Learning objectives

• To describe the morphologic features of different types of cystic pancreatic tumors, based on computed tomography, magnetic resonance imaging and endoscopic ultrasonography.

• To review the guidelines for management and the basic treatment algorithms.
Background

Introduction:

Despite the fact that pseudocysts are the most common cystic lesions of the pancreas (more than 85% of the total), the importance of differential diagnosis in cystic pancreatic tumors (CPT) is due to their malignant potential. Moreover, some solid neoplasias such as neuroendocrine tumors, adenocarcinoma or solid pseudopapillary neoplasm can present areas of cystic degeneration and simulate a true cystic neoplasia in imaging; therefore, due to its different prognosis and therapeutic approach, its differentiation is also important.

Frequency and diagnosis:

Recent studies based on computed tomography (CT) and magnetic resonance imaging (MRI) estimate a prevalence of CPT that ranges from 2.4 to 14%, with a similar overall frequency in both sexes and incidence which increases with age, although it is not known if this increase reflects a real risk with age or if it is due to the increasingly frequent use of these imaging techniques in persons of advanced age, due to the increase in life expectancy.

Both CT and MRI are indispensables in the study of CPT. CT is the preferred imaging modality for the detection, characterization and assessment of the extrapancreatic extension of the lesion. In addition, MR cholangiopancreatography makes it possible to determine the relation of the cystic lesions with the pancreatic duct (especially important in the differentiation of the IPMNs). In spite of the emerging use of diffusion-weighted imaging, currently the use of these sequences for the study of cystic neoplasias is less frequent than originally hoped.

Although there are morphological findings of each neoplasia, sometimes it is not possible to establish a definitive diagnosis only by CT and MR; therefore, other imaging tests are required, such as endoscopic ultrasonography (EUS), which, in addition to providing morphological information, allows for fine-needle aspiration (FNA) and cytologic and biochemical analysis of the cyst fluid. The combination of the cytologic analysis, biochemical markers and tumor markers make it possible to establish a diagnosis and to distinguish mucinous and non-mucinous lesions to avoid unjustified resections of benign lesions.
With regard to the tumor markers related to these types of neoplasms, the carcinoembryonic antigen (CEA) is elevated in mucinous lesions, generally above 192 ng/ml, so that a CEA lower than 5 ng/ml excludes non-mucinous tumors with a sensitivity close to 100% and a specificity of 86%. The other tumor markers have a limited value. With regard to biochemical markers, amylase is increased both in pseudocysts and in the intraductal papillary mucinous neoplasm (IPMN).
Findings and procedure details

Procedure:

Multidetector CT evaluation was performed with a multiphasic technique consisting of a precontrast scan, a pancreatic parenchyma phase and a portal venous phase. MR imaging was performed at 1.5 T field strength. Standard sequences include T1-weight; T2-weight, including fat saturation, MRCP and T1-weight after administration of a gadolinium contrast agent. EUS combines both endoscopic and US examination into a single modality and is often performed in conjunction with cyst fluid aspiration. Correlation between these three imaging modalities was also performed.

Imaging features:

SEROUS CYSTADENOMA

Serous cystadenomas are usually tumors which constitute approximately 20% of the total cystic lesions of the pancreas. They are most frequent in women (75%) with a mean age of 61.5 years. More than 80% are located in the body and tail of the pancreas and their development is generally asymptomatic.

This is a well-defined tumor, formed by multiple cysts up to 2 cm in size, arranged in a honeycomb configuration, separated by fibrous septa. CT may demonstrate sunburst calcification of the central scar in approximately 20-30% of cases while at MRI it appears as a mass composed of small hyperintense lesions in T2-weighted imaging, with septa and a central scar that may enhance after the administration of contrast. It is not connected to the pancreatic duct system and does not present dilation of the bile duct or Wirsung duct (figures 1 and 2).

There is a rare form of serous cystadenoma with oligomacrocytic pattern, indistinguishable from the mucinous cystic neoplasms.

Contrary to other cystic pancreatic tumors, the morphological characteristics at EUS are highly suggestive of this type of lesion. It is composed of multiple well-delineated anechoic formations of small size with internal septa.
After FNA of the cyst fluid, levels of amylase and CEA are undetectable.

MUCINOUS CYSTIC NEOPLASM

Contrary to serous cystadenomas, mucinous cystic neoplasms have malignant potential. They present a stroma similar to the ovary (ovarian-like stroma) underlying the mucinous columnar-epithelium, with a variable degree of atypia. They constitute approximately 10% of pancreatic cystic lesions; they are almost exclusively of the female sex with a mean age of 47 years. They develop either asymptomatically or with non-specific abdominal pain, nausea, loss of weight or back pain.

