeterminate cysts. The cyst fluid should be sent for CEA, amylase and cytology. In the future, safe techniques should be developed to improve the cytologic yield because it appears that the exact nature of the lining in mucinous cysts is predictive of their malignant potential.<sup>26,27</sup>

## Conflicts of Interest

The authors have no financial conflicts of interest.

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