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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.

10. References
[1] Khalid, A. and W. Brugge, ACG practice guidelines for the diagnosis and management of neoplastic pancreatic cysts. Am J Gastroenterol, 2007. 102(10): p. 2339-49.
[2] Laffan, T.A., et al., Prevalence of unsuspected pancreatic cysts on MDCT. AJR Am J Roentgenol, 2008. 191(3): p. 802-7.
[3] Lee, K.S., et al., Prevalence of incidental pancreatic cysts in the adult population on MR imaging. Am J Gastroenterol, 2010. 105(9): p. 2079-84.
[4] Girometti, R., et al., Incidental pancreatic cysts: a frequent finding in liver-transplanted patients as assessed by 3D T2-weighted turbo spin echo magnetic resonance cholangiopancreatography. JOP, 2009. 10(5): p. 507-14.
[5] Adsay, N.V., Cystic neoplasia of the pancreas: pathology and biology. J Gastrointest Surg, 2008. 12(3): p. 401-4.
[6] Habashi, S. and P.V. Draganov, Pancreatic pseudocyst. World J Gastroenterol, 2009. 15(1): p. 38-47.
[7] Maringhini, A., et al., Pseudocysts in acute nonalcoholic pancreatitis: incidence and natural history. Dig Dis Sci, 1999. 44(8): p. 1669-73.
[8] Volkan Adsay, N., Cystic lesions of the pancreas. Mod Pathol, 2007. 20 Suppl 1: p. S71-93.
[9] Thompson, L.D., et al., Mucinous cystic neoplasm (mucinous cystadenocarcinoma of low-grade malignant potential) of the pancreas: a clinicopathologic study of 130 cases. Am J Surg Pathol, 1999. 23(1): p. 1-16.
[10] Goh, B.K., et al., A review of mucinous cystic neoplasms of the pancreas defined by ovarian-type stroma: clinicopathological features of 344 patients. World J Surg, 2006. 30(12): p. 2236-45.
[11] Reddy, R.P., et al., Pancreatic mucinous cystic neoplasm defined by ovarian stroma: demographics, clinical features, and prevalence of cancer. Clin Gastroenterol Hepatol, 2004. 2(11): p. 1026-31.
[12] Fukushima, N. and M. Fukayama, Mucinous cystic neoplasms of the pancreas: pathology and molecular genetics. J Hepatobiliary Pancreat Surg, 2007. 14(3): p. 238-42.

[13] Furukawa, T., et al., Classification of types of intraductal papillary-mucinous neoplasm of the pancreas: a consensus study. Virchows Arch, 2005. 447(5): p. 794-9.

[14] Ishida, M., et al., Characteristic clinicopathological features of the types of intraductal papillary-mucinous neoplasms of the pancreas. Pancreas, 2007. 35(4): p. 348-52.

[15] Serikawa, M., et al., Management of intraductal papillary-mucinous neoplasm of the pancreas: treatment strategy based on morphologic classification. J Clin Gastroenterol, 2006. 40(9): p. 856-62.

[16] Sohn, T.A., et al., Intraductal papillary mucinous neoplasms of the pancreas: an updated experience. Ann Surg, 2004. 239(6): p. 788-97; discussion 797-9.

[17] Schnelldorfer, T., et al., Experience with 208 resections for intraductal papillary mucinous neoplasm of the pancreas. Arch Surg, 2008. 143(7): p. 639-46; discussion 646.

[18] Compton, C.C., Serous cystic tumors of the pancreas. Semin Diagn Pathol, 2000. 17(1): p. 43-55.

[19] Zanini, N., et al., Serous cystic tumors of the pancreas: when to observe and when to operate: a single-center experience. Dig Surg, 2008. 25(3): p. 233-9; discussion 240.

[20] Strobel, O., et al., Risk of malignancy in serous cystic neoplasms of the pancreas. Digestion, 2003. 68(1): p. 24-33.

[21] Galanis, C., et al., Resected serous cystic neoplasms of the pancreas: a review of 158 patients with recommendations for treatment. J Gastrointest Surg, 2007. 11(7): p. 820-6.

[22] Makni, A., et al., Acinar cell carcinoma of the pancreas: A rare tumor with a particular clinical and paraclinical presentation. Clin Res Hepatol Gastroenterol, 2011.

[23] Zamboni, G., et al., Acinar cell cystadenoma of the pancreas: a new entity? Am J Surg Pathol, 2002. 26(6): p. 698-704.