It is a well-defined tumor with cysts greater than 2 cm (oligocystic pattern), filled with mucin, often with a thick wall that enhanced at delayed imaging. 95% of cases are located in the body or tail of the pancreas and the "eggshell" peripheral calcifications suggest malignant character. It does not connect to the pancreatic duct system and sometimes it produces dilation of the bile duct and Wirsung duct by compression.

At EUS it appears as a unilocular or oligocystic lesion, with internal septa of variable thickness. It may present echogenic content due to the presence of mucin.

The fluid obtained after FNA is viscous due to its content in mucin and columnar cells. Typically, the concentration of CEA is above 192 ng/ml and the levels of amylase are low.

Approximately 17.5% of mucinous cystic neoplasms are malignant. The findings that suggest malignant character, in addition to the "eggshell" calcifications, are the presence of mural nodules, a size greater than 6 cm and thickening or irregularity of the wall of the main pancreatic duct (figures 3, 4, 5, 6 and 7).

INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM

IPMNs of the pancreas originate in the ductal epithelium, which leads to mucus secretions and therefore, dilation of the pancreatic ducts. They constitute approximately 20% of pancreatic cystic lesions and there are three forms: main-duct IPMN, side-branch IPMN, (benign in most cases), and mixed IPMN, involving both the main duct and side branches.

They present a similar frequency in women and men and an average age of onset of 65 years. Most lesions are detected causally in imaging studies, although when they are
symptomatic, they develop with abdominal pain, loss of weight, episodes of pancreatitis and pancreatic insufficiency.

Both at CT and MRI, the variant of the main duct is manifested as segmental or diffuse dilation of the main pancreatic duct. The presence of small intraductal nodules is characteristic and on occasions, atrophy of the pancreatic parenchyma can be seen.

At EUS ectasia of the pancreatic duct is observed along with cystic dilation of the lateral branches by secondary obstruction to the production of mucin.

The variant of the lateral branches has two different patterns: macrocystic and microcystic. At CT they usually appear as hypointensifying heterogeneous lesions, classically located in the uncinate process although it can appear in any location. At MRI they are observed as small hyperintense oval-shaped masses in T2-weighted sequences, often connected to the main pancreatic duct and which can be multifocal in up to 30% of cases.

The morphology at EUS varies from anechoic unilocular shapes to complex multicystic lesions. The calibre of the main pancreatic duct is normal and the connection between the lesion and the main duct can be observed by this technique.

The imaging findings are indistinguishable from other cystic neoplasms such as mucinous cystic neoplasms and the macrocystic variant of serous cystadenomas (figures 8, 9 and 10).

Cyst fluid analysis reveals high values of CEA and normal or high levels of amylase.

According to the World Health Organization, IPMNs can be benign (without dysplasia), borderline (mild-moderate degree of dysplasia) and malignant (carcinomas). The malignant forms are found in approximately 70% of the cases that affect the main conduct and in approximately 25% of the cases that affect only the lateral branches. The criteria for malignancy are: mural nodules, solid focal component, dilation of the main duct greater than 18 mm or prominence of the main pancreatic duct wall. Likewise, a size of less than 3 cm without mural nodules in the variant of the lateral branches is associated with a low degree of malignancy.

OTHERS
The **cystic neuroendocrine tumor** only represents 17% of all neuroendocrine tumors. It presents a similar frequency in women and men and a mean age of 53 years. Nevertheless, they are usually larger, more frequently symptomatic and with greater probability of being non-functioning than solid neuroendocrine tumors. Patients with cystic neuroendocrine tumors have a greater probability of developing a MEN I than patients with solid neuroendocrine tumors. The risk of metastases is the same for both variants.

They appear more frequently in the pancreatic body and tail. Due to the hypervascular nature of neuroendocrine tumors, they appear in imaging studies as cystic masses with internal septa and with a peripheral hypervascular ring. EUS imaging findings are non-specific: heterogeneous lesions, well-defined, completely cystic or solid with cystic components. The cyst fluid presents low levels of CEA and of amylase.

The **solid pseudopapillary neoplasm** is a rare tumor with low risk of malignancy. Approximately 91% of these tumors appear in women, with a mean age of 22 years. Clinically they appear with pain and palpable mass. It can be located anywhere in the pancreas, with a certain predilection for the tail. Approximately 20% present metastases in diagnosis.

