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Review

Management of cystic diseases of the pancreas

PANCREAS

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ABSTRACT

Pancreatic cysts are challenging to the gastroenterologist. Detection rate is increasing and neither criteria for a definitive diagnosis, nor a validated surveillance strategy is available. Pancreatic endosonography with or without sampling is necessary in most of the cases. However this technique requires expertise and is not widely available. While some cysts have a malignant potential or already malign at the diagnosis, most are benign and remain so for decades. We are going to review the existing data on this controversial subject.

Keywords: Cyst, pancreas, diagnosis, management, endosonography

Not too distant, just thirty years ago pancreatic cysts (PC) were considered so rare deserving publication (1). Nowadays, it is one of the most frequent abdominal incidental finding challenging gastroenterologists. Thanks to the progress in imaging technology, we are able to detect cysts as small as a few millimeters in the pancreas. The presence of pancreatic disease implies a negative connotation, for public and the involved subject is exposed to a great deal of anxiety after this diagnosis. Given to the absence of clearly established methods in approaching this condition, the gastroenterologist, sometimes, may fall short of relieving this anxiety. In the following chapter we are going to summarize the hitherto data in the diagnosis and management of this emerging disease.

HISTORY

Cystic neoplasm of the pancreas was first described by Becourt at 1830 (2). In 1872, Bozeman understood that, aspiration alone cannot cure these cysts and reported successful resection with the survival of the patient. In 1900, Reginald Fitz revealed the malignant potential of some cysts (3). In 1978 Compagno and Oertel divided the neoplasms into two types: serous and mucinous (4,5). Finally, in 1982, Ohashi described the, one would call today, intraductal papillary mucinous neoplasm (IPMN) (6). However our understanding in pancreatic cysts is still in evolution. Common cysts of the pancreas and surrounding organs' and tissues' which may be confused with PCs are shown in Table 1.

SCOPE OF THE PROBLEM

The detection rate of pancreatic cysts increases with age. While the prevalence is around 1% in subjects younger than 40, It reaches over 10% after the age of 70 (7). In autopsy series the frequency reaches 27.5% to 50% (8). Pancreatic cystic neoplasms (PCNs) account for 10-15% of all cystic lesions and 1-5% of all primary pancreatic neoplasms (9). The increased prevalence of pancreatic cysts is probably a reflection of increased diagnosis, because there is no increase in IPMN-related or pancreatic cancer-related mortality over time (10). Overall, there is no gender difference, however cystic neoplasms are more common in women: 2:1 to 3:1. Magnetic resonance imaging (MRI) is considered more sensitive in detection than computed tomography (CT). Transabdominal ultrasonography (TAUS) is the least and endoscopic ultrasonography (EUS) is the most sensitive imaging methods. EUS has the added advantage of easy sampling. However it is not widely available and requires a great deal of expertise, especially in reference to pancreas. Recent data revealed that in MR examination the incidental detection rate may reach to up to 20% (11-14). While some cysts are

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Table 1. Common cystic lesions of the pancreas and differential diagnosis

Post-pancreatitis
Pseudocyst
Pseudo-pseudocyst
Neoplastic
Serous cystadenoma
Mucinous cystadenoma
Intraductal papillary mucinous cystadenoma
Branch duct
Main duct
Mixed
Non-neoplastic mucinous cyst
Cystic neuroendocrine tumour
Cystic degeneration of a neoplasm
Solid pseudopapillary neoplasm
Ductal adenocarcinoma
Acinar cell neoplasms
Lymphoepithelial cyst
Cysts which may be confused with pancreatic cysts
Enteric duplication cysts
Left suprarenal gland cysts
Mesenteric cysts

harboring the risk of malignancy, most of them do not. However the benign neoplasms especially mucinous ones also require follow-up and it may be costly. Besides, follow-up may not be cost-effective. In a retrospective series of 79 patients with cyst size smaller than 20 mm, up to 10 years of follow-up, revealed no pancreas related death (15). One third of incidentally discovered cysts are smaller than 10 mm and a definitive diagnosis is not possible (16).

ETIOLOGY

The etiology of pancreatic cysts is far from clear. Interestingly hitherto data mostly concerned with the detection, differential diagnosis, and management of this disease. There is virtually no solid data about the etiology of the cysts. Pancreatic ductal adenocarcinoma (PDAC) and colloid carcinoma may develop in mucinous cystic neoplasm (MCN) and IPMN. Pancreatic intraepithelial neoplasia (PanIN) is considered as a precursor of ductal adenocarcinoma, and there are some genetic alterations which are found in both IPMN and PanIN (17,18). Some distinct genetic alterations do also exist for PDAC as well (19). We do not know whether these genetic alterations are responsible for development or progression and transformation of these lesions. The latter is more likely. MCN is composed of papillary cells producing mucin with a supporting ovarian-like stroma which suggests development from heterotopic islets of ovary left in pancreas in embryonic development, although this remains to be clearly established (20).

CLINICAL PRESENTATION

Over 70% of the cystic lesions of the pancreas are discovered incidentally (21). In pseudocysts, even if they are asymptomatic at the time of discovery, a history of pancreatitis is elicited in most of the time. In a cohort of 212 patients with incidental cysts who underwent operation, 28% were mucinous cysts, 27 % IPMN, 17% SCN, 3.8% were pseudocysts, and 2.5% were ductal adenocarcinoma (22). The presence of a history of pancreatitis does not validate pseudocyst, because IPMN causes acute recurrent pancreatitis as well. Any type of pancreatic lesion including PDAC may first present with an acute attack of pancreatitis as the result of obstruction of main pancreatic duct (MPD).

In case the cystic neoplasm is over 9 cm, it may cause pain due to the pressure to the adjacent organs. Pancreatic cystic neoplasms, usually, displace, not invade the adjacent organs. Because of this, such as common bile duct obstruction is rare in the PCNs in the head of pancreas. Asking for the presence of symptoms is an important part of work-up in the evaluation, because symptoms mandate a surgical resection even in the benign lesions like SCN. Of course the symptoms should be directly attributable to the PCN. Such as a functional GI disease may co-exist and its symptoms may be misinterpreted as the ones of PCN. This may lead an unnecessary operation. One should take into account that, most of the patients with PCNs are elderly and have co-morbidities which may make such an operation risky.

Some endocrine neoplasms like insulinoma may appear as cystic lesion and in this case symptoms of this particular neoplasm like hypoglycemia may be present.

LABORATORY EXAMINATION

Laboratory examination does not help much outside of direct examination of cyst fluid obtained with EUS-fine-needle aspiration (EUS-FNA). Even what it provides is not perfect, because fluid may not be obtained or the markers like CEA, and amylase are either not enough sensitive or specific.

IMAGING

The PCNs are, almost always referred to us, gastroenterologists, after they are discovered in an imaging modality. However, in an EUS examination towards another reasons, they may be discovered by a careful endosonographer as well.

While magnetic resonance (MR) is more sensitive, multidetector computed tomography (MDCT) with a specific setting may

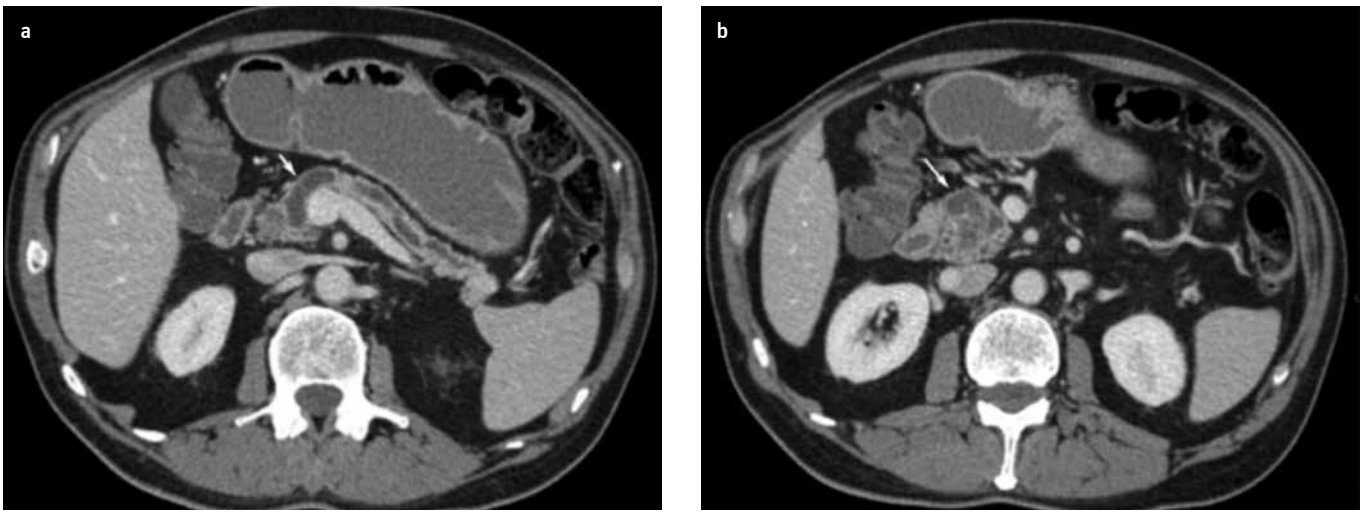


Figure 1. a, b. Main duct intraductal papillary mucinous neoplasm. Contrast-enhanced abdominal CT shows diffuse dilatation of pancreatic duct (arrow) **(a)**. Contrast-enhanced abdominal CT shows multiseptated cystic lesion in pancreatic head (arrow) **(b)**.