[24] Colombo, P., C. Arizzi, and M. Roncalli, Acinar cell cystadenocarcinoma of the pancreas: report of rare case and review of the literature. Hum Pathol, 2004. 35(12): p. 1568-71.

[25] Tapia, B., et al., Acinar cell carcinoma versus solid pseudopapillary tumor of the pancreas in children: a comparison of two rare and overlapping entities with review of the literature. Pediatr Dev Pathol, 2008. 11(5): p. 384-90.

[26] Brown, K., et al., Cystic glucagonoma: A rare variant of an uncommon neuroendocrine pancreas tumor. J Gastrointest Surg, 1998. 2(6): p. 533-6.

[27] Vandecaveye, V., et al., Cystic insulinoma of the pancreas in a patient with myotonic dystrophy: correlation of imaging and pathologic findings. JBR-BTR, 2003. 86(5): p. 268-71.

[28] Procacci, C., et al., Characterization of cystic tumors of the pancreas: CT accuracy. J Comput Assist Tomogr, 1999. 23(6): p. 906-12.

[29] Yuan, D., et al., Characterization and diagnostic accuracy of serous cystadenomas and mucinous neoplasms of the pancreas with multi-slice helical computed tomography]. Zhongguo Yi Xue Ke Xue Yuan Xue Bao, 2007. 29(2): p. 232-7.

[30] Cellier, C., et al., Intraductal papillary and mucinous tumors of the pancreas: accuracy of preoperative computed tomography, endoscopic retrograde pancreatography and endoscopic ultrasonography, and long-term outcome in a large surgical series. Gastrointest Endosc, 1998. 47(1): p. 42-9.
[31] Song, S.J., et al., Differentiation of intraductal papillary mucinous neoplasms from other pancreatic cystic masses: comparison of multirow-detector CT and MR imaging using ROC analysis. J Magn Reson Imaging, 2007. 26(1): p. 86-93.

[32] Irie, H., et al., MR cholangiopancreatographic differentiation of benign and malignant intraductal mucin-producing tumors of the pancreas. AJR Am J Roentgenol, 2000. 174(5): p. 1403-8.

[33] Sugiyama, M., et al., Predictive factors for malignancy in intraductal papillary-mucinous tumours of the pancreas. Br J Surg, 2003. 90(10): p. 1244-9.

[34] Visser, B.C., et al., Characterization of cystic pancreatic masses: relative accuracy of CT and MRI. AJR Am J Roentgenol, 2007. 189(3): p. 648-56.

[35] Sainani, N.I., et al., Comparative performance of MDCT and MRI with MR cholangiopancreatography in characterizing small pancreatic cysts. AJR Am J Roentgenol, 2009. 193(3): p. 722-31.

[36] Choi, J.Y., et al., Magnetic resonance pancreatography: comparison of two- and three-dimensional sequences for assessment of intraductal papillary mucinous neoplasm of the pancreas. Eur Radiol, 2009. 19(9): p. 2163-70.

[37] Yoon, L.S., et al., Another dimension in magnetic resonance cholangiopancreatography: comparison of 2- and 3-dimensional magnetic resonance cholangiopancreatography for the evaluation of intraductal papillary mucinous neoplasm of the pancreas. J Comput Assist Tomogr, 2009. 33(3): p. 363-8.

[38] Petrone, M.C. and P.G. Arcidiacono, Role of endoscopic ultrasound in the diagnosis of cystic tumours of the pancreas. Dig Liver Dis, 2008. 40(11): p. 847-53.

[39] Kubo, H., et al., Differential diagnosis of cystic tumors of the pancreas by endoscopic ultrasonography. Endoscopy, 2009. 41(8): p. 684-9.

[40] Sedlack, R., et al., Utility of EUS in the evaluation of cystic pancreatic lesions. Gastrointest Endosc, 2002. 56(4): p. 543-7.

[41] Song, M.H., et al., EUS in the evaluation of pancreatic cystic lesions. Gastrointest Endosc, 2003. 57(7): p. 891-6.

[42] Ahmad, N.A., et al., Can EUS alone differentiate between malignant and benign cystic lesions of the pancreas? Am J Gastroenterol, 2001. 96(12): p. 3295-300.

[43] Ahmad, N.A., et al., Interobserver agreement among endosonographers for the diagnosis of neoplastic versus non-neoplastic pancreatic cystic lesions. Gastrointest Endosc, 2003. 58(1): p. 59-64.

