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Cystic pancreatic neoplasms: diagnosis and management emphasizing their imaging features

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Abstract. – The incidence of cystic pancreatic neoplasms increased in the past decade, due to the recent advances in multidetector computed tomography and magnetic resonance imaging; several pancreatic cysts are incidentally encountered during diagnostic exams performed for non-pancreatic diseases. Indeed, cystic pancreatic tumors are currently considered relatively rare, accounting for approximately 10% of all pancreatic neoplasms. Serous cystadenoma, mucinous cystadenoma, intraductal papillary mucinous neoplasms and solid-pseudopapillary tumor represent about 90% of all pancreatic primary cystic tumours.

The non-optimal diagnostic preoperative accuracy in distinguishing benign from malignant cystic lesions ensures that up till now there are no well-defined guidelines regarding the management of cystic pancreatic neoplasms. Imaging findings often do not allow the diagnosis, because there is a considerable overlap among the cystic lesions; the best pre-operative characterization is obtained by the association of all diagnostic procedures available. For their different histology and behavior, cystic pancreatic neoplasms need to be managed according to various factors.

In this review, the main elements necessary for their management are assessed – radiological features, tumour dimensions, patients' characteristics, the mode of clinical presentation and the associated oncologic markers. A multidisciplinary approach – including gastroenterologists, radiologists and surgeons – should be adopted in order to perform a differential diagnosis and a correct management.

Key Words:
Pancreas, Pancreatic neoplasms, Pancreatic cyst, Disease management, Magnetic resonance imaging, Endoscopy ultrasonography.

Introduction

Cystic pancreatic lesions include a large spectrum of diseases, ranging from true pancreatic cystic lesions to aggressive neoplasms with cystic degeneration[1]. Cystic tumors are relatively rare, accounting for approximately 10% of all pancreatic neoplasms; only 1% of all pancreatic cystic tumors are malignant neoplasms[2,3]. Serous cystadenoma, mucinous cystadenoma, Intraductal Papillary Mucinous Neoplasms (IPMNs) and Solid-Pseudopapillary Tumor (SPT) represent about 90% of all pancreatic primary cystic tumours[2,4].

In many cases the diagnosis of cystic neoplasms with imaging alone is still impossible, as reported in previous works[5], and there is a considerable overlap among the cystic lesions. Even though several Authors have studied clinical diagnostical and therapeutic aspects, the appropriate management of patients with cystic pancreatic lesions still remains uncertain.

Some Authors, such as Salvia et al[6], studied clinical and imaging ability to determine the real nature of cystic pancreatic lesions in advance of tissue diagnosis. They found that preoperative diagnostic accuracy is far from optimal (78.4%); moreover they maintain that the best pre-operative characterization is obtained by the association of MRI/MRCP (magnetic resonance/ magnetic resonance cholangiopancreatography) and Contrast-Enhanced Ultrasonography (CEUS), while Endoscopic Ultrasonography (EUS) does not improve diagnostic accuracy ($p = 0.225$)[6].

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The non-optimal diagnostic preoperative accuracy in distinguishing benign from malignant cystic lesions ensures that up till now there are no well-defined guidelines regarding the management of cystic pancreatic neoplasms[7]. Moreover, there is common agreement that the natural history of asymptomatic cysts is unknown[8,9].

Consequently, in past years many Authors recommended that all cystic lesions of the pancreas should be resected[10,11]. Although surgical management guarantees that all premalignant and malignant lesions are resected, it also exposes patients with benign lesions to the risks of surgery without sure benefit; as a consequence, several recent studies recommend a more selective approach to surgery.

The most important features which may help in distinguishing between benign and malignant tumors are: cross-sectional imaging findings (Table I), tumor size, patient's age and other characteristics, clinical appearance and tumoral markers; these features are discussed below in our paper.