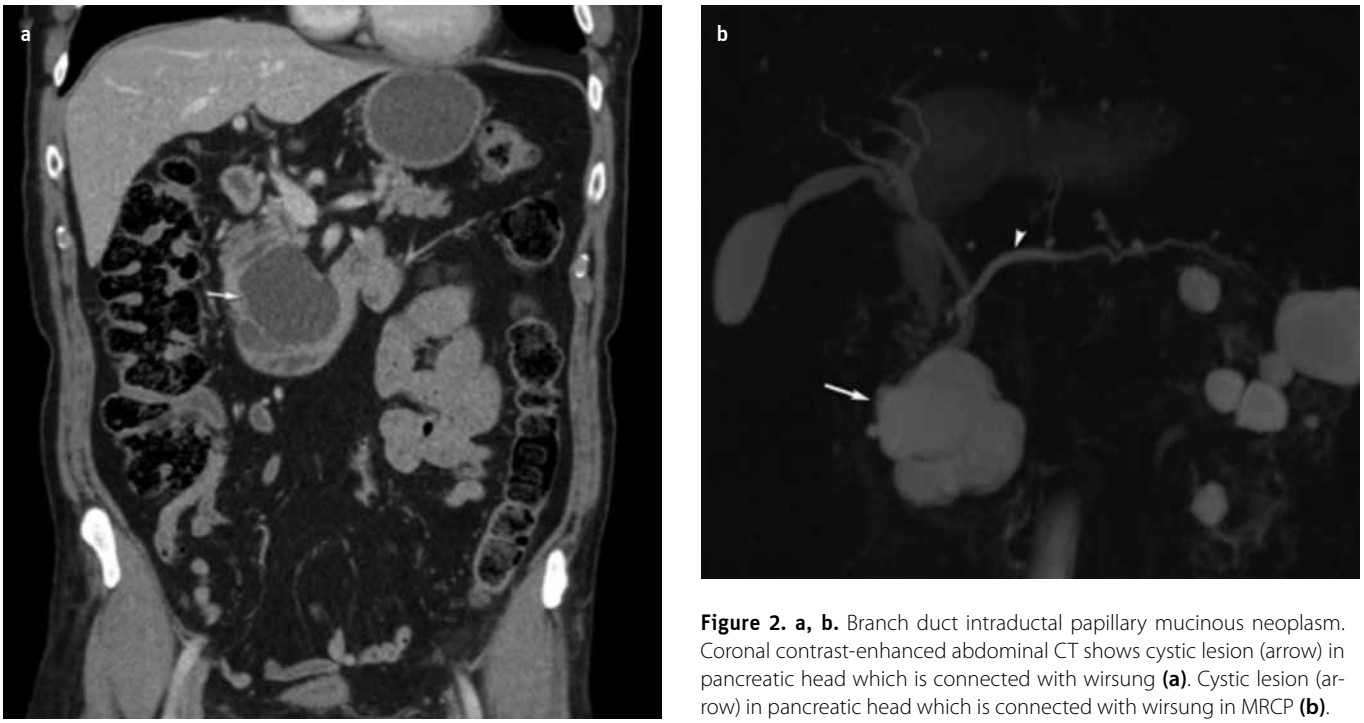


Figure 2. a, b. Branch duct intraductal papillary mucinous neoplasm. Coronal contrast-enhanced abdominal CT shows cystic lesion (arrow) in pancreatic head which is connected with wirsung **(a)**. Cystic lesion (arrow) in pancreatic head which is connected with wirsung in MRCP **(b)**.

be better for characterization of the pancreatic cysts. Magnetic resonance cholangiopancreatography (MRCP) is used for the evaluation of duct connection. The value of positron emission tomography-computed tomography (PET-CT) is controversial. It may have some role for the assessment of malignant transformation. We are going to discuss the particularities of these methods towards different types of cysts under relevant titles.

ENDOSCOPIC ULTRASOUND (EUS) IMAGING OF PANCREAS

Technical aspects

If advanced cross-sectional imaging changed our perspective for the frequency of pancreatic cysts, EUS did the same for the management. Pancreas used to be considered a difficult organ to approach before the arrival of EUS, but not any more. EUS provides access to all parts of pancreas either trans-gastrically or -duodenally. Cysts can be detected, characterized, and sampled; fluid is aspirated in case there is enough volume. Pseudocyts are drained and even some investigational treatments are delivered via EUS.

For pancreatic examination we usually, if not always, use linear device. For the examination of possible very small lesions, in case we fail to find a lesion with linear EUS, we, sometimes do a second examination with radial device. However in case you do not have radial device, no reason to feel deficient in reference to pancreas. We start examining pancreas from proximal stomach,

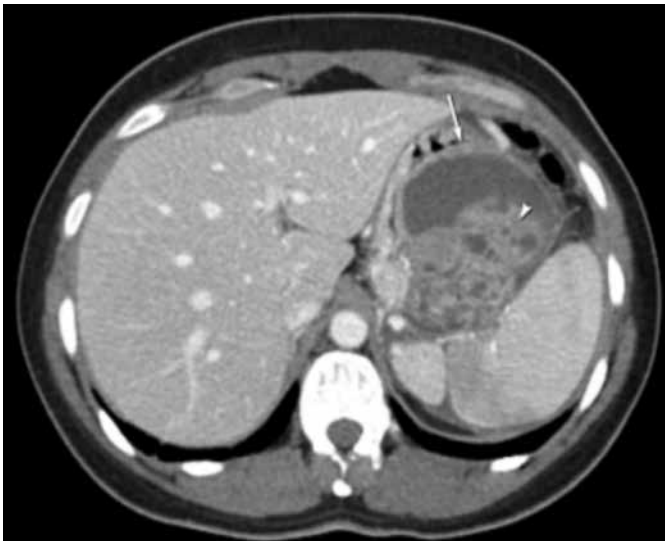


Figure 3. Mucinous Cystic Neoplasm. Contrast-enhanced abdominal CT shows thick walled cystic lesion (arrow) with thick enhanced septa (arrow head) in pancreatic tail.

nearly 50 cm. from teeth. When we enter into the stomach, the first organ we see is the left lobe of the liver. When we perform an around 130 grade clockwise rotation just at the level of left branch of portal vein and turn the inner knob towards up direction we see the body of the pancreas. When we do a 5 cm. pull back with further up and clockwise rotation, we examine the tail of the pancreas which is closely between spleen and left kidney. In most of the time the left adrenal is also in vision while performing the examination for the body and tail of the pancreas. When we push endoscope further in the plane of body, with a slight clockwise rotation we examine the neck of the pancreas. The head and uncinate process of the pancreas are examined from the first and second parts of the duodenum. Insertion of the linear, even the therapeutic one, to this level is very easy in case you apply the following rules and there is no obstruction. Of course you must beware of the potential diverticula as well. When the tip of the endoscope touches the pylorus and we apply a gradual right twist at a slight down position, the tip slides smoothly into the bulbus. Once we are in bulbus we apply a further right twist with 30-40 grade clockwise rotation and we actually pull the scope back, the tip glides into the second part. In case the forward movement stops, we go with to-fro movements in the same fashion. We never push it blindly which would result with the perforation of the bulbus. I, personally, never used a balloon, however it may aid to hold your position and eases a gradual pull. I generally push the tip up to the third level. At this level, the first structure we see is abdominal aorta. With a up twist and a counter- clockwise rotation we examine the coeliac take-off and the origin of superior mesenteric artery as well as renal arteries. Upon pulling back, we examine the uncinate process which is relatively hyperechogenic relative to the head. With further pull we examine the head of pancreas, superior mesenteric vein, a small part of splenic vein and portal confluence as well as hepatic artery and gastroduodenal artery. A complete view of the pancreatic head with MPD, papilla vateri and common bile duct can be obtained from bulbus.

EUS: Diagnostic performance

In pancreatic cysts, the rate of accurate diagnosis based on EUS morphology alone, is 40% to 93% and depends on the experience of endosonographer. While in Western countries and United States, EUS-guided puncture of cysts is frequently performed, in Japan, in case there is a suspicion of a mucinous lesion it is avoided (23). The predictive value of EUS-FNA in deciding for surgery was reported as high as 95%. The cytologic yield of EUS-FNA is rather poor: The overall accuracy of EUS-FNA cytology was reported as 50% (24-26). Interim analysis of a recent study demonstrated that the rate of sufficient material is 49 % for fluid analysis and, 31% for cytology (27). However the yield may be increased with some special techniques as puncturing the wall at the expense of increased risk of pancreatitis (28). In case the presence of atypical cells is considered as the diagnostic criteria for malignancy the accuracy of cyst fluid cytology, increases to 85% (29). The differential diagnosis of EUS is challenging and effective use of EUS may prevent unnecessary surgery. Even in a tertiary hospital, 20% of resected PCNs were found benign (30). Without EUS, the imaging diagnosis of pancreatic cysts is not accurate enough because of the overlapping features.

Side effects: Whether EUS-FNA carries a higher risk of infection in cysts than solid pancreatic lesions is controversial. In general an antibiotic is injected pre-peri- or post-procedurally. However, there is a risk of antibiotic-related adverse event and efficacy of using antibiotic is yet to be confirmed (31). The risk of pancreatitis is overall 0-2% and it is said to be increased with pancreatic duct puncture (32). Mostly, the pancreatitis is mild, severe cases are too rare. Severe bleeding is also very rare and the bleeding is mostly intracystic. After completing the suction of fluid, sometimes, the endosonographer observes that the cavity is immediately filled with fluid with echogenic reflections. It resolves spontaneously in days without sequel causing no clinical symptom or sign.

PSEUDOCYSTS

It comprises two thirds of all pancreatic cysts. However in incidentally discovered cysts, pseudocyts hold the place of second to cystic pancreatic neoplasms in frequency, given to the increased detection of small lesions in asymptomatic subjects. Pseudocyts are unilocular and their size is usually more than 30 mm. They, generally contain floating debris inside, and may be found in any part of pancreas. Aspiration with 22 G and even 25 G needle yield fluid for examination. While the aspirated fluid is, generally, muddy-brown, may be clear or white turbid. It does not contain mucus. In some cases, aspiration may not be

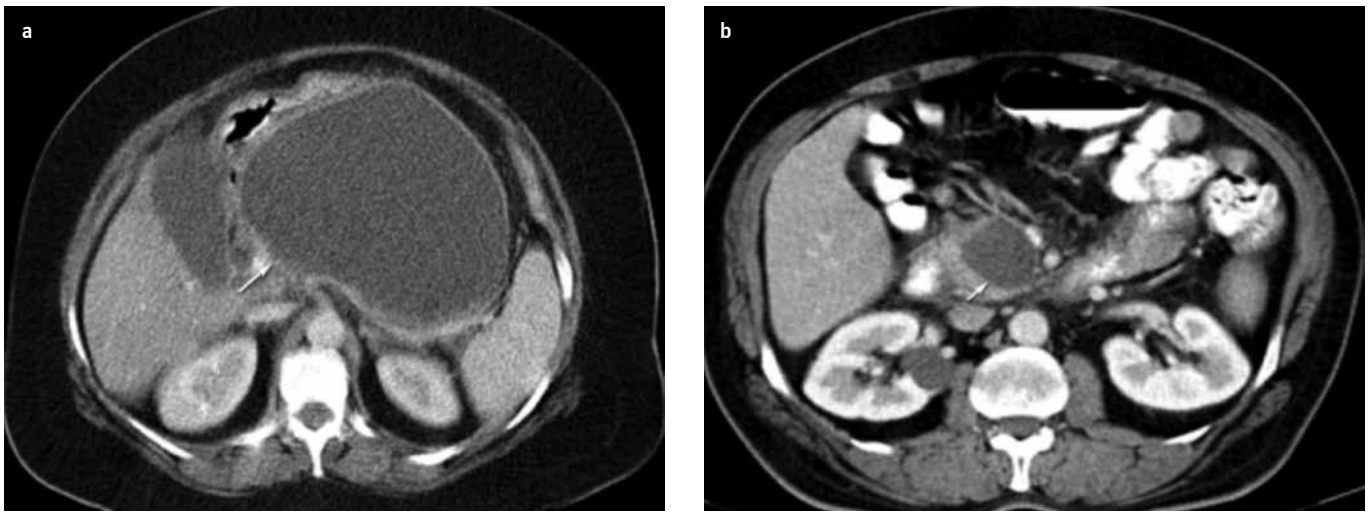


Figure 4. a, b. Pseudocysts. Contrast-enhanced abdominal CT shows thin walled cystic lesion without septa and solid component which protrude the stomach anteriorly in peripancreatic area (arrow) **(a)**. Contrast-enhanced abdominal CT shows thin walled cystic lesion without septa and solid component in pancreatic head (arrow) **(b)**.

