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Endoscopic Ultrasonography in Management of Cystic Disease of the Pancreas

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1. Introduction

The recent advances in pancreatic imaging lead to higher detection of pancreatic cysts [1]. It has become very common for general practitioners as well as gastroenterologists to face the dilemma of further management of a large number of incidentally found pancreatic cysts. In this chapter, we will discuss the epidemiology, pathogenesis and the role of EUS in managing pancreatic cysts.

2. Epidemiology

The prevalence of pancreatic cysts is much higher than previously estimated. Earlier reports suggested that the prevalence of pancreatic cysts in adult populations to be around 2.5% [2] . Recent studies using Magnetic Resonance Imaging (MRI) showed a higher prevalence of pancreatic cysts in the general population up to 13% [3]. This prevalence increases with age and for an unknown reason it is extremely high (more than 50%) in liver transplanted patients [4].

3. Pathology

Pancreatic cysts can be classified according to their malignant potential or according to their morphological features. Initially, pancreatic cyst could be classified as pseudocyst which indicates the lack of the epithelial lining of the cyst wall, true cyst with epithelial lining or cystic degeneration or necrosis of solid pancreatic masses [5]. Pseudocyst are common after acute or chronic pancreatitis as a result of extravasation of pancreatic fluid from the disrupted pancreatic duct [6]. Pseudocyst complicating acute pancreatitis has no malignant potential and the majority of them will resolve spontaneously [7]. The management of pseudocyst is beyond the scope of this review.
True pancreatic cysts can be further divided into cysts lined with mucinous epithelium (mucinous cystic neoplasms and Intraductal Papillary Mucinous Neoplasm [IPMN]), cysts lined with clear cell (serous cystic tumors) or cysts lined with acinar cells. In addition, cystic degeneration of solid tumor can occur such as cystic neuroendocrine tumors and pseudopapillary tumors [8].
The hallmark of mucinous cystic neoplasms (mucinous cystadenoma) of the pancreas is the presence of ovarian stroma [9]. More than 90% of patients with mucinous cystic neoplasms are females and more than 90% of these lesions are within the body - tail region of the

pancreas [10]. Macroscopically, mucinous cysts are large and multilocular with thick wall. Mucinous cystic neoplasms usually do not communicate with the pancreatic duct. Ten to 15% of the discovered mucinous cystic neoplasms were found to have invasive carcinoma or at least carcinoma in situ [11, 12].

Unlike mucinous cystic neoplasms, IPMN arises within the pancreatic duct and it is characterized by papillary projections containing neoplastic mucin producing cells [13]. Macroscopically, IPMN appears as cystic dilations of the pancreatic duct. Cysts are varying in size and they are filled with mucin. Occasionally mucin could be seen extruding from the ampulla which is virtually pathognomonic for IPMN. IPMN can be divided according to its anatomical location as main duct - branch duct- and mixed-IPMN. The histological classification divides IPMN into four main categories: gastric, intestinal, pancreatobiliary and oncocytic type [14]. Both classifications are very important in determining the malignant potential of the disease. For example, the malignant potential of main duct - and of intestinal type of IPMN is much higher than branch duct IPMN and gastric type IPMN [15]. IPMNs are equally distributed between males and females and their incidence increases with age [16]. In a retrospective trial of 208 patients who underwent pancreatic resection of IPMN, 64 % of main duct IPMN were malignant while only 18 % of branch duct IPMN were harboring malignant cell on pathological examination [17].

Serous cystic tumors of the pancreas are lined by glycogen rich cell secreting serous fluid [18]. Macroscopically, it has sponge appearance with large number of minute cysts with occasional central scar. Usually serous cysts are large in size with a diameter of several centimeters. Serous cystic tumors are more common in females over 60 years old [19] with rare malignant potential (~3%) [20, 21].

The cystic form of acinar cell tumor is rare [22]. It could be present in a benign form as acinar cell cystadenoma, in addition to the malignant form known as acinar cell cystadenocarcinoma [23, 24]. This rare tumor entity should not be confused with solid pseudopapillary tumor of the pancreas in which the cystic component is rather a degenerative process than true cyst as in the cystic form of acinar cell tumors [25]. Both tumors, however, occur in young patients and should be included in the differential diagnosis in cystic tumor of the pancreas in pediatric and young adults. The cystic form of neuroendocrine tumor is another example of cystic degeneration within solid tumor. There are few case reports describing cystic glucagonoma and cystic insulinoma in the literature [26, 27]. The cyst is usually filled with clear fluid secreted by the neuroendocrine cells and not necrotic materials as in the case of solid pseudopapillary tumor[5]. It is also worth mentioning that cystic degeneration can occur in any solid tumor of the pancreas including ductal adenocarcinoma.