Imaging Findings

Serous Cystadenoma

Serous cystadenoma is one of the most common types of pancreatic cystic tumors, representing 1-2% of all pancreatic exocrine tumors[2]; it occurs more frequently in women – 1.5:1 female-to-male predominance – over 60 years-old[5,12,13]; its clinical presentation is frequently aspecific: patients often refer weight-loss and vague abdominal pain; more often the lesion is accidentally discovered.

Tumors may present different sizes, and lesions up to 27 cm have been reported[14]. Most patients generally do not require any treatment as long as they are asymptomatic[15].

Serous cystadenoma are typically encountered in the head of the pancreas and have three main morphologic patterns: in 70% of cases, serous cystadenomas are characterized by a polycystic pattern; the honeycomb pattern is seen in approximately 20% of patients, whereas the oligocystic appearance has been reported in less than 10% of cases[3,16].

The polycystic or microcystic pattern (Figure 1) appears as a well circumscribed mass with a bosselated collection of cysts; cysts are delineated by a thin-wall and have a diameter ranging from a few millimeters to 2 cm[12-16]; on MRCP images, lesions show a homogeneous high signal intensity. Typical imaging findings for these polycystic forms are a lobulated contour and a central scar. The latter occurs in up to 30% of cases and may present with or without stellate pattern of calcifications on CT; delayed imaging may occasionally help the detection of the central scar[17,18]; on T2-weighted images, the fibrous component is typically hypointense[2]. In the honeycomb pattern, pancreatic cystadenomas consist of numerous millimetric cysts. The honeycomb pattern is frequently encountered as a lobulated and well defined mass, showing soft-tissue or mixed attenuation on CT images, due to small numerous cysts; the millimetric cysts are detected hyperintense on MRI T2-weighted images[4,16].

The macrocystic or oligocystic pattern represent a morphological variant of serous cystadenoma: in this pattern the tumor is composed of a large cyst, more than 2 cm in diameter[15,16], and it

Table I. Main imaging characteristics of cystic pancreatic neoplasms.

	Serous cystadenoma	Mucinous cystadenoma	IPMN	SPT
Ø Cysts	From a few mm to 2 cm	Usually > 2 cm	Variable	Variable, unilocular
Contours	Lobulated	Smooth, well encapsulated	lobulated or smooth	Smooth
Solid or nodular component	Absent	Possibilities of mural nodules	Possibilities of mural nodules	Solid papillary component
Communication with main duct	Absent	Absent; tumor can cause obstruction	Often present	Absent; tumor can cause obstruction
Calcifications	Calcifications in a central scar	Peripheral, eggshell calcifications	Unusual	Possibilities of hemorrhagic calcifications

