Commentary

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Although considered uncommon historically, cystic neoplasms of the pancreas have been diagnosed with increasing frequency over the last two decades, due mainly to the widespread use (and availability) of advanced cross-sectional imaging techniques.

This "epidemic" in the diagnosis of pancreatic cystic neoplasms has been paralleled by an increasing number of studies focusing on the clinical behavior and management of these diseases. As a result, our knowledge of pancreatic cystic neoplasms has improved dramatically. Three main histologic types have been identified (SCNs, MCNs, IPMNs), and detailed pathologic as well as molecular and clinical data have been investigated for each one of these cystic neoplasms.

Current guidelines for the management of pancreatic cystic neoplasms are based on relatively distinctive features shown at cross-sectional imaging. One must be aware that a certain degree of morphologic overlap exists between different lesions, and the possibility of preoperative misdiagnosis should always be considered.

The most appropriate management of pancreatic cystic neoplasms still remains unclear and, for mucinous neoplasms in particular, the clinical and radiologic work-up is not always able to predict the likelihood of progression to invasive cancer in a given patient. This uncertainty has generated controversies on whether to offer resection or enroll patients in surveillance protocols with periodic check-ups. Several other unsettled aspects exist, including the appropriate timeframe for surveillance, the role of analysis and cytology of cystic fluid, the role of atypical, non-anatomic resections and of lymphadenectomy, the recurrence rate and association with ductal adenocarcinoma and other non-pancreatic neoplasms, in case of IPMNs.

Such dilemmas are encountered frequently in the everyday practice of physicians working in tertiary centers dealing with pancreatic surgery, in which pancreatic cystic neoplasms represent now a substantial group of diseases referred for treatment. Several questions often remain unanswered when dealing with a patient affected by a cystic lesion in the pancreas: is the lesion completely benign? Does it have malignant potential? And if so, how long does it take to become malignant? What is the best management, surveillance, or surgical resection? And if operative resection is advocated, what type of resection is most appropriate?

To address these questions, familiarity with the morphologic spectrum of these lesions, and

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R. Mantke et al. (eds.), *International Practices in Pancreatic Surgery*,
DOI 10.1007/978-3-540-74506-8_17, © Springer-Verlag Berlin Heidelberg 2013

collaboration among surgeons, radiologists, gastroenterologists and pathologists is mandatory.

At our Institution, more than 6,000 patients with pancreatic diseases were managed between 1985 and 2011, 20 % of whom were affected by cystic lesions. In the same period, more than 2,200 pancreatic resections were carried out, 23 % of which were for cystic neoplasms.

SCAs occur more frequently in middle-aged women than men. Any portion of the pancreatic gland can be affected, but SCAs are detected more frequently in the pancreatic head. SCAs are usually asymptomatic and discovered incidentally on cross-sectional imaging performed for unrelated complaints. When present, the most common symptom is abdominal discomfort or low-grade pain. A correct clinical and radiologic diagnosis is of paramount importance, because these neoplasms, unlike other cystic neoplasms of the pancreas, are virtually always benign. Whenever possible, a conservative approach represents the treatment of choice.

On CT, these previously-called microcystic tumors appear as a non-enhancing mass deforming the profile of the gland. The density is homogeneous or slightly superior to that of water and isodense in respect to the parenchyma. When calcifications are present, the location is quite always central, punctate or globular, as opposed to the lamellar calcifications seen in mucinous cystic tumors. Usually a central fibrous scar is visible in the larger masses because the scar forms later on in the disease and may appear as the classic starburst radial calcification. Maximal visualization of septa occurs in the pancreatic parenchymal phase as well as the honeycomb appearance. The presence of central calcification in correspondence with scars or septa definitively characterizes a cystic mass as a SCA.

Magnetic Resonance Imaging (MRI), coupled with the MRCP technique, provides a precise evaluation of spatial relationship between the mass and the biliary or pancreatic duct, thereby discriminating SCAs from intraductal papillary mucinous neoplasms (IPMNs), especially when the lesion is located on the head or in the uncinate process of the gland.

A recent study from our institution (Malleo et al. 2012) of 145 patients with SCA enrolled in a surveillance protocol with serial MRI + MRCP showed that the overall mean growth rate was only 0.28 cm/year. There were two distinct phases of growth during follow-up, with the first 7 years growth at 0.1 cm/year, and after 7 years at 0.6 cm/year. The rare oligocystic/macrocystic variant, a history of other non-pancreatic malignancies, and patients' age were demonstrated to impact on tumor growth. Tumor size at the time of diagnosis was not a predictor of growth and should not be used for decisional purposes. A surveillance protocol with MR + MRCP was proposed for all well-characterized and asymptomatic SCN, but patients with factors that impact on tumor growth should be informed about an increased likelihood of a pancreatic resection in the long-term. A follow-up time frame of 2 years seems to be appropriate. In conclusion, we no longer consider a 4-cm diameter to be a sufficient criteria to pursue resection as suggested by others (Tseng et al. 2005).