[44] Eloubeidi, M.A., et al., Acute pancreatitis after EUS-guided FNA of solid pancreatic masses: a pooled analysis from EUS centers in the United States. Gastrointest Endosc, 2004. 60(3): p. 385-9.

[45] Gress, F., et al., EUS-guided fine-needle aspiration of the pancreas: evaluation of pancreatitis as a complication. Gastrointest Endosc, 2002. 56(6): p. 864-7.

[46] Gress, F.G., et al., Endoscopic ultrasound-guided fine-needle aspiration biopsy using linear array and radial scanning endosonography. Gastrointest Endosc, 1997. 45(3): p. 243-50.

[47] O'Toole, D., et al., Assessment of complications of EUS-guided fine-needle aspiration. Gastrointest Endosc, 2001. 53(4): p. 470-4.
[48] Attasaranya, S., et al., Endoscopic ultrasound-guided fine needle aspiration and cyst fluid analysis for pancreatic cysts. JOP, 2007. 8(5): p. 553-63.

[49] Stelow, E.B., et al., Intraductal papillary-mucinous neoplasm of the pancreas. The findings and limitations of cytologic samples obtained by endoscopic ultrasound-guided fine-needle aspiration. Am J Clin Pathol, 2003. 120(3): p. 398-404.

[50] Michaels, P.J., et al., Intraductal papillary mucinous neoplasm of the pancreas: cytologic features predict histologic grade. Cancer, 2006. 108(3): p. 163-73.

[51] Huang, P., et al., Fine-needle aspiration of pancreatic serous cystadenoma: cytologic features and diagnostic pitfalls. Cancer, 2006. 108(4): p. 239-49.

[52] Belsley, N.A., et al., Serous cystadenoma of the pancreas: limitations and pitfalls of endoscopic ultrasound-guided fine-needle aspiration biopsy. Cancer, 2008. 114(2): p. 102-10.

[53] van der Waaij, L.A., H.M. van Dullemen, and R.J. Porte, Cyst fluid analysis in the differential diagnosis of pancreatic cystic lesions: a pooled analysis. Gastrointest Endosc, 2005. 62(3): p. 383-9.

[54] Frossard, J.L., et al., Performance of endosonography-guided fine needle aspiration and biopsy in the diagnosis of pancreatic cystic lesions. Am J Gastroenterol, 2003. 98(7): p. 1516-24.

[55] Centeno, B.A., et al., Cyst fluid cytologic analysis in the differential diagnosis of pancreatic cystic lesions. Am J Clin Pathol, 1994. 101(4): p. 1516-24.

[56] Wiersema, M.J., et al., Endosonography-guided fine-needle aspiration biopsy: diagnostic accuracy and complication assessment. Gastroenterology, 1997. 112(4): p. 1087-95.

[57] Salla, C., et al., Endoscopic ultrasound-guided fine-needle aspiration cytology in the diagnosis of intraductal papillary mucinous neoplasms of the pancreas. A study of 8 cases. JOP, 2007. 8(6): p. 715-24.

[58] Banerjee, S., et al., Antibiotic prophylaxis for GI endoscopy. Gastrointest Endosc, 2008. 67(6): p. 791-8.

[59] Al-Haddad, M., et al., Safety and efficacy of cytology brushings versus standard FNA in evaluating cystic lesions of the pancreas: a pilot study. Gastrointest Endosc, 2007. 65(6): p. 894-8.

[60] Bruno, M., et al., Preliminary experience with a new cytology brush in EUS-guided FNA. Gastrointest Endosc, 2009. 70(6): p. 1220-4.

[61] Al-Haddad, M., et al., Safety and efficacy of cytology brushings versus standard fine-needle aspiration in evaluating cystic pancreatic lesions: a controlled study. Endoscopy, 2010. 42(2): p. 127-32.

[62] Sendino, O., et al., Endoscopic ultrasonography-guided brushing increases cellular diagnosis of pancreatic cysts: A prospective study. Dig Liver Dis, 2010. 42(12): p. 877-81.

[63] Thomas, T., et al., EUS-guided pancreatic cyst brushing: a comparative study in a tertiary referral centre. JOP, 2010. 11(2): p. 163-9.

[64] Brugge, W.R., et al., Diagnosis of pancreatic cystic neoplasms: a report of the cooperative pancreatic cyst study. Gastroenterology, 2004. 126(5): p. 1330-6.

[65] Park, W.G., et al., Diagnostic performance of cyst fluid carcinoembryonic antigen and amylase in histologically confirmed pancreatic cysts. Pancreas, 2011. 40(1): p. 42-5.