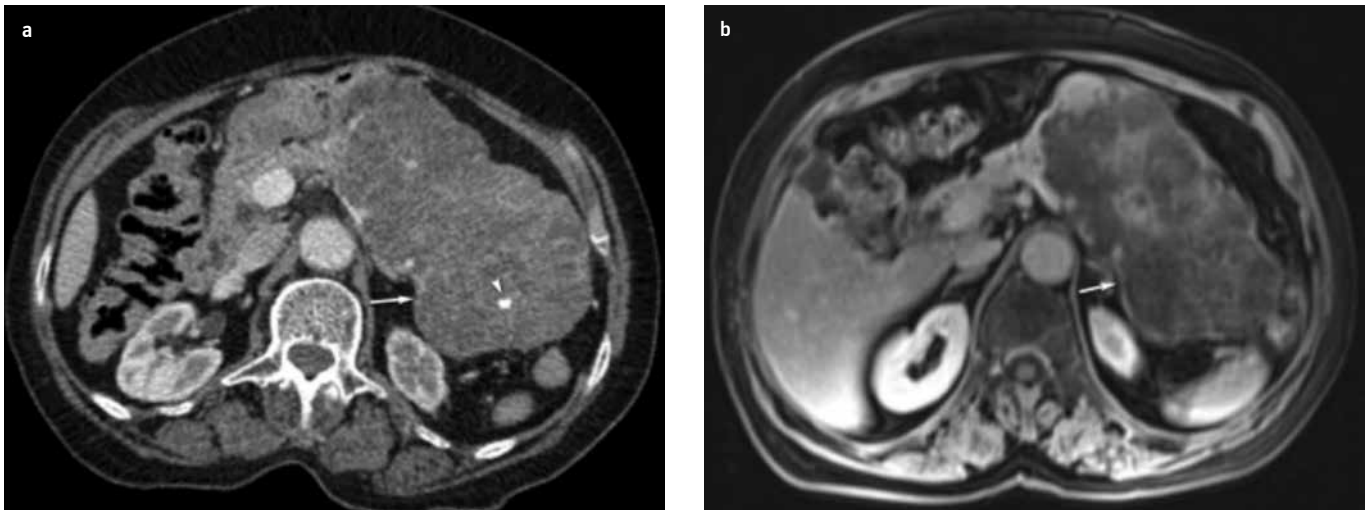


Figure 5. a, b. Serous cystic neoplasm. Contrast-enhanced abdominal CT shows honeycomb appearance (arrow) (cystic lesion with thick enhanced multiple septa and solid component), containing macrocalcification (arrow head) in pancreatic tail **(a)**. Contrast-enhanced abdominal MR shows honeycomb appearance (arrow) (cystic lesion with thick enhanced multiple septa and solid component) in pancreatic tail **(b)**.

possible, because of thick fluid, which requires the use of 19 G needle. The amylase content is over 2000 U/L (usually tens of thousands) and CEA level is very low or undetectable.

A rare entity which is called as pseudopseudocyst is characterized by inflammatory exudative fluid collection.

In case pseudocyts are larger than 60 mm and symptomatic, endoscopic drainage is required. Drainage is postponed until 8 weeks after an acute pancreatitis attack to allow time for maturation of the wall. In case a cyst does not resolve until 24 weeks, it is unlikely that it would resolve later.

For drainage we always use an EUS-guided approach, even if there is bulging to the stomach or duodenum. For drainage form stomach, we try to position the therapeutic linear endoscope tip in the below position: First we try to achieve a straight position to ease the insertion of needle, second we try to find a place from which the cyst is close to the stomach wall, and we try to achieve a vessel-free area. We either put the patient to the prone position with deep sedation, or supine position with general anesthesia. In the last years, we increasingly use the latter approach, because we usually insert a fully covered, or more recently, a specifically designed cysto-gastrostomy metallic stent and after the deployment of the stent, the gush of the fluid is so brisk that it would result with aspiration in an un-intubated subjects.

We always perform the procedure under x-ray guidance, however it is not an absolute necessity, especially with the newly introduced single action fully covered metallic stent (X-lumena company, USA) which is not available in this country.

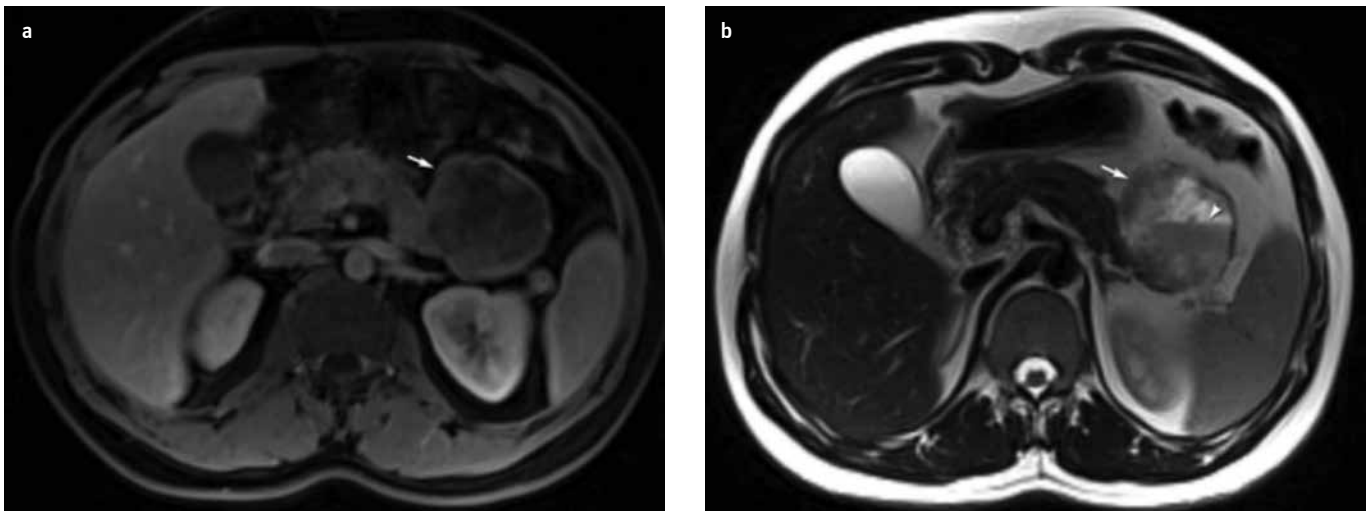


Figure 6. a, b. Solid pseudopapillary neoplasm. Contrast-enhanced abdominal MRI shows cystic lesion (arrow) which have thick, enhanced wall and enhanced solid component **(a)**. T2 weighted abdominal MRI shows cystic lesion (arrow) which containing liquid-liquid level (arrow head) due to haemorrhage **(b)**.

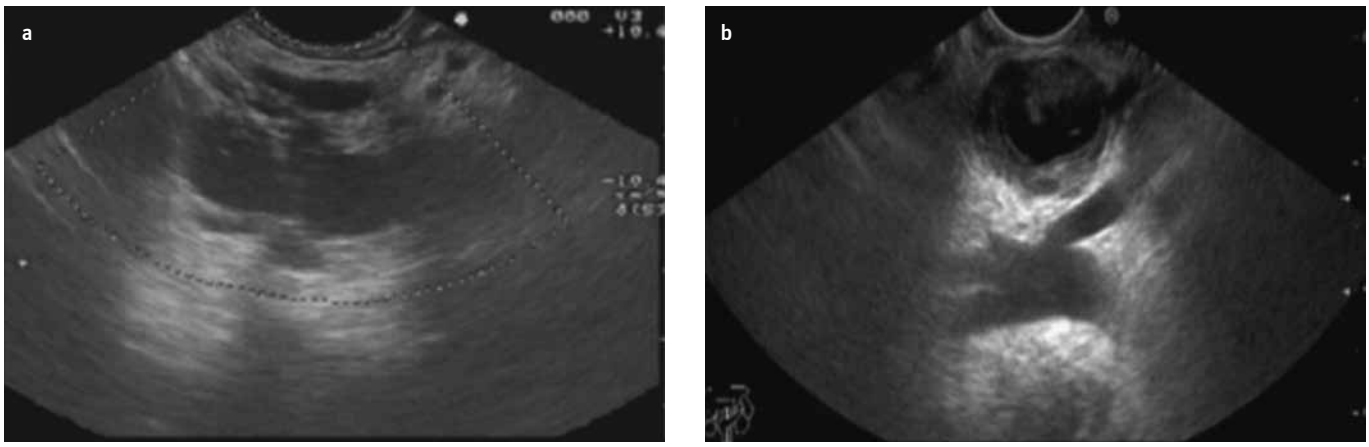


Figure 7. a, b. EUS Picture of Main Duct IPMN. Huge MPD dilation **(a)** with diffuse wall thickening and internal papillary projections **(b)**.

After we insert a 19 G needle into the cyst, we confirm the location with aspiration and than insert a 0.035 guide-wire with EUS and x-ray guidance and loop it in the cavity. We withdraw the needle carefully and replace it with needle-knife with a lumen allowing guide-wire. When we arrive at the stomach wall, a resistance is felt. We push the needle out and try to check the position endoscopically with a slight up movement. However it must be done carefully in order not to lose the correct position. Furthermore, while the insertion is straight in EUS-guidence, it is angled in endoscopic guidance, because of the side viewing nature of the scope. In the first place we try to push the needle-knife without electrical current into the cavity which is not successful in more than half of the cases. In case this is not successful we administer endocut-I current (Erbe company, Germany) until the catheter is in the cavity. Then, we replace the needle-knife catheter with a 5-7-10 graded bougie dilator for further dilation and we finally put the fully covered metallic stent. We deploy the metallic stent with combined x-ray-endoscopic guidance, and complete the procedure with endoscopic view. The main complication is maldeployment of the stent which results with free peritoneal perforation. Actually the picture is evident while the patient is on the table. In this case, we first perform transabdominal ultrasonography which reveals the presence of free peritoneal air. Afterwards we introduce a large bore needle, or better a veres needle to deflate the peritoneal space. In case the stent is present it is withdrawn and the puncture site is clipped. In most of the cases operation is not necessary. However prophylactic antibiotic use is advised. The other significant complication is hemorrhage which is rarely significant. If it is, immediate blood replacement must be followed by the transfer of the patient to the operation theatre. A delayed complication is the infection of the cyst cavity which is treated by antibiotics. In some cases, percutaneous drainage may be needed. The stent is usually withdrawn after 8 weeks, in case the drainage is satisfactory. However the use of fully covered metallic stent issue is yet to be resolved, our experience dictates that it is easier and more efficiacous than multiple plastic stents. Furthermore, the large bore (up to 16 mm) cystogastrostomy stents, allows the passage of gastroscope into the cavity which would be used for the removal of necrotic tissue.