They are usually well-defined tumors, with hyperintense areas in T2-weighted MRI in relation to the cystic components. Hyperintense areas may also appear in T1-weighted due to processes of hemorrhagic degeneration. Peripheral calcifications are present in approximately 31% of cases. At EUS they appear as heterogeneous masses, well-defined, predominantly solid with internal cystic areas. The CEA levels of the cyst fluid may be variables and those of amylase are low.

**Management and follow-up:**

The decision for surgical treatment is based both on the malignant potential and on the presence of symptoms related to the lesion. In general, all symptomatic CPT in an operable patient should be assessed for surgical resection. In the case of an incidental and asymptomatic CPT, it is important to distinguish mucinous and no-mucinous, to establish the risk of malignant degeneration. After these evaluations and depending on the age and the basal situation of the patient, surgical treatment or imaging surveillance will be indicated.

In the case of **serous cystadenoma**, malignant transformation is rare; thus, surgery is only recommended in symptomatic patients. Nevertheless, recent studies have demonstrated the existence of aggressive variants; therefore, imaging surveillance is
recommended at 6-12 months, extending to 2 years, to demonstrate the absence of growth. For lesions surgically resected with free surgical margins, imaging surveillance is not necessary.

With regard to **mucinous cystic neoplasm**, due to its malignant potential, surgery is recommended in all cases. There is no risk of recurrence after surgery of the benign mucinous cystadenoma with negative margins; thus, imaging surveillance is not necessary. Nevertheless, in operated patients with pathological anatomy compatible with malignant mucinous cystadenoma, imaging surveillance at 6-month intervals is recommended due to the elevated risk of recurrence.

In the **intraductal papillary mucinous neoplasm**, all symptomatic cases must be resected. Management guides recommend surgery for the variants of the main pancreatic duct and the mixed forms that present a size larger than 3 cm. Resection is also recommended in the variants of the asymptomatic lateral or secondary branches with a size of less than 3 cm but with high-risk imaging features or rapid cyst growth (more than 2 mm per year).

The lesions of small size that derive from the lateral branches without criteria of malignancy require imaging surveillance. Annual imaging is recommended for tumors smaller than 1 cm, 6-12-month follow-up for lesions from 1 to 2 cm and 3-6-month follow-up for lesions larger than 2 cm.

Due to the risk of recurrence, imaging surveillance is recommended after surgery, a 6-month interval for malignant IPMN and annual imaging for benign IPMN.

Both in **cystic neuroendocrine tumors** and in **solid pseudopapillary neoplasms**, the preferred treatment is surgery.
Fig. 1: (a), (b) and (c): Contrast-enhanced CT images show cystic lesion in the pancreatic head with calcifications. (d) and (e): EUS shows anechoic well-defined lesion.

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Fig. 2: (a), (b) and (c): Contrast-enhanced CT images show multilocular cystic lesion in the pancreatic head. (d): T1-weighted MRI of another patient: hypointense multilocular lesion.
Fig. 3: (a) T2-weighted and (b) LAVA MR images show unilocular cyst in the pancreatic tail. (c) EUS scan shows a thin septa (arrow) in the cyst.

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Fig. 4: (a) and (b): Contrast-enhanced CT images show unilocular cystic lesion in the pancreatic tail. (c): T2-weighted MRI of the same patient showing unilocular cyst in the pancreatic tail.
Fig. 5: (d): CT allowing for FNA of the same cyst on figure 4. (e): EUS showing unilocular lesion with echogenic content due to the presence of mucine.
**Fig. 6:** (a): Contrast-enhanced CT image demonstrating small cystic lesion, with no septa. (b): EUS of the same patient, showing small anechoic and well-defined lesion.

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Fig. 7: (a): T1-weighted contrast-enhanced MRI demonstrating polilobulated hypointense lesion. (b) and (c): EUS of the same patient, showing polilobulated echogenic lesion.

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Fig. 8: (a) Axial contrast-enhanced CT and (b) T2-weighted MR images demonstrate multiple small cystic folci involving the pancreatic head. (c) EUS shows similar morphology.

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Fig. 9: (a) and (b): Axial contrast-enhanced CT and (c): T1-weighted MRI with contrast demonstrating multiple small cystic folci involving the pancreatic head.

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Fig. 10: (a) and (b): Axial contrast-enhanced CT images demonstrating multiple small cystic folci involving the pancreas with dilation of the bile and Wirsung ducts.

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Conclusion

CPT may range from benign to malignant lesions and it is important their differential diagnosis in making decisions regarding the treatment of affected patients. An accurate characterization can sometimes be difficult at cross-sectional imaging. EUS permits high-resolution imaging of morphology, while FNA allows for cyst fluid collection for cytological and biochemical analysis.
References