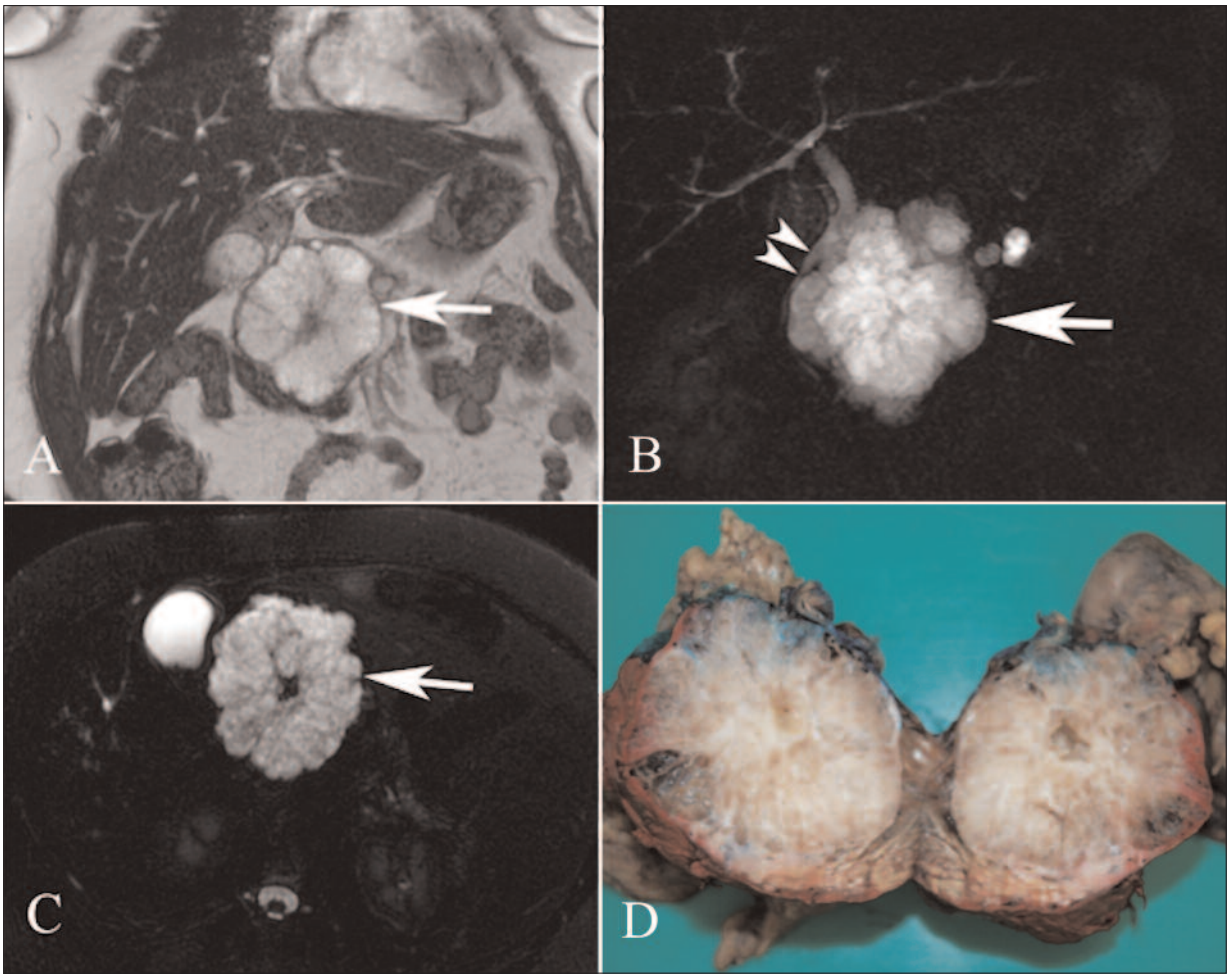

Figure 1. Serous cystadenoma in the head of pancreas. ***A,*** Coronal T2-weighted image shows a round-shaped, well defined cystic lesion (*white arrow*) in the head of pancreas consisting of numerous small cysts and a central scar. ***B,*** 2D MRCP image shows the biliary duct (*arrowheads*) displaced by neoplasm (*arrow*). ***C,*** Axial MRCP shows the central scar. ***D,*** surgical specimen appears very similar to the MRCP image.

can be very difficult to make a differential diagnosis from mucinous cystoadenoma or macrocystic tumors. The macrocystic serous cystadenoma shows a lobulated contour, whereas mucinous cystic neoplasms (cystadenomas) have smooth contours with or without septation, and IPMNs have a pleomorphic or clubbed, finger-like cystic shape. The macrocystic or oligocystic pattern also includes the unilocular cystic cystoadenoma, and it is necessary to take care in making a differential diagnosis of this form from a pseudocyst.

Mucinous Cystadenoma

Mucinous cystoadenoma represents about 10% of pancreatic cystic neoplasms. It occurs most frequently in females (female to male ratio = 6:1), with the greatest incidence between the fourth and sixth decade[2,19]. These lesions are most frequently located in the body and in the tail of the pancreatic parenchyma[4].