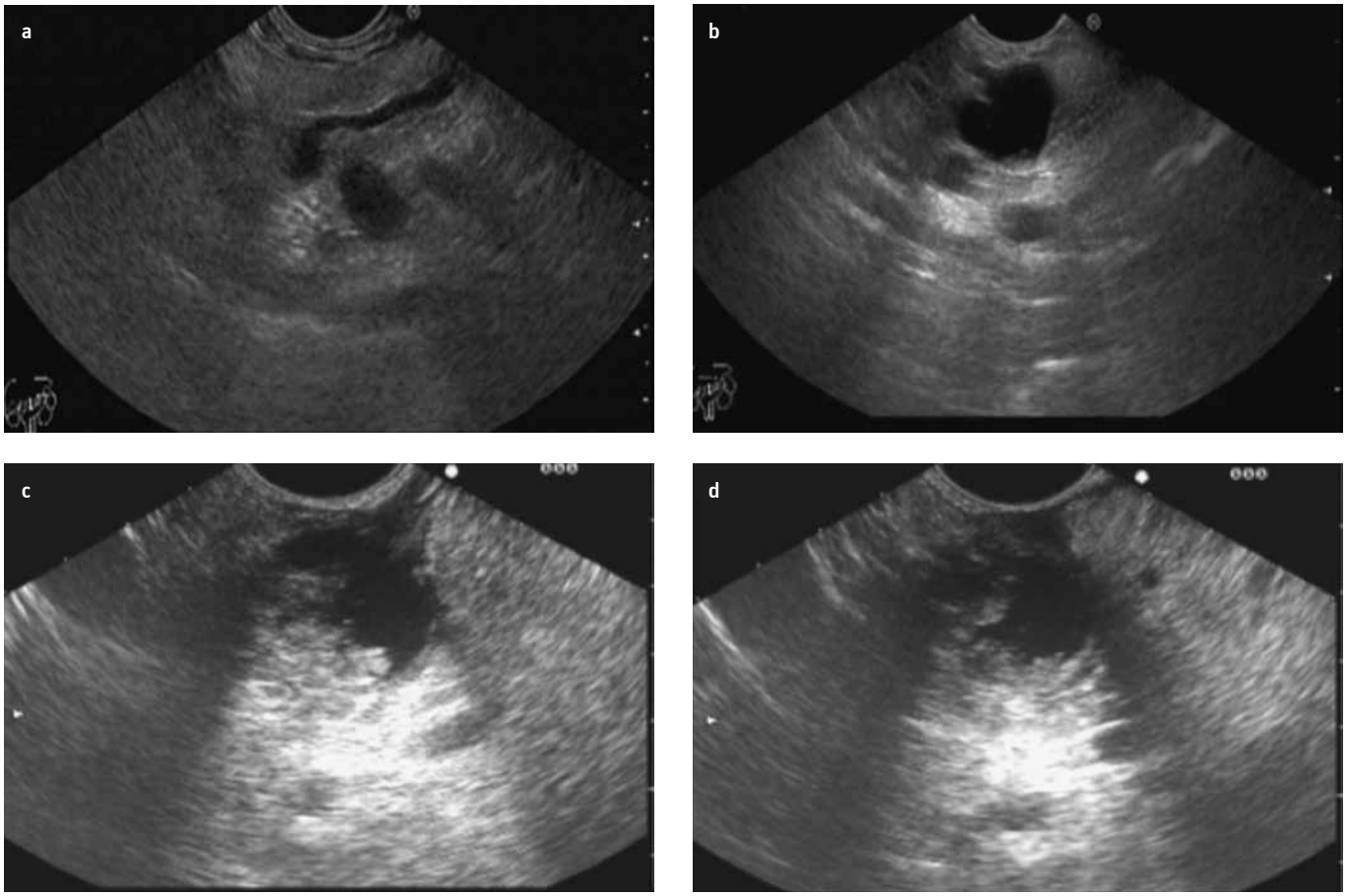


Figure 8. a-d. EUS Picture of Branch Duct IPMN. Unilocular cysts with **(a)** and without **(b)** MPD dilation. BD-IPMN with significant papillary projections (mural nodules) **(c, d)**.

SEROUS CYSTIC NEOPLASM (SCN)

Serous cystic neoplasms (SCN) represent 1% to 2% of pancreatic neoplasms and 25% of all cystic tumours (33). They are, usually, diagnosed on the ground of imaging: A microcystic lesion with thin walled septa which are vascular, a central scar (present in 30% in CT examination), calcifications, and a poorly developed capsule that it is difficult to distinguish the cyst form the surrounding parenchyma, confirm the diagnosis in an elderly patient (34). The classical honeycomb pattern is present in 20% of the patients. In some cases the lesion is oligocystic that may be confused with IPMN. Most of the patients whose cysts are smaller than 15 cm are asymptomatic. In this case, if the radiologic findings are conclusive, there is no absolute need for EUS examination. However, it may be useful to corroborate diagnosis. In half of the patients, it is possible to aspirate fluid for CEA determination that excludes a mucinous tumour. In the remainder the aspiration attempt would result with the aspiration of blood which is an indirect clue for SCN. The aspirate stains negative for mucin. The acquired cells have glycogen-rich clear neoplasm that stains positive with PAS. There is an unilocular variant of SCN which is, usually, localized in the head. In some cases of SCN the lesion may obstruct the MPD and it may be dilated, sometimes mimicking main duct-IPMN. SCN is a benign neoplasm and, malignant transformation risk is virtually non-existent. It is slowly growing, and most of the afflicted patients are elderlies with comorbidities. Therefore, the decision for resection should be cautious, unless there are clear-cut signs of compression symptoms which are not frequent. The growth rate is usually 0.6 cm per year. However in case the cyst is over 4 cm, the growth rate may reach up to 2 cm per year (35).

MUCINOUS CYSTIC NEOPLASM (MCN)

Mucinous cystic neoplasm (MCN) represents of 2% of all pancreatic neoplasms and one third of all cystic neoplasms (36). It is mostly a cystic neoplasm of women (female: male ratio is 20:1) and, usually diagnosed at the perimenapousal age. The average age at diagnosis is 48. MCN, is consisted of papillary mucin secreting cells supported by fibrous ovarian type of stroma. Female hormones have a certain role in the progression of these cysts. It is, mostly, located either in body or tail of the pancreas and has a peripheric location. In most of the MCNs, MR and MRCP makes the correct diagnosis. MRCP is very effective in demonstrating communication between cyst and pancreatic duct and its absence with suggestive features of mucinous cyst is usually diagnostic. However, lack of communication with the main pancreatic duct is a controversial issue at the moment, because, amylase level is, sometimes, elevated

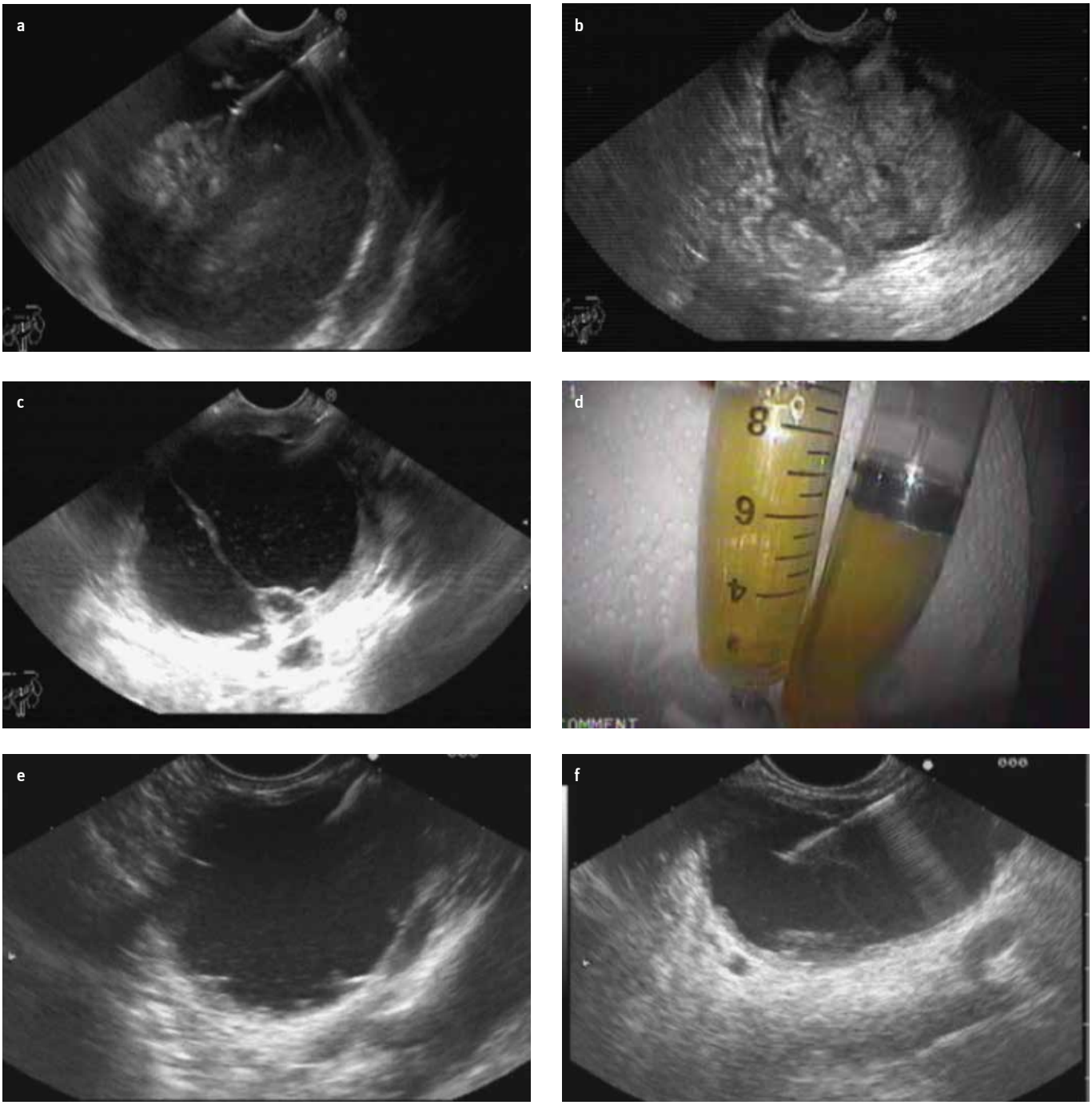


Figure 9. a-f. Mucinous Cystic Neoplasm (MCN). MCN **(a)** Mucinous cystadenocarcinoma **(b)**. Unilocular cyst. The aspirated fluid appears serous. However CEA level was very high and surgery confirmed the diagnosis of MCN **(c, d)**. CEA and Amylase were undetectable in the aspirated fluid. However surgery revealed MCN. The diagnosis of MCN may be challenging in such cases **(e, f)**.

which points towards small communications, which may not be evident in imaging. MCN is considered to have a malignant potential. However, malignant transformation happens, at the most 15% (8% to 29-36%) of the patients eventually and the risk is very low in cysts with a diameter less than 30 mm without mural nodules (36). Aspirated fluid, traditionally, reveals high CEA (over 200 ng/mL). Rarely cyst CEA may be low. Many MCNs that are malignant demonstrate peripheral calcification, a thickened cyst wall, papillary proliferations and a hypervascular pattern and may show vascular involvement (37). Pure colloid carcinoma as it is in IPMN is rare in MCN (38).

