Incidental Intraductal Papillary Mucinous Neoplasm, Cystic or Premalignant Lesions of the Pancreas

The Case for Aggressive Management

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KEYWORDS

- Intraductal papillary mucinous neoplasm • Cystic intrapancreatic lesion
- Cystic pancreatic tumor differentiation

KEY POINTS

- Because main-duct and mixed type intraductal papillary mucinous neoplasms are highly associated with malignant transformation, they both should be treated with surgical-oncologic intent.
- Serous cystadenoma (SC) is the only lesion that may appear microcystic; computed tomography often reveals a sponge or honeycomb-like lesion with countless small cysts separated by slender septa.
- SCs are benign cystic tumors that derive from pancreatic centroacinar cells.

INTRODUCTION

Incidental cystic intrapancreatic lesions are daily findings in abdominal radiology. In fact, previously undetected cystic intrapancreatic lesions are found in 1.2% to 2.6% of abdominal multidetector computed tomography (CT) examinations and in 13.5% to 19.9% of abdominal MRI studies.[1–5] Although there have been major efforts to systematically define a standard of care for these lesions,[6–8] there is currently no consensus how these lesions should be managed.[5] Postmortem

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autopsies revealed intrapancreatic cystic lesions in up to 25% of autopsies.[9] Therefore, it is not surprising that the discovery of incidental pancreatic lesions is increasingly common with technologic diagnostic advancements. Clinical recommendations for the treatment of incidental pancreatic lesions are urgently needed. This article provides a perspective and guideline on the clinical management of incidental intraductal papillary mucinous neoplasms (IPMNs) and cystic or premalignant lesions of the pancreas.

Generally, 4 major types of cystic intrapancreatic incidentalomas are distinguished based on location, main pancreatic duct communication, and occurrence of septae, loculations, or calcifications: (1) unilocular or oligolocular (pseudocyst, IPMN, serous cystadenoma [SC], mucinous cystic neoplasm [MCN]), or multilocular (oligocystic SCs, branch-duct IPMN [BD-IPMN], MCN); (2) microcystic SC; (3) macrocystic (MCN, SC, or IPMN); and (4) cysts with a solid component (IPMN, MCN).[5,10]

Unilocular or Oligolocular Cysts

Unilocular cysts associated with a history of pancreatitis are pseudocysts in most cases.[5] If diagnosed in elderly women, however, unilocular cysts located in the pancreatic head featuring a lobulated contour but lacking wall enhancement or mural nodules may be specific for SC.[5] Calcification in the tumor periphery can be a characteristic for MCN.[5,10–12]

Multilocular Cystic Lesions

Multilocular intrapancreatic cystic lesions can be pleomorphic, lobulated, or feature a smooth shape with septations.[5,10,12,13] Oligocystic SCs usually feature a lobulated shape with either internal septations or no septation at all.[5,10,12,13] A pleomorphic shape is typical for BD-IPMNs. A smooth shape with septation is specific for MCNs.[5,10,12,13]

Differentiation of cystic tumors may be difficult because of their overlapping morphology.[14] However, oligocystic SC appears as multicystic or cystic-lobulated with septations, whereas MCN features a smooth shape, with or without septations. SCs typically show central calcification within the fibrous stroma. MCN may feature peripheral eggshell calcification.[5,10,15,16]

Microcystic Lesions

SC is the only lesion that may appear microcystic. CT often reveals a sponge or honeycomb-like lesion with countless small cysts separated by slender septa. In about 20% of SCs, the septa may merge into a central stellate scar, which may calcify. Because microcystic lesions (**Fig. 1**) may easily be mistaken for solid structures in CT scans, a T2-weighted MRI and endoscopic ultrasonography (EUS) should be performed.[5,10,17,18]

Cysts with or Without a Solid Component

Cysts with solid components should be considered highly suspicious for malignancy. Solid tumors with cystic components may be solid pseudopapillary tumors, malignant adenocarcinoma, cystic pancreatic endocrine tumor, and metastasis. Cystic tumors with a solid component may be MCNs and IPMNs that transformed to malignant tumors or cystic degeneration.[5,10] Either way, incidentalomas with this appearance are highly suspicious for malignancy.

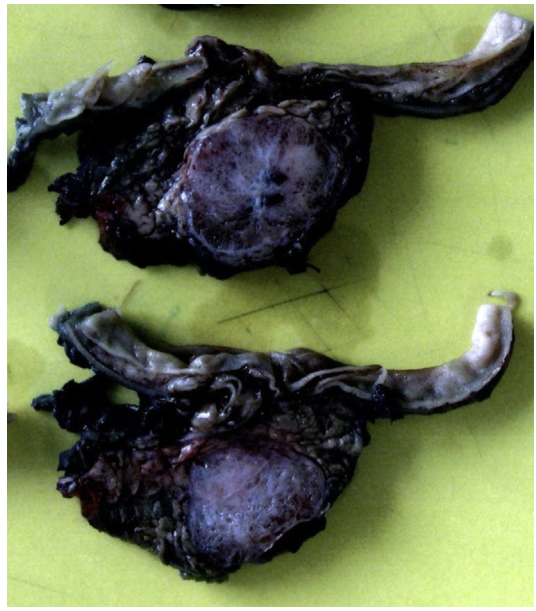

Fig. 1. Macroscopic pathologic examination of a microcystic cystadenoma.