[66] Linder, J.D., J.E. Geenen, and M.F. Catalano, Cyst fluid analysis obtained by EUS-guided FNA in the evaluation of discrete cystic neoplasms of the pancreas: a prospective single-center experience. Gastrointest Endosc, 2006. 64(5): p. 697-702.
[67] Nagula, S., et al., Evaluation of cyst fluid CEA analysis in the diagnosis of mucinous cysts of the pancreas. J Gastrointest Surg, 2010. 14(12): p. 1997-2003.

[68] Wada, K., p16 and p53 gene alterations and accumulations in the malignant evolution of intraductal papillary-mucinous tumors of the pancreas. J Hepatobiliary Pancreat Surg, 2002. 9(1): p. 76-85.

[69] Sugio, K., et al., High yields of K-ras mutations in intraductal papillary mucinous tumors and invasive adenocarcinomas induced by N-nitroso(2-hydroxypropyl)(2-oxopropyl)amine in the pancreas of female Syrian hamsters. Carcinogenesis, 1996. 17(2): p. 303-9.

[70] Sasaki, S., et al., Differential roles of alterations of p53, p16, and SMAD4 expression in the progression of intraductal papillary-mucinous tumors of the pancreas. Oncol Rep, 2003. 10(1): p. 21-5.

[71] Schoedel, K.E., S.D. Finkelstein, and N.P. Ohori, K-Ras and microsatellite marker analysis of fine-needle aspirates from intraductal papillary mucinous neoplasms of the pancreas. Diagn Cytopathol, 2006. 34(9): p. 605-8.

[72] Khalid, A., et al., Pancreatic cyst fluid DNA analysis in evaluating pancreatic cysts: a report of the PANDA study. Gastrointest Endosc, 2009. 69(6): p. 1095-102.

[73] Mertz, H., K-ras Mutations Correlate with Atypical Cytology and Elevated CEA Levels in Pancreatic Cystic Neoplasms. Dig Dis Sci, 2011.

[74] Sreenarasimhaiah, J., et al., A comparative analysis of pancreas cyst fluid CEA and histology with DNA mutational analysis in the detection of mucin producing or malignant cysts. JOP, 2009. 10(2): p. 163-8.

[75] Gan, S.I., et al., Ethanol lavage of pancreatic cystic lesions: initial pilot study. Gastrointest Endosc, 2005. 61(6): p. 746-52.

[76] DeWitt, J., et al., EUS-guided ethanol versus saline solution lavage for pancreatic cysts: a randomized, double-blind study. Gastrointest Endosc, 2009. 70(4): p. 710-23.

[77] DeWitt, J., C.J. DiMaio, and W.R. Brugge, Long-term follow-up of pancreatic cysts that resolve radiologically after EUS-guided ethanol ablation. Gastrointest Endosc, 2010. 72(4): p. 862-6.

[78] Oh, H.C., et al., Endoscopic ultrasonography-guided ethanol lavage with paclitaxel injection treats patients with pancreatic cysts. Gastroenterology, 2011. 140(1): p. 172-9.

[79] Kang, M.J., et al., Cyst growth rate predicts malignancy in patients with branch duct intraductal papillary mucinous neoplasms. Clin Gastroenterol Hepatol, 2011. 9(1): p. 87-93.

[80] Rodriguez, J.R., et al., Branch-duct intraductal papillary mucinous neoplasms: observations in 145 patients who underwent resection. Gastroenterology, 2007. 133(1): p. 72-9; quiz 309-10.

[81] Waters, J.A. and C.M. Schmidt, Intraductal papillary mucinous neoplasm--when to resect? Adv Surg, 2008. 42: p. 87-108.

[82] Mimura, T., et al., Predictors of malignant intraductal papillary mucinous neoplasm of the pancreas. J Clin Gastroenterol, 2010. 44(9): p. e224-9.

[83] Tanaka, M., et al., International consensus guidelines for management of intraductal papillary mucinous neoplasms and mucinous cystic neoplasms of the pancreas. Panreatology, 2006. 6(1-2): p. 17-32.
[84] Sahai, A.V., *The role of EUS for diagnosis of pancreatic cysts: observe, needle, or brush?* Endoscopy, 2010. 42(2): p. 153-4.

[85] Maker, A.V., et al., *Cytology from pancreatic cysts has marginal utility in surgical decision-making.* Ann Surg Oncol, 2008. 15(11): p. 3187-92.
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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