4. Role of imaging in diagnosing pancreatic cystic lesions

Although the advances in diagnostic imaging allowed more discovery of incidental pancreatic cyst, CT scan has only 50 to 60% accuracy in differentiating between different types of pancreatic cysts [28]. The new generation multi-slice helical CT scan has higher accuracy in differentiating between serous and mucinous cysts with a diagnostic accuracy of 70 to 80% [29]. The accuracy of a CT scan is not that impressive either in differentiating benign from malignant cysts. In a study of 47 patients with IPMN who underwent surgical resection, the diagnostic accuracy of a CT scan in differentiating invasive from non-invasive cyst was 76% [30]. Magnetic Resonance Imaging (MRI) of the pancreas could have better

diagnostic performance in differentiating mucinous from non-mucinous cysts   in comparison with the CT scan[31]. In addition, MRI enables more characterization of cyst features suggestive of malignancy such as mural nodule, thick septae, solid component or main pancreatic duct dilation [32, 33]. However, studies comparing the relative accuracy of MRI and CT scan in differentiating benign from malignant cysts did not show any difference between the two modalities. In a retrospective study of 58 pancreatic cystic lesions irrespective of the cyst size, the relative accuracy of CT and MRI was similar [34]. In another well-designed retrospective trial by Sainani et al, 38 small (less than 3 cm) pancreatic cysts were included. All patients had a CT scan, MRI and histopathological diagnosis. CT and MRI had overall similar performance. The accuracy of CT scan and MRI in differentiating mucinous from non-mucinous cyst was 71% and 84% respectively, while the accuracy of CT vs MRI in differentiating benign from malignant cyst was 75-78% vs 78-86% (not statistically significant) [35]. Recently, 3D MRCP was shown to improve the image quality of pancreatic cysts [36]. However, 3D MRCP had similar diagnostic performance to 2D MRCP in differentiating benign from malignant cysts [37].

5. Role of Endoscopic Ultrasonography (EUS)

5.1 Cyst morphology

EUS has emerged as an important tool in the diagnosis of pancreatic cysts. EUS allows close inspection of pancreatic cysts and delineates the characteristic features of the cyst that might not be apparent on CT or MRI. For example, serous cystadenoma (SCA) has a typical honeycomb appearance with multiple microcysts separated with thin septae and occasionally central scar [38]. Mucinous cystadenoma (MCA) is usually present in the body and tail of the pancreas as a well-circumscribed, rounded, anechoic cyst without any communication with the pancreatic duct. Branch duct IPMN has a similar appearance to MCA but it is not rounded, occasionally multicystic with communication with the pancreatic duct [39]. In some occasions, MCA cannot be differentiated from branch duct IPMN if the communication with the pancreatic duct is not clear. Main duct IPMN appears as a cystic dilation of the main pancreatic duct and it could be either segmental or diffuse in nature. EUS can also identify features that are worrisome for malignancy such as solid component, thick septae or lymphadenopathy [40, 41]. However, EUS alone cannot differentiate benign from malignant cysts [42]. In a retrospective study of 47 patients who underwent EUS examination prior to surgical resection of the pancreatic cyst, the diagnostic accuracy of EUS to differentiate benign from malignant cyst was 76% [30]. Furthermore, interobserver agreement among endosonographers to differentiate mucinous from non mucinous cysts was evaluated by Ahmad et al. by using videotapes of 31 pancreatic cystic lesions. The interobserver agreement among the eight endosonographers included in the study was shown to be only fair (kappa =0.24). Accuracy rates of EUS to differentiate benign from malignant lesions ranged from 40 to 93% which highlights the variability among endosonographers [43]. The result of this study should be taken with a grain of salt since the endosonographers were evaluating video tapes which are different than performing the actual procedure and interpreting the findings.