Mucinous tumors are generally found as a cystic mass composed of cysts larger than 2 cm; cysts are lined by mucin-producing columnar cells and are divided by enhancing septa; often peripheral calcifications are detected along the wall[13]. The lesions are hypointense on T1-weighted MR images and hyperintense on T2-weighted MR images; however, the signal intensity could be different, depending on the proteinaceous content of mucin[13] or internal hemorrage/debris[4]. Eggshell calcifications are not frequently revealed on MR images; if detected, they have to be considered a specific sign of the tumor, highly predictive of malignancy[4]. The cystic mass sometimes causes mild compression and

obstruction of the duct[4]; the tumors are round to oval shaped and present a smooth external surface[5]. Occasionally nodules on the wall of tumors may be detected.

Mucinous cystadenoma may also present as a unilocular lesion; differential diagnosis from pseudocystic lesion may be very hard, and the clinical history, especially any episode of pancreatitis, may help in the diagnosis. Mucinous cystic neoplasms could be potentially malignant and for this reason clinicians have to consider – according to age and other risk factors – the possibility of resection. The risk of degeneration increases with the presence of mural nodules and thickened wall[2].

IPMN

IPMNs are rare pancreatic cystic neoplasms – accounting for 1% of all exocrine pancreatic neoplasms – and they develop from the pancreatic ducts[20]. The definition "intraductal papillary mucinous tumor" was introduced in 1996[21], based on the histological origin from the epithelial lining at any level of the pancreatic ductal system. They have a spectrum of cytological architecture, ranging from none to borderline or marked atypia, and they can also be associated with invasive carcinoma[22]. IPMNs most commonly occur in elderly men and arise more often in the pancreatic head[23]. Previous history of diabetes mellitus, chronic pancreatitis, peptic ulcer and insulin use has been associated with these neoplasms[4]. Clinical presentation of IPMNs may be related to the gradual distension of the pancreatic ducts, which provokes pancreatitis-like symptoms[2]. They are currently classified into three types: primary IPMN, when the tumor arises from the main pancreatic duct; secondary IPMN, including tumors originating from the secondary ducts (Figure 2); mixed IPMN (Figure 3), when both main pancreatic duct and branch ducts are involved[3,25].

Primary IPMNs may show a segmental or diffuse involvement of the main pancreatic duct; secondary IPMNs can be present in a multifocal appearance, when multiple side-branches are involved.

Diffuse primary IPMN appears as uniformly and diffuse dilatation of the main pancreatic duct, homogeneously hyperintense on T2-weighted images and MRCP acquisitions. The main duct dilatation in primary IPMNs has to be differentiated from those observed in chronic pancreatitis; the degree of dilatation observed with IPMNs is often disproportionate to the parenchymal atrophy[26,27]. The presence of other unilocular or multilocular cysts associated to the main ductal dilatation – located in the uncinate process and pancreatic tail, are often depicted in the mixed pattern of IPMNs (Figure 3) and may help to differentiate from other mucinous tumors[28,29].