The decision for resection should be taken by discussing the issue with the patient. Given to the fact that these patients are relatively young, and the tumor location generally allows distal pancreatectomy, there is a trend for surgical resection. In case there is no malignancy in resected specimen, follow-up is not necessary. However, if malignancy is present, there is a high

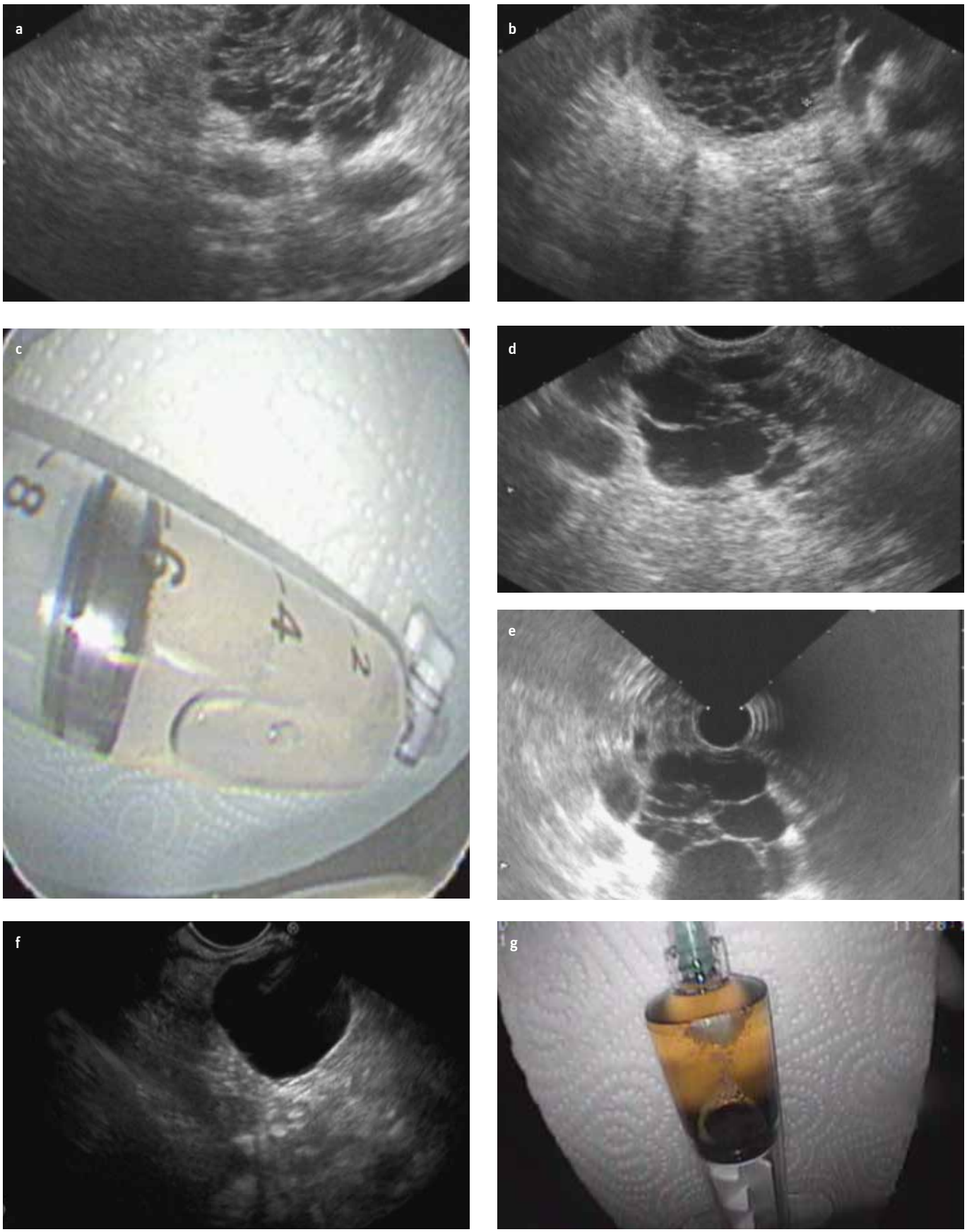


Figure 10. a-g. Different EUS pictures of Serous cystic neoplasm. Classical honeycomb pattern **(a)**. EUS appearance is highly characteristic, but the aspirated fluid is clear. However the CEA and amylase levels were very low supporting diagnosis **(b, c)**. Oligocytic serous cystadenomas **(d, e)**. The cyst is unilocular, however aspirated fluid appears serous. CEA and amylase levels were too low and surgery revealed SCN **(f, g)**.

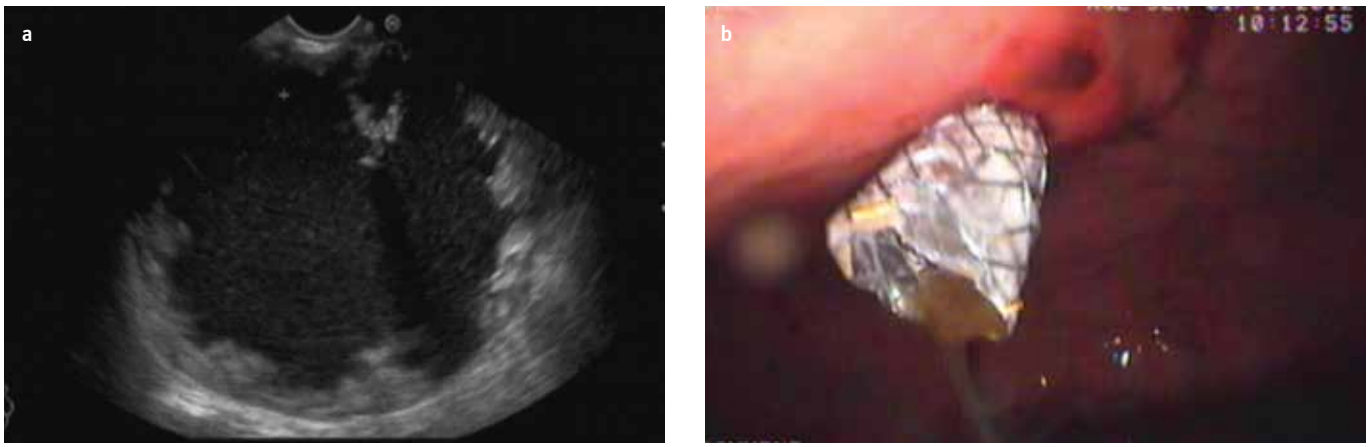


Figure 11. a, b. Pseudocyst **(a)**, and cystogastrostomy with fully covered metallic stent **(b)**.

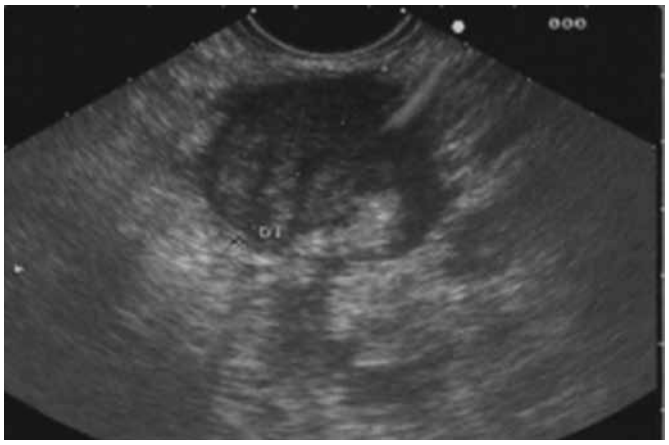


Figure 12. Ductal adenocarcinoma on the background of MCN.

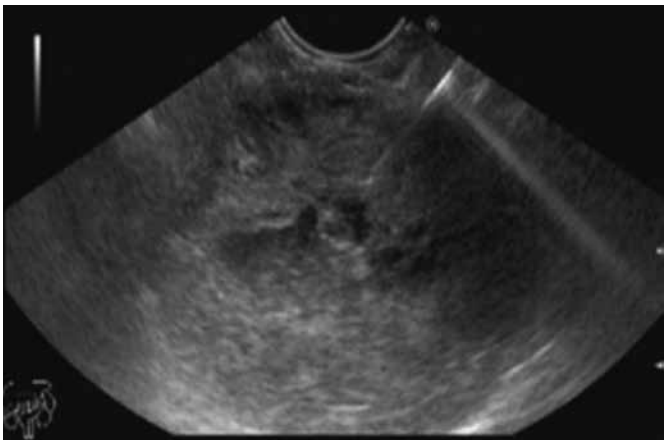


Figure 13. Solid pseudopapillary neoplasm.

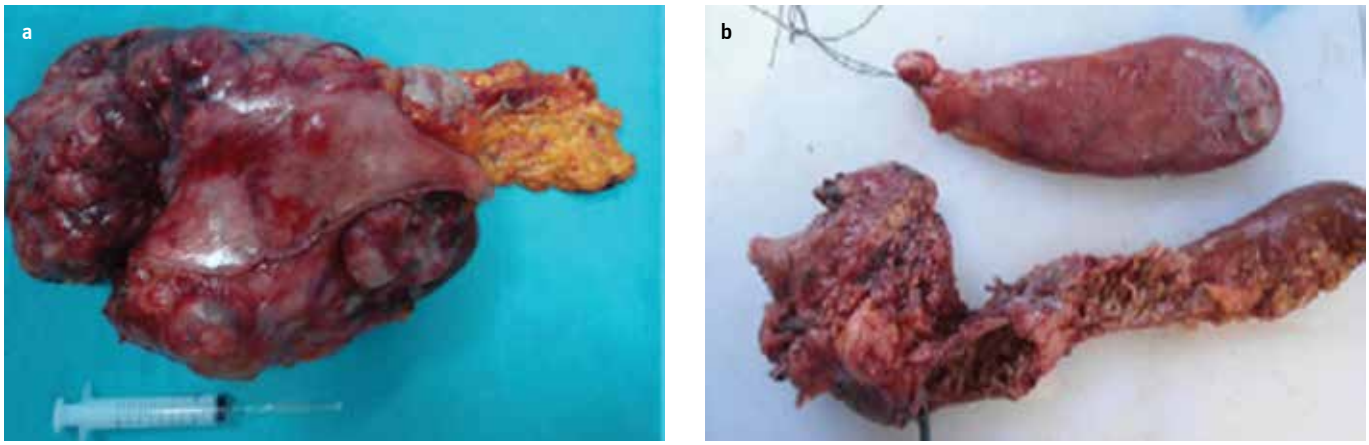


Figure 14. a, b. IPMN **(a)** and Ductal adenocarcinoma on the background of IPMN **(b)**.

risk of recurrence, and these patients should be followed-up 6 monthly with CT or MRI. While five year survival rate for the resection of benign MCN is 95%, it is 50-60% for malign MCN (39).

INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM (IPMN)

Intraductal papillary mucinous neoplasm (IPMN) is a mysterious disease for which, virtually, nothing has been known until 30 years ago. However, it is receiving more attention because of increased diagnosis and high risk of malignant transformation. It is diagnosed mostly after the age of 60, however it may be diagnosed in younger subjects as well. It does not show gender predilection. Recent years witnessed accumulation of abundant knowledge about this disease. Histologically, five types are present: 1- Gastric foveolar, 2- Intestinal, 3- Pancreato-biliary, 4- Oncocytic, and 5- Tubular (38).

While gastric foveolar type is usually benign, cystadenocarcinoma may develop in intestinal, and ductal adenocarcinoma

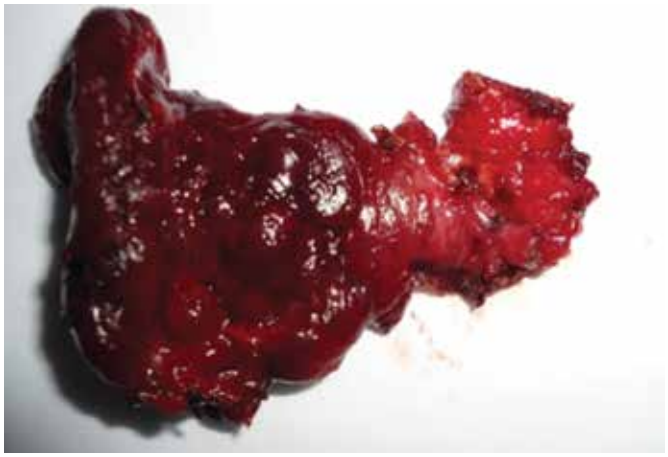


Figure 15. Serous cystic neoplasm.

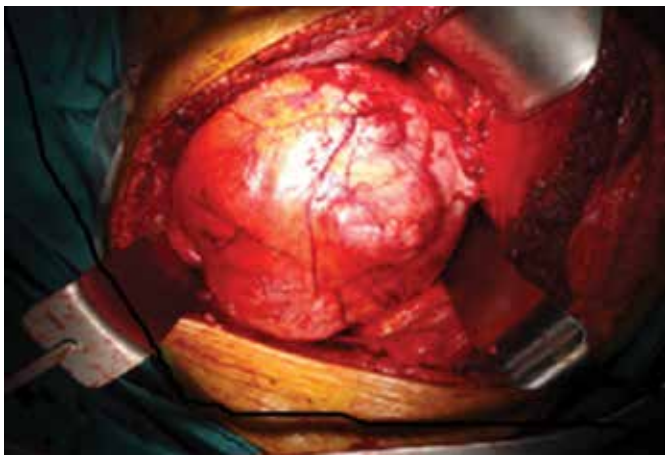


Figure 16. Pseudocyst.

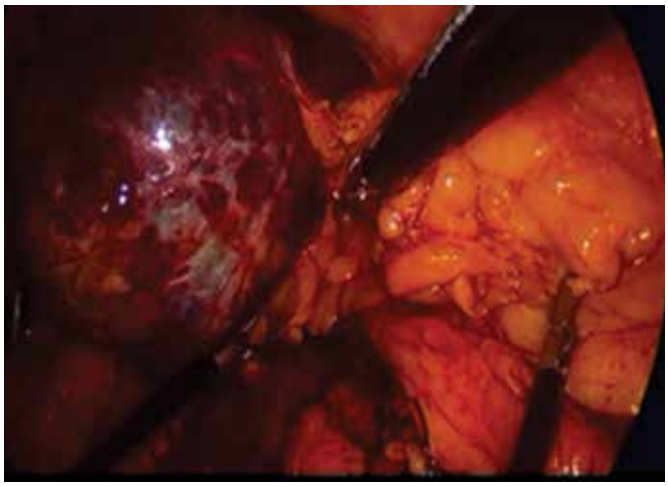


Figure 17. Solid pseudopapillary neoplasm.

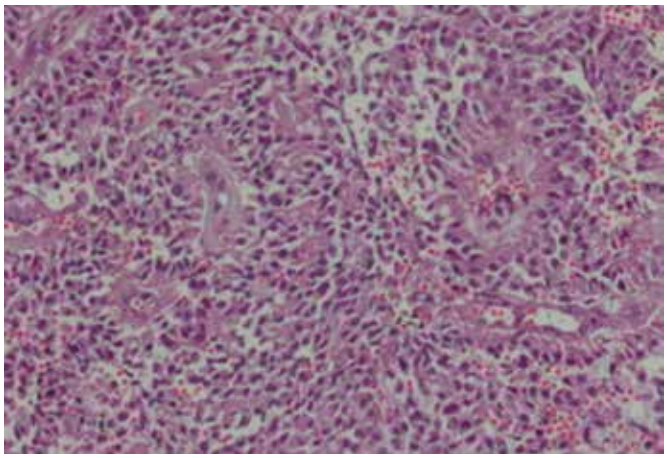


Figure 18. Solid pseudopapillary neoplasm. Perivascular papillar projections; solid islands of discohesive layers forming monotonus cells (H&E).

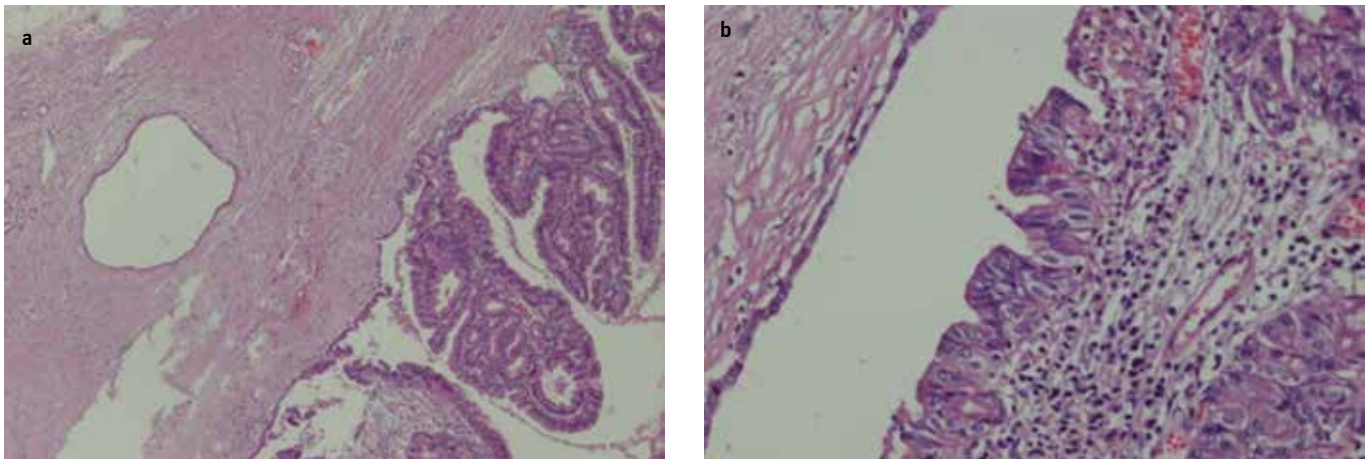


Figure 19. a, b. Intraductal papillary mucinous neoplasia with borderline features of malignancy. Mucinous epithelium, forming complex papillary projections. Patchy areas of increased epithelial layers associated with atypia.

in pancreato-biliary type. These definitions, at the present time, mostly, be made in surgically resected specimens. IPMN is usually diagnosed with CT, MR, and MRCP. The final diagnosis, however, rests with EUS. These cysts are either unilocular or macrocystic and fluid is obtained with FNA in most of the cases. If the fluid is highly viscous, aspiration may not be possible. In this circumstance even if a drop of fluid is obtained, tenacious nature points toward a mucinous cyst. If a drop of fluid is hold between the thumb and index finger and stretched apart, a string is formed in mucinous cyts. It was reported that if the string is more than 4 mm, it strongly suggests mucinous cyst (40). When we have enough fluid, which requires that the cyst is at

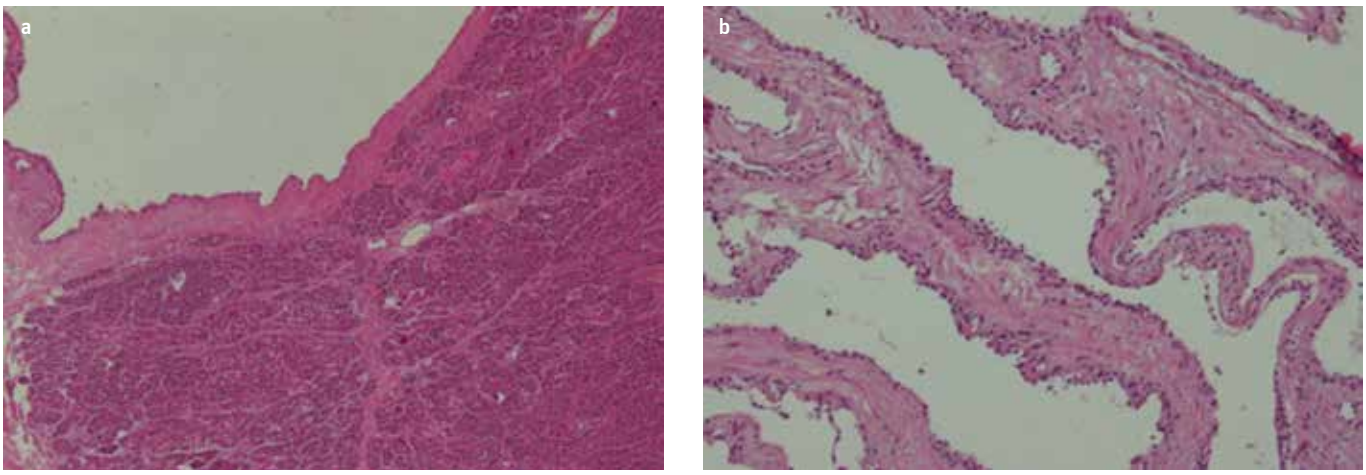


Figure 20. a, b. Serous cyst. Cyst surrounded by single layer cuboidal cells with clear cytoplasm adjacent to pancreatic aciner structures.