5.2 Cytological evaluation

In addition to cyst characterization, EUS allows fine needle aspiration (FNA) of the cyst for cytology and measurement of molecular markers. FNA of pancreatic cyst is safe with

complication rate of 0.5 to 2% as acute pancreatitis, bleeding or infection [44-47]. Although cytology of pancreatic cyst has high specificity, its sensitivity is very low in differentiating mucinous from non-mucinous cysts. Sedlack et al in a retrospective study of 111 patients at Mayo Clinic found that cytology had 100% specificity and 27% sensitivity for mucinous cysts. This translates into 55% diagnostic accuracy [40]. Similar results were confirmed by Attasaranya et al from Indiana University in a retrospective study of 48 patients with pancreatic cysts. The specificity of cytology to differentiate mucinous from non-mucinous cyst was 90% with sensitivity of 12.5% [48]. What can explain such high specificity and low sensitivity for cytology is that the presence of sticky fluid on aspiration or mucin in cytology is highly diagnostic for mucinous cysts. However, aspirate can be acellular or with minimal cellularity in up to 72% of aspirated cysts [49, 50]. FNA is not useful in SCA with diagnostic accuracy of only 17% [51]. Giving the innumerable microcystic structure of SCA, FNA is often non diagnostic due to the lack of fluid aspirate. However, the presence of glycogen rich cells is highly specific for SCA [51, 52]. In terms of differentiating benign from malignant cyst, cytology has an accuracy of 50% in most of the trials reported in the literature [53-56]. The presence of tight epithelial cell clusters with hyperchromic cell nuclei and high nuclei to cytoplasm ratio is suggestive of malignant cysts [50, 57]. Giving the higher risk of bacteremia in FNA of cystic lesions of GI tract in comparison with solid lesions, the American Society of Gastrointestinal Endoscopy (ASGE) recommends antibiotics administration prior to FNA of cystic lesions of the pancreas [58].

Recently, a new through the needle cytology brush system (Echobrush, Cook Endoscopy, Winston-Salem, NC) was developed in order to improve the diagnostic accuracy of the FNA. This system was initially evaluated at Mayo Clinic Florida in a pilot study of 10 patients with pancreatic cysts who prospectively underwent standard FNA followed by FNA with Echobrush. Echobrush was superior to the standard FNA in 7 of the 10 patients. However, two of the 10 patients (who stopped anticoagulation 5 days prior to the procedure) had bleeding complication after the procedure; in one patient the bleeding stopped on its own, while angiographic embolization was required to stop the bleeding in the 2nd patient [59]. Similar findings were replicated by Bruno et al in cases series of 39 patients with 12 pancreatic cysts. Six of 12 patients with pancreatic cysts had an adequate cellularity sample with only 1 Echobrush pass [60]. In a larger study by the same group at Mayo Clinic Florida, Echobrush was more likely to detect intracellular mucin on cytology specimen compared to EUS-FNA in 39 pancreatic cysts larger than 2 cm. However, two patients developed acute pancreatitis and one patients developed post brushing acute bleeding [61].

Sendino et al from Spain reported an increased accuracy of Echobrush compared to conventional FNA in a group of 22 patients with pancreatic cystic neoplasms (cellular diagnosis in 91%). However, the authors witnessed complications of this procedure in 3 patients (10%) which included a subacute retroperitoneal haemorrhage in a patient on anticoagulation who died one month after the procedure [62]. The most recent study by Thomas et al from United Kingdom did not show any difference in the cytology yield between Echobrush and the standard FNA in prospective study of 51 patients [63]. In conclusion, more studies are needed to evaluate the efficacy and the safety of the new Echobrush system prior to recommending it for routine clinical practice. To date, Echobrush should be avoided in patients with pancreatic cystic neoplasms who are in need for anticoagulation.