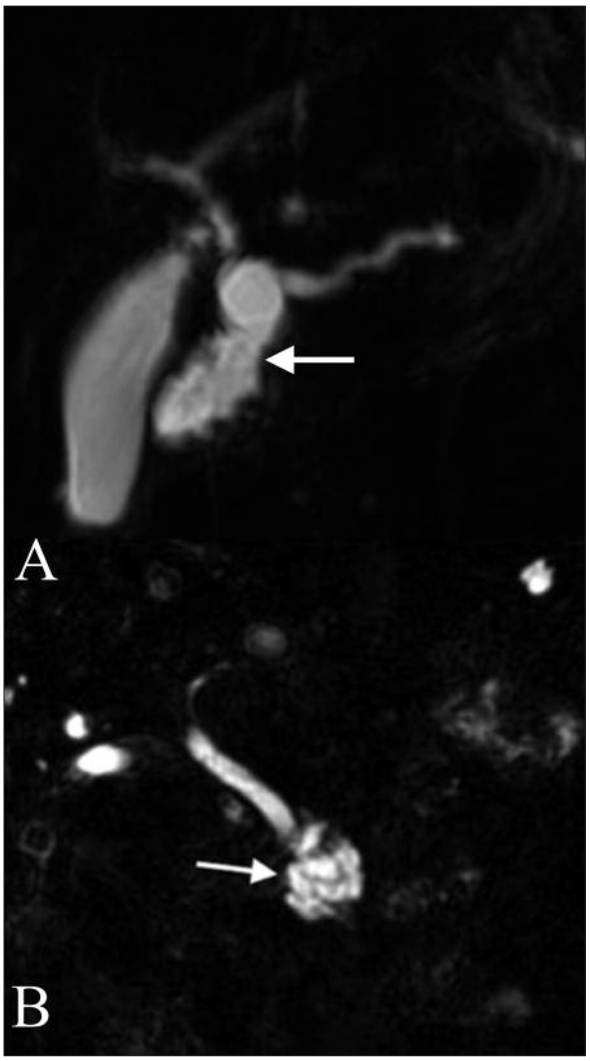

Figure 2. ***A,*** shows IPMN (*white arrow*) arising from main pancreatic duct: MRCP image clearly show cystic enlargement of the main pancreatic duct, more evident in the head of the pancreas. ***B,*** shows IPMN (white arrow) arising from side-branches in the uncinate process of the pancreas; the lesion consists of multilocular cystc areas with high signal-intensity on MRCP acquisition; there is no dilatation of the main pancreatic duct.

Side branches IPMNs can be arranged in a microcystic or macrocystic pattern. The microcystic pattern is characterized by multiple thin septa separating fluid-filled lacunae, and it mimics a serous cystoadenoma. The macrocystic pattern,

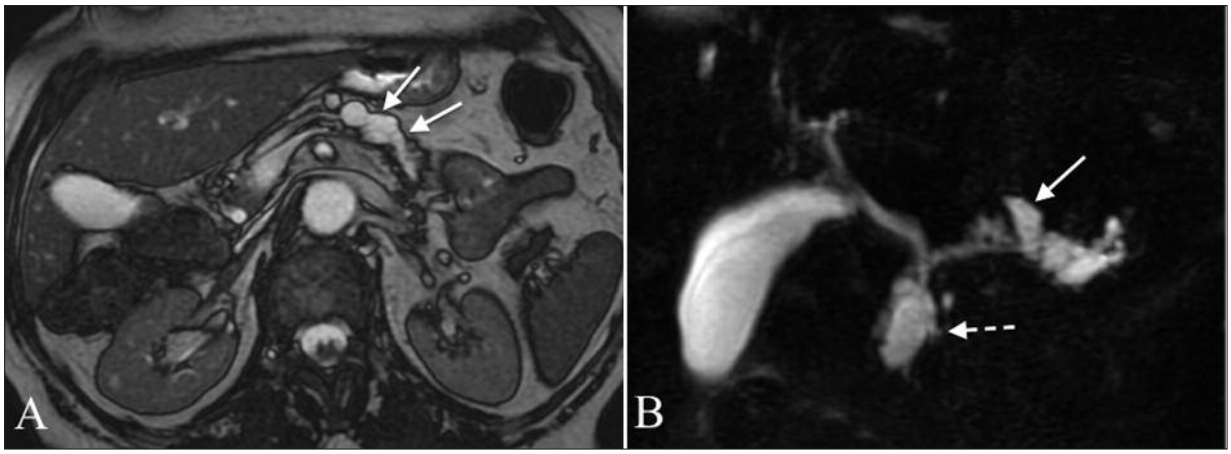

Figure 3. Mixed IPMN of the pancreas. ***A,*** The images show the presence of multiple cystic areas (*white arrows*) in the pancreatic parenchyma. ***B,*** Cysts are centered along the course of the main pancreatic duct (*white dashed arrow*), but there are also cysts located in peripheral areas of the parenchyma, well distinguishable from the main duct as depicted on figure 5B (*white arrow*); these cysts arise from side branches.

which is much more frequent, is characterized by a unilocular or multilocular internal architecture, with the multilocular architecture related to the presence of sparse septa. The finding of a communication through lesion and pancreatic duct is highly suggestive to the diagnosis of secondary or mixed IPMN[4]; three-dimensional MRCP sequences could help radiologists in the evaluation of pancreatic duct anatomy[30]. However, the absence of a communication does not allow us to exclude IPMN.