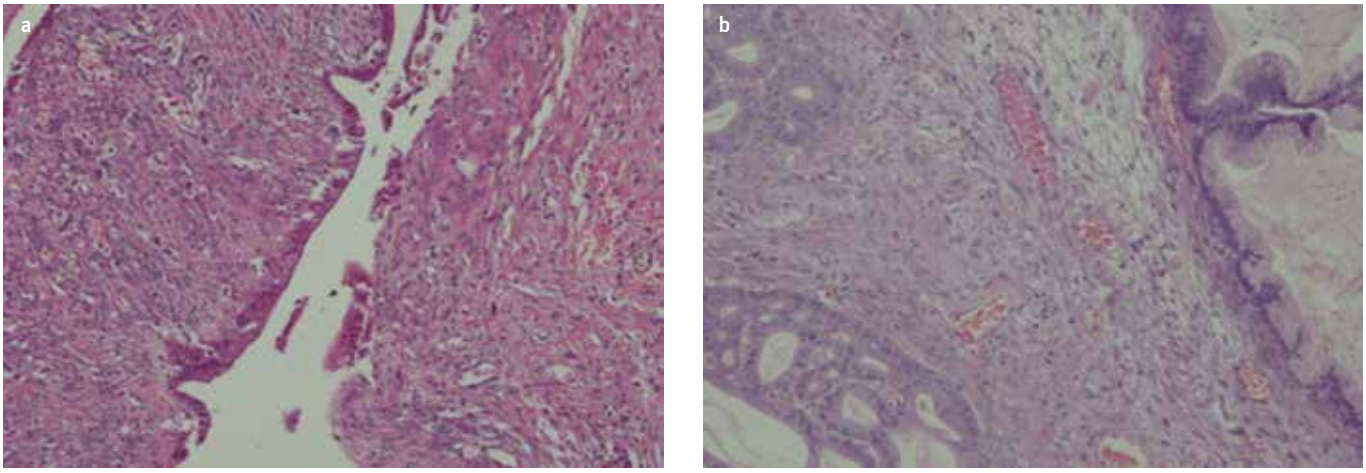


Figure 21. a, b. Mucinous cystic neoplasm. The cyst surrounded by columnar mucinous epithelial cells and the typical ovarian type stroma beneath.

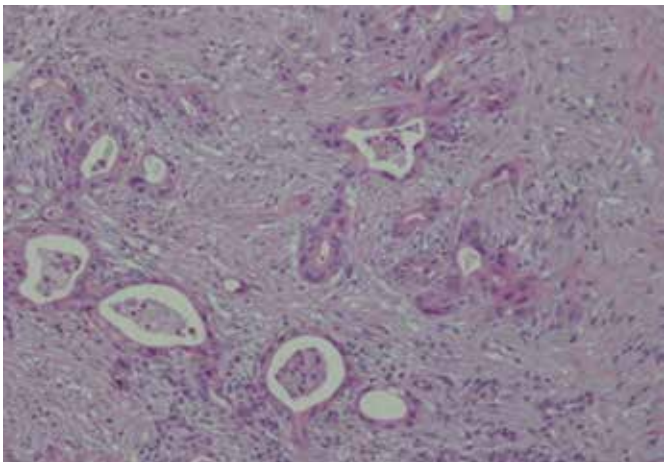


Figure 22. Ductal adenocarcinoma. Atypical epithelial cells forming glandular structures in desmoplastic stroma.

least 15 mm, we send the sample for CEA determination. If the cyst CEA level is above 200 ng/mL, it is almost certainly a mucinous cyst. However lower levels do not exclude diagnosis. The cyst fluid amylase level is elevated even if it is not as high as it is in pseudocysts. Recently, the significance of cyst fluid amylase levels for the differential diagnosis was challenged, because it may be found to be elevated in cysts without any communication with the pancreatic duct (41). From this discussion, it is evident that in less than one third of IPMN cases, the diagnosis may not be certain. It was reported that decreasing amylase, rather than increasing CEA may point towards a malignant transformation, because proliferation of tissue obstructs the communication between the cyst and the duct (42). In branch duct (BD)-IPMN, if the cyst size is below 30 mm, the MPD diameter is less than 6 mm, and mural nodules are absent, the malignancy risk is very low (36). Mural nodules are internal projections of papillary tissue. While in the past mural nodules are, uniformly, considered as an ominous sign, in recent years, it appeared that in less than one third of the subjects, the mural nodules in EUS are not associated with malignancy, and the height of the mural nodules come into consideration. It was published that, malignancy risk is high in type III or IV mural nodules (43,44). Yamaguchi reported that the mean diameter of mural nodules was 5.1 mm in benign lesions and 20.5 mm in malign lesions (45). In EUS the rate of describing the mucus as an intracystic lesion reaches 65 %. While EUS is more sensitive (75% vs. 24%), CT is more specific (100% vs. 83%) in reference to diagnosing mural nodules (46). In BD-IPMN, the risk of overall

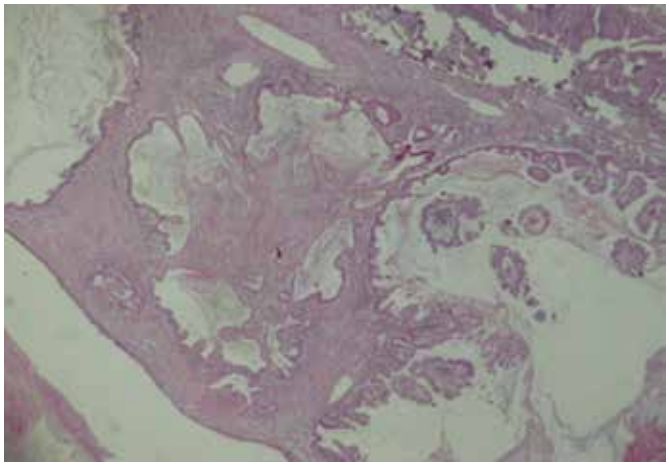


Figure 23. Colloid carcinoma. Cysts surrounded with well differentiated columnar mucinous epithelial cells and invasive adenoid structures in stroma with extracellular mucin.

malignancy is around 25% (from 8% to 29-36%) (27,45,47,48). Cytological yield is poor with EUS-FNA: Cytology was positive in only 29% of malignant mucinous tumours. However the specificity is quite high, 83% (25). The rate of sufficient material obtained by EUS-FNA was reported as 31% for cytology, and 49% for fluid analysis (27). The benefit of prophylactic antibiotics is controversial and warrants a large prospective study. While the use of antibiotics did not provide significant benefit, some reactions were noted (31). At the present time, this issue is at the discretion of physician. The concern for peritoneal seeding was not corroborated in mucinous neoplasms (49).

In case IPMN involve main pancreatic duct (MPD), it is called as MD-IPMN, MPD appears, hugely dilated (usually over 10 mm) and is filled with echogenic material (mucin). In endoscopy, mucin protruding form papilla vateri is observed: the so-called "fish-mouth" sign. While malignancy is found in 58% to 92% of main duct tumours, the rate is 6% to 46% in branch duct IPMN (47). As the age of the patient increases, the rate of malignancy increases as well. Many malign mucinous neoplasms have peripheral calcification, a thickened cyst wall, papillary proliferations, and a hypervascular pattern, and, sometimes, vascular involvement (37).

There is another variant of IPMN which involves both BD and MPD that is called as Mixed-type-IPMN. In mixed as well as MD IPMN, it is very difficult to discern up to which level the tumour extends, and serial in-theatre, resection margin pathology is needed, to decide to stop or go on with further resection (creeping pancreatectomy). In some cases of IPMN, some part of inner wall may be denuded, and pathologically be confused with pseudocyst. Very recently, non-neoplastic variant of IPMN was described (Mucinous non-neoplastic cyst, MNNC). This is usually unilocular and localizes in the head of the pancreas. The particularity of this cyst is that, it has mucinous content, however it is not neoplastic, the CEA level is low and the risk of malignant transformation, virtually, does not exist (50).

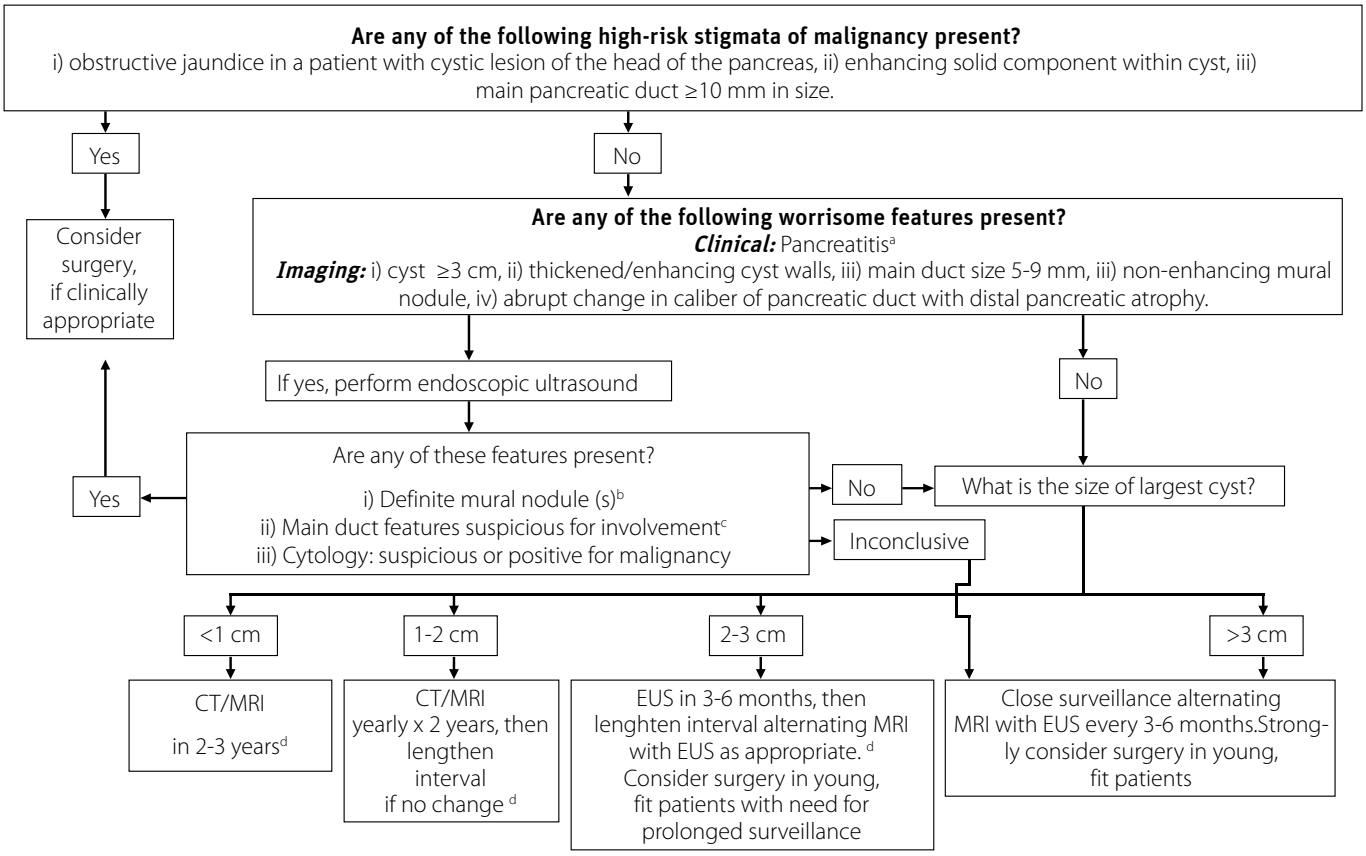
In BD-IPMN, surgery is advised for symptomatic patients with cysts of any size, cysts over 30 mm., or with features suggesting malignancy described above. After resection, 6 monthly follow-up is necessary. For asymptomatic patients with <10 mm BD-IPMN yearly cross-sectional imaging suffices, for 10 mm to 20 mm it should be six monthly. For cysts between 20 mm to 30 mm, 3-6 monthly follow-up preferably with EUS is suggested (Sendai and Fukuoka criteria) (51,52) (Table 2). Patients with IPMN also necessitates a surveillance for other synchronous extra-pancreatic malignancies as well. However there is no established protocol for this. In a series including surgically resected BD-IPMN, the rate of malignancy was <10% in cysts <2 cm without mural nodules, 24% in cysts 2-3 cm in size regardless of nodularity, and 44% for cysts >3 cm with mural nodules (53). Overall increase in size of the cyst 5 mm. or more may be considered an indication for surgery outside of consensus-guidelines indicated resection. However the size alone is not a decision making variable, in case the size is 3 cm or below. CT findings are helpful in the evaluation of complex cystic structures. In asymptomatic patients with pancreatic cysts smaller than 3 cm, the frequency of occult malignancy was found 3.3%, whereas 90% of patients with malignant lesions were symptomatic (54). Recently IPMN was considered as a diffuse pancreatic pre-malign or malign condition, because the risk of concurrent PanIN and another IPMN are increased (21% to 41%) in these subjects (55-59). However the same studies showed, in case there are multiple IPMNs in pancreas, the risk of malignancy is lower. Another interesting observation is the increased risk of synchronous or metachronous primary extrapancreatic tumours, such as cancers of stomach, colon, rectum, lung, breast or liver in patients with IPMN (60,61). In an analysis of 183 resected invasive IPMNs, 66% were classified as PDAC derived from IPMN and 17% as PDAC concomitant with IPMN (62). The five year survival is 57% in colloid and 16% in tubular carcinoma (63).