Mucinous Cystic Neoplasms (MCNs) are cystic epithelial neoplasms occurring almost exclusively in women and are located preferentially in the body and tail of the pancreas. MCNs are formed by epithelial cells producing mucin, all of which are supported by ovarian-type stroma (a required finding for the diagnosis of MCN), showing no communication with the pancreatic ductal system. According to the grade of epithelial dysplasia they may be classified into mucinous cystic neoplasm with low-grade dysplasia, moderate dysplasia, or high-grade dysplasia (carcinoma in situ).

When our series was combined with the Massachusetts General Hospital experience (Crippa et al. 2008), the incidence of malignancy for MCN was 17.5 %. Early diagnosis of malignant transformation of mucinous cystic neoplasm is essential, because the prognosis, once the invasive malignant form occurs, is the same as ductal adenocarcinoma, while in the forms of non-invasive, carcinoma in situ, resection is cureative.

A thickened wall, presence of papillary proliferations arising from the wall or septa, evidence of peripheral "egg shell" calcifications as well as invasion of surrounding vascular structures are considered the best signs of malignancy at

imaging. The diagnosis will be more evident if extracapsular extension of the lesion is detected on contrast-enhanced CT. When thick walls, thick septa and calcifications are present simultaneously, the probability of malignancy is 95 %. When fewer than three signs are present, the probability of malignancy decreases to almost zero when there are no calcifications or septae, and the wall is thin. Because calcifications cannot be detected by MRI, CT is the primary imaging modality for these patients.

All MCNs should be resected, both cystadenomas and cystadenocarcinomas, when possible. Current thinking is that all MCNs may progress to malignancy, and the life-expectancy of most of these patients, middle-aged women, will allow the development of mucinous cystadenocarcinoma; unfortunately, once established, cystadenocarcinoma has a very low rate of resectability and a very poor prognosis. Predictors of malignancy are large size (≥4 cm), the presence of nodules, septae and eggshell calcification. In these cases, a "standard," anatomic, oncologic pancreatic resection should be performed, avoiding middle pancreatectomies and spleen preservation during the left pancreatectomies. Interestingly, lymph node metastases were never found in our series, even in MCN with associated cancer (Crippa et al. 2008). Based on this finding, more limited resections could be considered, and a laparoscopic approach can be ideal in such cases.

Intraductal Papillary Mucinous Neoplasms (IPMNs) represent the most frequent cystic neoplasm of the pancreas, even in asymptomatic patients, in which they represent an incidental finding. In our experience, IPMNs are one of the most common indications for pancreatic resection, up to 25 % of all resections.

IPMNs may affect the main pancreatic duct (MD-IPMN), branch ducts (BD-IPMN) or both ("mixed duct" IPMN). The great majority of IPMNs are detected and then characterized with cross-sectional imaging study, such as CT and MRCP. The radiologic and endoscopic features of IPMNs vary with their morphologic type. The typical feature of MD-IPMNs is dilation of the main pancreatic duct >1 cm, eventually extending into the secondary branches that may appear as cysts. The dilation can affect the duct only in the distal pancreas or, if it is located in the head or in the uncinate process, can be present throughout because of obstructive effect. BD-IPMNs appear as cysts or a cluster of cysts without dilation of the main duct and are located more commonly in the head-uncinate region. It is estimated that 40–60 % of BD-IPMNs can be multifocal. Calcifications occur in 10 % of patients, and nodules and papillary projections, which are associated with the presence of a malignant neoplasms, usually appear as filling defects within the cystic lesions. The pancreatic gland may appear as enlarged with signs of pancreatitis or atrophic. CT and MRCP can localize the tumor and assess its relationship with vessels and other organs. MRCP is particularly useful in the characterization of single or multifocal BD- IPMNs, given its ability to demonstrate a communication between the main duct and the cyst.

At our Institution the initial assessment of patients with suspected IPMN usually involves contrast-enhanced ultrasonography (CEUS), which is able to identify and characterize the "cysts" in great detail.

In those patients in whom the diagnosis is uncertain, endoscopic ultrasonography (EUS) may be helpful. EUS can identify the dilated main pancreatic duct and provide morphologic detail of any solid component, nodules, or small projections, in the main duct and/or in the cyst communicating with it. Moreover, EUS represents a safer approach for sampling of fluid and targeted biopsies by fine needle aspiration or core biopsy.

Examination of fluid sampled from IPMNs provides information to help in diagnosis by analyzing viscosity, the presence of mucin or mucinous cells, and an increased value of Carcinoembryonic antigen (CEA).

The best management of IPMN is still debated. During a consensus conference held in Sendai (Tanaka et al. 2006), a group of surgeons, gastroenterologists, and pathologists produced the first guidelines in the management of IPMNs. A secondary, updated set of guidelines is being developed currently. Before 2006, all patients with a diagnosis of IPMN were considered potentially at risk for developing malignancy, and therefore

resection was always proposed. After the Sendai meeting two different approaches have been defined when considering MD-IPMN (together with the mixed form) or BD-IPMN.

17.1 Main Duct-IPMN

Patients affected by IPMN involving the main duct or the mixed form, when medically fit, should always be candidates for resection because of the high prevalence of in situ and invasive carcinoma found in the resected specimens (40 % invasive, 30 % only in situ).