The prognosis of intraductal tumors is strongly dependent on their location in the pancreatic parenchyma: primary IPMNs have a higher risk of degeneration (60-92%)[29,31,32], whereas IPMTs arising from secondary branches have a lower risk (6-40%)[33].

However, differentiation between malignant and benign lesion is essential to choose appropriate treatment. Sahani et al[34] identified as malignancy predictors the marked dilatation of the main pancreatic duct (> 1 cm), the large size of tumor (3-5 cm), and the presence of thickened septal structures and intraluminal masses arising in the dilated duct[34]. In a work published in 2010, Salvia et al[35] summarized clinical and morphological features associated with high risk of malignancy. These features include presence of symptoms (jaundice, new onset or worsening of diabetes, dilatation of main pancreatic duct (> 10 mm), diameter of the cystic lesion > 30 mm, presence of nodules or solid components[35].

Surgical treatment should be recommended in cases of primary IPMNs, while clinical and radiological follow-up have to be considered as the best choice for side-branches-IPMNs without any morphological suspicion of malignant transformation. Multifocal side-branch-type IPMN represents an exception: it has a higher risk of malignant degeneration than unique forms, and surgical treatment may be indicated if symptoms, tumor marker or sign of radiological progression are present[36]; signs of progression are the enlargement of lesions or the involvement of the main pancreatic duct, the appearance of mural vegetations or parietal contrast enhancement[37]. In these cases an extensive surgical resection, up to total pancreasectomy, may be called for.

In any case, even in cases of malignancy, IPMNs are often resectable and patients have better prognosis than subjects with ductal adenocarcinoma[38].

SPT

The SPT accounts for 0.13-2.7% of all exocrine pancreatic neoplasms[39]. Franz reported this tumor for the first time in 1959[40-43]. In 1996 the World Health Organization (WHO) defined this neoplasm as "solid pseudopapillary tumor of the pancreas"[41]. This tumor predominantly affects young women[43], with greatest incidence in the second and third decade, and a female to male ratio of 10:1.

There are typical and atypical morphologies of Gruber-Franz tumor[44,45]: in the typical pattern the tumor is round-shaped and appears as an encapsulated mass; it has a cystic nature, with solid component that shows a slow fill-in enhancement

after contrast administration; the solid and cystic spaces are better demonstrated by MRI, thanks to its contrast resolution[46]. On T2-weighted MR images, papillary areas are hypointense whereas the intralesional fluid-filled spaces show high signal. EUS clearly depicts cystic areas and solid components of tumor.

In atypical appearance the solid pseudopapillary tumor of the pancreas may present as a tumor with hepatic metastases or main pancreatic duct obstruction[47].