CONTROVERSIES IN CLASSIFICATION OF PANCREATIC CYSTS

Certain characteristics of pancreatic cysts are summarized in Table 3. However it is evident from the ongoing discussion that we are yet to have a satisfactory categorization of pancreatic cysts. Our existing classification is probably an over-simplification of an otherwise highly complex disease. That would pose a challenge to the clinician:

1- It is virtually impossible to acquire enough fluid for examination form cysts below 15 mm.
2- It is not possible to aspirate fluid form, on average half of the cysts, either because the solid component predominates as the case in microcystic serous cystic adenomas or IPMN with highly viscous content.
3- In some IPMN, the CEA level is between 50-195 ng/mL which is a gray area for the diagnosis. In some MCN, it may even be lower than 50 ng/mL.

Table 2. Fukuoka criteria for the surveillance of IPMN and MCN



[a]Pancreatitis may be an indication for surgery for relief of symptoms.
[b]Differential diagnosis includes mucin. Mucin can move with change in patient position, may be dislodged on cyst lavage and does not have Doppler flow. Features of true tumor nodule include lack of mobility, presence of Doppler flow and FNA of nodule showing tumor tissue
[c]Presence of any one of thickened walls, intraductal mucin or mural nodules is suggestive of main duct involvement. In their absence main duct involvement is incolclusive
[d]Studies from Japan suggest that on follow-up of subjects with suspected BD-IPMN there is increased incidence of pancreatic ductal adenocarcinoma unrelated to malignant transformation of the BD-IPMN(s) being followed. However, it is unclear if imaging surveillance can detect early ductal adenocarcinoma, and, if so, at what interval surveliance imaging should be performed.

EUS: endoscopic ultrasonography; FNA: fine-needle aspiration; CT: computed tomography; MRI: magnetic resonance imaging

(From Tanaka M, Fernandez-del Castillo C, Adsay V, et al. International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. Pancreatology 2012;12:183-97.)

4- The role of cyst fluid amylase in differential diagnosis is uncertain. In some patients amylase level is too high (over 20.000 U/L), CEA is too low but there is no history of pancreatitis.
5- It is, usually not possible to diagnose histologic type of IPMN to decide about resection, because, use of larger bore needle like 19 G or core biopsy needles may be difficult to insert, especially through duodenum and there is no evidence that use of these increase the yield. Aggressive biopsy may increase the risk of pancreatitis and bleeding. Fortunately an overwhelming majority of these incidents are self-limited.
6- The negative predictive value of Sendai guideline is good, however positive predictive value is not (20%). It means in 4/5 of guideline-indicated resections, no malignancy is found (51, 64-66).
7- Finally, as PanIN and even small IPMNs are considered as pre-PDAC lesions, there is increasing attention focused on these lesions. PanINs are considered not to be detectable by imaging, however subcentimetric IPMNs (diminutive cysts) are (67). Studies on screening for these lesions by means of ultra-sensitive imaging and/or molecular pathologic examinations in the family members of PDAC or, even IPMN patients may shed further light on this subject.

SOLID PSEUDOPAPILLARY NEOPLASM (SPN)

Solid pseudopapillary neoplasm (SPN), is a rare tumour with a low potential for malignant behavior. It is, originally, not a cystic tumour, but a solid tumour with cystic degeneration due to hemorrhagic necrosis. Many are incidental. More than ninety percent of the patients are female and it is mostly diagnosed before the age of 35. However it happens in men as well. It, generally, appears as a solid-cystic mass. But, it may also appear echo-poor solid appearing mass as well as purely cystic lesion. Cytologic findings include branching papillae with myxoid

Table 3. Characteristics of different pancreatic cysts

	Pseudocyst	SCN	MCN	IPMN
Age, M:F	Any, 1:1	50-70 ys, 1:2	40-60 ys, 1:20	50-70, ys, 1:1
Symptoms	>90% symptomatic	<9 cm, asymptomatic	Mostly asymptomatic	~ 70% symptomatic
Localization	Any	Body/Tail > Head	Body/Tail	Head > Body/Tail
EUS morphology	Unilocular, thin septa, debris	Mostly microcystic infrequently oligocystic 20% Honeycomb 5% Unilocular Thick vascular septa	Unilocular/Macrocystic Peripheral localization No connection with PD	Unilocular/ Macrocystic Connection with PD PD dilation
Cyst Fluid				
Macroscopy	Muddy-brown	Sanguineous	Clear/Viscous	Clear/Viscous
Chemistry				
Amylase (U/L)	>20.000	<250	<2000	>2000
CEA (ng/mL)	<0.5	<0.5	>50	>50-200
Cytology	Neutrophils/Macrophages Histiocytes	Cuboidal cells that stain positive for glycogen	Mucinous columnar cells	Mucinous columnar cells
Management	Drainage if over 6 cm and symptomatic	Resection if symptomatic	Resection if symptomatic or >3 cm or mural nodules or atypical cytology	Resection if symptomatic or >3 cm or mural nodules or atypical cytology
Prognosis	Good	Excellent	Depends on presence or absence of malignancy	Depends on BD or MD type and presence of malignancy
Follow-up	Questionable	Probably no	Not necessary after resection with non-malignant pathology	Necessary even after successful resection

EUS: endoscopic ultrasonography; BD: branch duct; SCN: serous cystic neoplasm; MCN: mucinous cystic neoplasm; IPMN: intraductal papillary mucinous neoplasm

stroma. The neoplastic cells are monomorphic which may be confused with neuroendocrine tumour cells and appropriate immunostains (vimentin, CD10, beta-catenin) are needed. Presence of calcifications which is irregular in distribution is not rare.

LYMPHOEPITHELIAL CYSTS (LEC)

Lymphoepithelial cysts (LEC) is a benign neoplasm which represents 0.5% of all pancreatic cystic lesions. It is found mostly in middle aged men. EUS reveals peripancreatic solid appearing, hypoechoic lesion with very well defined borders. The cyst is layered with squamous epithelium inside and lymphoid tissue outside. Aspirated fluid is thick and, mostly, milky. In case it is symptomatic, resection is contemplated.

PANCREATIC ENDOCRINE TUMOURS (PET)

Pancreatic endocrine tumours (PET) is not a rare tumour in pancreas. It may either be functional or non-functional. The most frequent functional one is insulinoma. PET is a hypoechoic tumour with overt vascularity which is even detected in plain colour or power doppler imaging without contrast agent administration. Sometimes this hypoechoic image may be confused with an anechoic cyst. However the vascularity may be helpful, vascularization of septa in a cyst may also be confounding. In case of cystic degeneration of PET, differential diagnosis requires EUS-guided FNA.

Other neoplastic cysts, by name, are acinar cell cystadenocarcinoma, cystic teratoma, cystic choriocarcinoma, and angiomatous neoplasms (angioma, lymphangioma, hemangioendothelioma).

Congenital true cysts of the pancreas are rare and they may be a part of polycystic disease, Von Hippel Lindau disease, or cytic fibrosis.

Parasitic cysts (echinococcal and rarely, taenia solium cysts) are infrequent. However the former may be found in the vicinity of the pancreas and they may be confused with pancreatic cysts.

Finally enteric cysts (duplication cysts) may be confused with pancreatic cysts

SUMMARY AND FUTURE

Pancreatic cystic neoplasms is second to pseudocyst as cystic structures and second to ductal adenocarcinoma as neo-

plasms. Their management is not straightforward. More than eighty percent of the lesions are incidentally discovered, and the patients are asymptomatic. Furthermore, more than 30% of the cysts are less than 10 mm, and hence indetermined. In such small cysts, the risk of malignancy is very low even in long term. In larger cysts, we are able to aspirate fluid for examination. However, the accuracy of cytology is around 30% and even the determination of CEA and amylase levels are inconclusive in around 1/3 of the cases, let alone macroscopic findings. Our knowledge in reference to the pathogenesis of cystic neoplasms is not perfect. Furthermore IPMN may be a part of a diffuse pancreatic disease which entails PanIN. Genetic markers are not conclusive.

Local ablation methods may be a choice, while the cyst is small. However, their efficacy and safety are yet to be validated.

In the future, probably, we are going to have better imaging tools and markers for diagnosis, as well as better ablation methods for indetermined cysts.

Endosonography suits best for the management, because it has the capacity for imaging, acquiring material for examination as well as for administration of therapeutic agents.

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