The operative management of MD- IPMNs represents a challenge for the surgeon. While in other pancreatic neoplasms the preoperative imaging can locate the tumor accurately and plan a pancreatic resection accordingly, this is not always the case in MD- IPMNs. The segmental dilation of the main pancreatic duct in the preoperative studies may occur both proximal and distal to the tumor, because of mucin overproduction, making the localization of the neoplasia more difficult.

A typical resection (pancreatoduodenectomy, left pancreatectomy, total pancreatectomy, according to the site and extension of the disease) with lymph node dissection must be performed. Limited resections, such as middle pancreatectomy, have been proposed for MD-IPMN, but we had too great a rate of positive resection margins and recurrences when central pancreatectomy was performed for what appeared to be MD-IPMN localized the proximal body of the gland, and similar results have been reported by other authors. For these reasons, we believe that standard resections should be performed in this setting. Because IPMN extends along the pancreatic duct and it can do so without a macroscopically-evident lesion, it is important to exclude residual tumor with frozen section.

Three different aspects of ductal mucosa can be detected by analyzing the operative margin: (1) normal ductal epithelium in the main duct means that radical resection is achieved; (2) de-epithelialized with denuded epithelium that should not be considered as a negative margin, because the abnormal epithelium may have sloughed off and local recurrence can occur; (3) adenoma, borderline, or carcinoma that requires an extension of the resection up to total pancreatectomy in selected individuals.

In cases of de-epithelialization, adenoma, or borderline tumor at the margin, the optimal strategy remains controversial: we usually extend the resection a few centimeters to obtain a new margin, trying to obtain a negative resection margin. In our experience with 140 patients affected by MD-IPMN who underwent resection, the rate of negative margins in the surgical specimen was 60 %, and the results of the intraoperative, frozen section analysis modified the operative plan, leading to an extension of the resection or to total pancreatectomy in 29 patients (20 %) (Salvia et al. 2004).

Recurrence in the pancreatic remnant may develop even if the transection margin is negative and even in patients with noninvasive disease. The presence of a "positive" resection margin, multicentric IPMNs with synchronous "skip" lesions along the main duct, still present (but not detectable) at the time of operation and metachronous lesions (given that IPMN may be a marker of a "field defect" associated with a propensity for tumor development) may be responsible for recurrence in the pancreatic remnant after resecting a MD-IPMN.

17.2 Branch-Duct IPMN

According to the Sendai criteria (Tanaka et al. 2006), a strict follow up is suggested for patients with BD-IPMN less than 3 cm, with no nodules nor duct dilation (which would imply a mixed IPMN), in which progression toward cancer is considered low.

Follow up can be performed MRCP repeated 6 months after the first diagnosis and then yearly together with following serum CA19.9 dosage, unless there is an increase in size, the development of nodules, or the onset of symptoms. We believe that non-operative management of patients affected by BD-IPMN should be carried out in experienced centers, because data from large series is needed to validate this approach.

In our earlier experience of 109 patients with BD-IPMN (Salvia et al. 2007), 20 patients (18 %) underwent immediate resection because of symptoms and/or parameters associated with malignancy; pathologic diagnosis of BD-IPMN was always confirmed, and 2 patients (10 %) had an invasive carcinoma, while 1 (5 %) had carcinoma in situ. Eighty-nine patients (82 %) were followed up for a median of 32 months. After a mean follow-up of 18 months, 5 patients (6 %) had an increase in size of the lesion and underwent resection. The pathologic diagnosis was branch-duct adenoma in three patients and borderline in two; no patient developed malignancy on follow-up. These findings have been substantiated by other studies. Tanno et al. (2008) reported a follow up study of IPMN, showing similar results compared with our study; the authors found that the presence of mural nodules was the only predictive factor of malignancy in BD-IPMNs.

In contrast, other Institutions have advocated prompt resection for BD-IPMN. As illustrated in a dedicated chapter of this book, the Heidelberg group suggests that the incidence of malignant BD-IPMN may be greater than what has been reported in other studies, and that currently used predictors of malignancy may be inadequate.

One may argue (and we would agree with their argument) that such results may be reflective of a selected population. More importantly, most studies about BD-IPMN have focused on patients who have undergone resection, but little is known about the real incidence of invasive cancer in patients under surveillance programs. Recently, Cauley et al. (2012) published results on primary surveillance of 292 patients with BD-IPMN. These patients were defined as low risk and high risk for malignancy, according to clinical, serologic, and radiographic criteria. Interestingly, among the low-risk patients, only 12 % developed criteria for resection during the surveillance period. Of these patients, only 4 % presented high-grade dysplasia and only 1 % invasive cancer, underscoring the low malignant potential of BD-IPMNs with no obvious worrisome signs or characteristics of their IPMN.

In conclusion, correct diagnosis and appropriate management of pancreatic cystic neoplams (especially BD-IPMN) is still hampered by our lack of knowledge of the biologic behavior of these diseases. As a result, there still is heterogeneity in the choice of which treatment to offer to patients. We believe that further studies and continuous discussion among different groups will soon shed some light on one of the most fascinating topics in Pancreatology.

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