5.3 Molecular markers

The measurement of intracystic markers and in particular of Carcinoembryonic Antigen (CEA) has emerged as an additional tool in evaluating pancreatic cysts. In a landmark prospective study published in 2004 by the cooperative pancreatic cyst study, 341 patients with pancreatic cysts underwent FNA. The utility of CEA, CA 72-4, CA 125, CA 19-9, and CA 15-3 in differentiating mucinous from non-mucinous cyst was evaluated. Only CEA was proven to be valuable in differentiating mucinous from non-mucinous cyst. The study suggests that an intracystic CEA level higher than 192 ng/ml can predict the presence of mucinous cyst with diagnostic accuracy of 79% which was higher compared to EUS morphology alone (accuracy 51%) and cytology (accuracy 59%) (p:<0.05) [64]. In a retrospective study of 126 patients with proven pathological diagnosis of pancreatic cyst, CEA level of 200 ng/ml had a sensitivity of 60%, specificity of 93% and diagnostic accuracy of 72% in differentiating mucinous from non-mucinous cyst [65]. Although CEA was proven useful in differentiating mucinous from non-mucinous pancreatic cysts, the CEA utility in differentiating benign from malignant cysts is questionable. A pooled analysis of 12 trials proposed that a CEA level of 800 ng/ml can differentiate benign from malignant cyst (48% sensitive and 98% specificity) [53]. Another trial suggested that a CEA level of 6000 ng/ml can differentiate benign from malignant cyst [66]. However, many trials did not find CEA useful in differentiating benign from malignant cysts [65]. In a retrospective long-term follow-up study (median follow up period is 21 months) of 267 patients with pancreatic cysts, Nagula et al found that intracystic CEA level had no correlation with malignant changes of the cyst or with the cyst progression in size [67]. The above mentioned data indicate that intracystic CEA level should be limited to differentiation between mucinous and non-mucinous cyst.

Cyst amylase level is usually elevated in pseudocyst and IPMN, given the communication of these cysts with the pancreatic duct [66]. Interestingly, malignant IPMN cyst was found to have a higher amylase level compared to benign IPMN cysts [65].

Identifying DNA mutations in the cysts by genetic markers is considered the new frontier in differentiating benign from malignant pancreatic cysts. Several mutations were found to be associated with progression of pancreatic cysts from non-dysplastic to dysplastic cysts such as k-*ras*, p-16 and p53 mutations [68-70]. Currently, it is commercially available to measure k-*ras* point mutations and loss of heterozygosity (LOH) analysis of tumor suppressor gene [71]. The PANDA study, which is a landmark study in the area of the utility of DNA markers in evaluating pancreatic cyst, prospectively enrolled 113 patients with pancreatic cysts and proven pathology. Elevated cyst DNA content and k-*ras* mutation were associated with malignant cyst. The presence of k-*ras* mutation in this study had high specificity of 96%, but low sensitivity of 37% in diagnosing malignant cysts [72]. k-*ras* mutation correlated with atypical cytology and a high CEA level in a study of 60 patients with pancreatic cysts measuring less than 3 cm in size and without mural nodule or pancreatic duct dilation [73]. The above results are dissimilar with another trial of 27 patients who underwent EUS with FNA and measurement of CEA level, k-*ras* mutation and LOH mutation. In this trial, correlation between histology, CEA level, k-*ras* mutation and LOH mutation occurred in 35% of cases, all of which were benign cases. In addition, the sensitivity of k-*ras* and LOH mutation to detect malignant cysts was significantly low compared to CEA (33% and 50% vs 66%, respectively). Given the high specificity of k-*ras* mutation to detect malignant cyst (92%), the authors of the study recommended ordering DNA mutation analysis only in patients with equivocal results or when malignancy is suspected [74].

6. Role of EUS in pancreatic cyst ablation

EUS has emerged from being a merely diagnostic utility to be an effective therapeutic utility in various gastrointestinal disorders. Management of pancreatic cyst is an example of this transformation. In addition to the important role of EUS in diagnosing pancreatic cysts, new studies are currently evaluating the role of EUS in pancreatic cyst ablation with the use of different agents. Ethanol lavage of the pancreatic cyst was successful in ablating 35% of included cysts in a small study of 25 patients [75]. A randomized controlled trial of 58 patients compared ethanol lavage to saline lavage for cyst ablation found that ethanol lavage was more effective in decreasing cyst diameter compared to saline lavage. Thirty-three patients from both arms of the study underwent a second ethanol lavage with complete cyst resolution in 12 patients (33.3%). Ethanol lavage was generally safe with a 5% rate of acute pancreatitis. Twenty-two per cent of patients who underwent ethanol lavage complained of mild abdominal pain after the procedure [76]. In a long-term follow-up study of the same 12 patients who had complete cyst resolution, follow-up CT scan was available in 9 patients. No cyst recurrence was seen in the mean follow-up period of 26 months [77]. A combination of ethanol and Paclitaxel was used in a recent prospective trial of 52 patients. Paclitaxel is a chemotherapeutic agent which can prevent cyst growth in the long-term without leakage from the cystic space. 62% of patients enrolled in this trial had complete cyst resolution. The procedure was generally safe with 1 case of mild pancreatitis and 1 case of splenic vein obliteration reported [78]. Critiques of this study include the questionable injection of chemotherapeutic agent in a cyst most likely benign in nature.