Management Based on Imaging Appearance: the Overlap of Cystic Pancreatic Lesions

Taking into account principal imaging features of each cystic pancreatic neoplasms, some Authors tried to create an "imaging-based classification system for guiding management" of these lesions[4]. Sahani et al distinguish four subtypes of pancreatic cysts: unilocular cyst, microcystic lesions, macrocystic lesions and cysts with a solid component[4]. Unilocular cyst management is based on size and presence or not of symptoms: patients with asymptomatic, small (< 3 cm) and thin-walled cysts should undergo imaging follow-up (CT or MRI), but symptomatic patients should undergo EUS-guided needle aspiration or surgical resection. Microcystic lesions category only includes serous cystoadenoma, which is a benign lesion, so imaging surveillance is recommended in asymptomatic patients while symptomatic lesions should be resected. Macrocystic lesions include both mucinous cystic neoplasms and IPMNs. All mucinous neoplasms should be resected because of their potential malignancy; IPMNs should be differently managed according to their origin from principal duct or from side-branches because occurrence of malignancy is higher in main duct and mixed IPMNs than in side-branch IPMNs. Therefore surgical resection is recommended for the first ones whereas management for side-branch IPMNs depends on the risk-benefit ratio taking into account patients' age, clinical presentation, surgical risk, cysts size and morphological features: small (< 3 cm) septated cysts should be followed-up.

In fact, Salvia et al[35] evaluated non-operative management of secondary branches IPMNs in a prospective study, performing contrast enhanced US and MRCP. Lesions were less than 3.5 cm in diameter and without nodules or solid components. Their study included a total of 109 patients. A first group (20 patients, 18.3%) required immediate surgery for the presence of symptoms or clinical and morphological features associated with malignancy. Among this group, Authors found only 2 patients with invasive carcinoma and 1 patient with carcinoma in situ. The remainder of patients were evaluated with a median of 32 months of follow-up. After a mean follow-up of 18.2 months Salvia et al[35] reported only 5 patients with increase in size of lesion. These patients underwent surgery and their final diagnosis was branch-duct adenoma in 3 cases and borderline lesions in 2 patients. Therefore, this study confirms that some side-branches could be managed by imaging.

Finally, we retain all cysts with a solid component should be resected because of their high malignant potential.

The Role of Fine Needle Aspiration (FNA)-EUS

EUS allows to obtain many important details about cystic lesions, such as wall thickness, presence of septa and nodules; in addition it provides measurement of the main pancreatic duct, identifying stenosis along its length, and shows the presence of enlarged lymph nodes[48-50].

Besides, EUS offers the possibility of collecting liquid from cystic lesion – performing a fine-needle aspiration; the fluid content is evaluated for the color, viscosity and presence of mucin, which can then be used to identify between mucinous and serous tumor. The diagnostic accuracy of FNA-EUS is 92-96%[51]. In cystic tumors less than 6 cm – but also in those less than 2 cm in diameter – the EUS accuracy ranges from 82 to 91%, much higher than those obtained using CT and MRI[52].

In a recent work, van der Waaij et al[53] demonstrated that CEA and CA 72.4 levels in the cystic fluid of the mucinous lesions are much higher (typically over 800 ng/ml) to those of non-mucinous ones. In particular, a value > 800 ng/mL has a specificity of 98% for a mucinous cyst using a meta-analysis of pooled data from 12 studies at different institutions[53]. Moreover, CEA and CA72.4 levels are higher in malignant mucinous neoplasms[54-58]. In a previous report by Brugge et al[56] a CEA level of 192 ng/mL has a diagnostic sensitivity of 75%, a specificity of 84% and an accuracy of 79% in differential diagnosis of mucinous and non-mucinous cysts. The collected fluid could be also analyzed for its cellular contents, although there is a little presence of cellular material in the fluid, and consequently it is difficult to obtain an adequate sample.

Performing EUS-FNA, detection of K-ras mutation in the pancreatic juice of IPMNs is associated with risk of malignancy, even if the procedure has a low sensitivity (less than 20%)[35].

Finally, FNA-EUS gives the possibility to perform a selective biopsy of suspected areas, which may have uncertain nodules or thick segments along the lesion's walls[59].

Location, Patient Characteristics, Tumor Size, Oncological Markers

In the management of pancreatic cystic neoplasms is recommended to consider other independent factors, such as cysts location – it is less complex to remove tail lesions rather than head pancreatic lesions – and patients' proper surgical risk.

Also Sakorafas et al[60] recommend a more aggressive treatment policy for cystic tumors located in body or tail of the pancreas, because of the less destructive surgical procedure[60].

In American College of Gastroenterology guidelines resection is recommended for mucinous cystic neoplasms in patients at acceptable risk for perioperative complications, for IPMN especially in the main-duct variety and for solid pseudopapillary tumors, regardless of the stage; instead, serous cystoadenomas should be resected only if symptomatic or if the diagnosis remains uncertain[61].

Other Authors[62] suggest needle biopsy and aspiration as a safe procedure able to help clinicians to reach the diagnosis.

Size is a well-known criterion in selecting patients to undergo surgery. Many Authors have suggested different tumor sizes that may be associated with a higher risk of malignancy. Allen et al[8] maintain that the risk of malignancy is similar to the risk of surgical mortality in highly selected patients – with small (< 3 cm) and asymptomatic cysts without solid components. In their opinion these patients should be followed radiographically. A careful follow-up is certainly required, as resection should be performed if changes occur within the cyst or if patients develop symptoms.

Buscaglia et al[63] tried to develop a predictive model for pancreatic cyst malignancy in order to improve patient selection for surgical management. They identified the presence of CEA ≥ 3594 ng/ml in cyst fluid, as optimal cut-off points for surgical resection, in addition to age > 50 and cyst size > 1.5 cm. In addition, white race and weight loss are independently associated with cyst malignancy in their analysis[63]. Also male gender has been associated with higher risk of malignancy[54].

Sakorafas et al[60] recommended surgical treatment for serous cystoadenomas > 4 cm and for mucinous cystoadenomas of any size, while other Authors[64] tried a conservative approach for mucinous cystoadenomas < 3 cm, with low-risk appearance (no mural nodes, no Wirsung dilatation, no peripancreatic adenopathy). Serous cystadenomas may be very large in size, and sometimes requires surgery for the development of "mechanical" symptoms; enlarged tumours located in the head of the pancreas may create biliary and pancreatic obstructions, with subsequent ittero and pancreatitis.

Some Authors suggest different management of patients based on clinical characteristics such as age and gender, presence of symptoms, cyst size or location, comorbidities[9,65-67]. Spinelli et al[9] found that age greater than 70 years and presence of symptoms are predictors of malignant or premalignant pathology, while cyst size, cyst location and gender do not correlate with final pathology. Indeed, they recommend surgical resection for pancreatic cysts that increase under observation, are symptomatic and are discovered in healthy older patients.

Fritz et al[68] studied the role of CA 19-9 in IPMN: they found that this marker is useful for differentiating between invasive and benign IPMN.

All cited researchers agree on the necessity of surgical resection if clinical symptoms are present for all cystic pancreatic neoplasms, even if it is a serous cystoadenoma[60]. Also changes in imaging appearance, such as increase in size or development of mural nodule, are considered predictive of malignant evolution and so Authors suggest surgical resection in these cases; however, in Ceppa et al[69] series biliary and pancreatic ductal dilatation and suspicious cytology but not age, symptoms or tumor size are associated with malignancy.

Conclusions

Cystic pancreatic neoplasms have different histology and behavior, so they are managed differently according to various factors. A multidisciplinary approach is called for, in order to verify clinical features, imaging findings, laboratory tests and surgical modalities in each patient; the

correct management should ideally consider all the features previously discussed.

In view of these considerations, some basic concepts may be applied to manage pancreatic cystic neoplasms:

– All serous cystoadenomas may be followed-up using imaging, with the exception of symptomatic cases (especially in patients with compression upon the biliary duct).
– According to international consensus guidelines[70], mucinous tumors should be resected, especially mucinous cystic neoplasms and main duct IPMN.
– Only small (< 3 cm) asymptomatic branch-side IPMN need to be carefully followed up; their resection should be recommended when lesions are ≥ 3 cm in diameter, when lesions have a mural nodule or show main pancreatic duct dilatation (> 6 mm), and in cases of asymptomatic patients[70,71].

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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