More studies are needed to evaluate the long-term efficacy of these new technique and to define which types of cysts are more responsive to cyst ablation. It is also worth mentioning that the majority of cysts included in these studies are either mucinous or serous cysts. Cyst with communication with the pancreatic duct such as IPMN cannot be ablated because of the risk of inducing stricturing of the pancreatic duct.

7. Role of EUS in surveillance of pancreatic cysts

In addition to the role of EUS in establishing the diagnosis of pancreatic cyst , EUS is a useful tool in surveillance of patients with cysts of unclear malignant potential. This role is particularly important in side branch IPMN in which disease progression could vary from patient to another. There is abundant evidence now that smaller side branch IPMN cysts are usually benign and that malignant potential of these cysts is correlating with its size [79]. Three cm in size was proposed as a cut off value in differentiating benign from potentially malignant branch duct IPMN. Branched ducts IPMN less than 3 cm in size and without any mural nodule are usually benign [80]. Surveillance EUS can monitor those patients with branch duct IPMN for size progression or for development of worrisome features such as mural nodule or mass component and accurately refer them to surgery. It is also worth mentioning that symptomatic side branch IPMN should be referred to surgery regardless of its size [81]. Guidelines also advocate referring all patients with MCA and main duct IPMN to surgery, if they are surgically fit. [82, 83]

8. Integrating EUS in clinical practice

EUS should be used in the context of the clinical data and its result should not be interpreted in isolation of other finding. For example, an isolated cyst in the tail of the pancreas in a

middle age female is most likely mucinous cystadenoma rather than branch duct IPMN. The same principle applies to interpreting FNA and cytology results. FNA has low yield in a cyst smaller than 1 cm without any worrisome features. Also, if the patient is not a surgical candidate either because of multiple comorbidities or advanced age, FNA cannot be justified [84]. For this reason the decision for FNA should be taken on case by case basis. Negative or non diagnostic cytology of suspicious pancreatic cyst should not deter the clinician from considering surgery of the cystic lesion especially if the cyst has features of malignancy. In 29 patients with pancreatic cystic lesions who underwent EUS FNA prior to surgical resection, more than 2/3 of cysts with negative cytology and 90% of cysts with non diagnostic cytology were harboring malignant or premalignant tissue on surgical specimens [85].

9. Conclusions

The role of EUS in the management of pancreatic cyst is crucial. However, EUS results should be incorporated in the overall clinical assessment of the patients.

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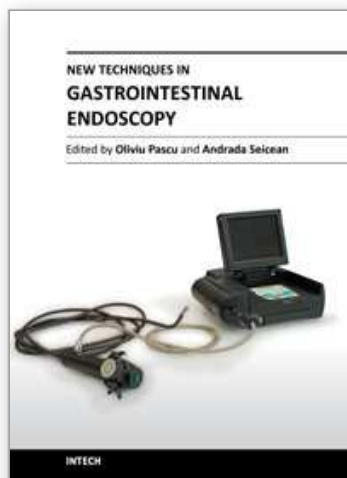
New Techniques in Gastrointestinal Endoscopy

Edited by Prof. Oliviu Pascu

As result of progress, endoscopy has became more complex, using more sophisticated devices and has claimed a special form. In this moment, the gastroenterologist performing endoscopy has to be an expert in macroscopic view of the lesions in the gut, with good skills for using standard endoscopes, with good experience in ultrasound (for performing endoscopic ultrasound), with pathology experience for confocal examination. It is compulsory to get experience and to have patience and attention for the follow-up of thousands of images transmitted during capsule endoscopy or to have knowledge in physics necessary for autofluorescence imaging endoscopy. Therefore, the idea of an endoscopist has changed. Examinations mentioned need a special formation, a superior level of instruction, accessible to those who have already gained enough experience in basic diagnostic endoscopy. This is the reason for what these new issues of endoscopy are presented in this book of New techniques in Gastrointestinal Endoscopy.

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