Cystic Lesions with or Without Pancreatic Duct Communication

In radiologic practice, communication of the cystic lesion to the pancreatic main and branch duct may indicate an IPMN. Rarely, this can be observed in MCNs.[19]

TYPES OF CYSTIC INCIDENTALOMAS

The classification of cystic pancreatic neoplasms is based on the type of epithelium and a mucinous or nonmucinous content.[20–22] MCNs and IPMNs account for most mucinous neoplasms.[22–24] The following nonmucinous cystic lesions may occur in the pancreas: cystic pancreatic ductal adenocarcinomas (PDAs), serous cystic neoplasms (SCNs), cystic pancreatic neuroendocrine tumors (PNETs), pseudocysts, solid pseudopapillary neoplasms (SPNs), and other rare lesions.[22] PDA, PNET, MCN, IPMN, and SPN are considered neoplastic or have high-risk potential for malignancy, whereas pseudocysts (**Fig. 2**), serous cysts, and simple cysts are nonneoplastic or have low-risk potential for malignancy.[22,25,26]

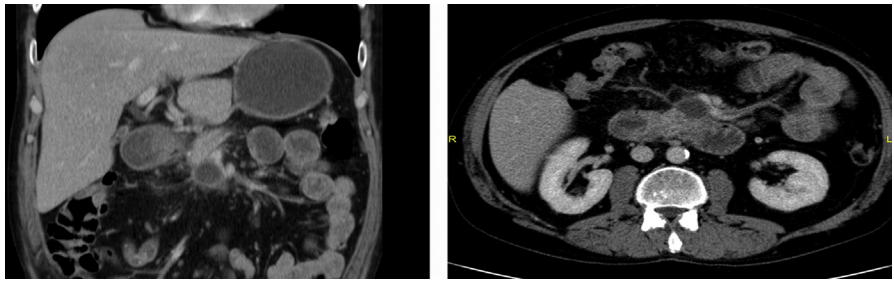

Fig. 2. Incidental occurrence of a pancreatic pseudocyst. CT scan of a pancreatic pseudocyst. Incidental occurrence of a pancreatic pseudocyst. CT scan of a pancreatic pseudocyst. Coronal ct scan of the abdomen (*left*). Transversal ct scan of the abdomen (*right*).

Previous studies have shown that SC, MCN, and IPMN account for most of the pancreatic cysts found in asymptomatic individuals.[16]

Serous Cystadenomas

SCs are benign cystic tumors that derive from pancreatic centroacinar cells (**Fig. 3**). SCs usually manifest as numerous fluid-filled cysts and occur in any part of the pancreas.[26] Occasionally, SC appear as an oligocystic lesion, which can be challenging to differentiate from MCN if found in the pancreatic tail or body.[26–29] On radiologic imaging, SC manifests as a focal, well-demarcated lesion with a central scar or sunburst calcification visible in 20% of SCs.[26] EUS, on the other hand, often reveals a honeycomb-like appearance.[21,26] When acquired, cytologic analysis exhibits cuboidal glycogen-staining cells in 50% of cases.[26,30–32] Therefore, cytologic diagnosis can be difficult. SCs are considered benign and should only be resected if symptomatic or if malignancy cannot be fully excluded.[26]

Mucinous Cystic Neoplasm

MCNs are mucinous cysts that contain ovarian-like stroma (**Figs. 4** and **5**). They occur almost exclusively in women and usually present as unilocular cysts in the body and/or tail of the pancreas.[33] About 15% of MCNs contain invasive cancer.[33,34] Risk factors for malignancy include size greater than 6 cm and nodules.[34] Previous studies demonstrated that the risk of high-grade dysplasia or invasive cancer decreases dramatically to less than 0.4% when MCNs are smaller than 3 cm and without nodules.[35]

Intraductal Papillary Mucinous Neoplasms

IPMNs (**Fig. 6**) were first described by Ohhashi and colleagues[36] in 1982 and are considered a specific tumor-entity. By definition they can be distinguished from PDAs and MCNs.[36] Histopathologically, IPMNs feature dysplastic changes of the epithelium, with grade of dysplasia ranging from low or intermediate to high (IPMN

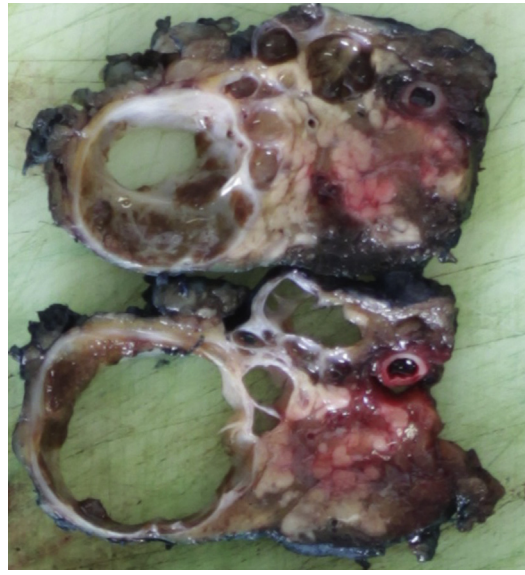

Fig. 3. Macroscopic pathologic examination of a SC.

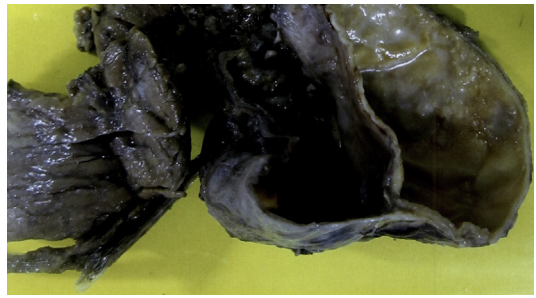

Fig. 4. Macroscopic pathologic examination of an MCN.

with carcinoma in situ), which are considered to be noninvasive up to IPMNs with invasive carcinoma (invasive IPMN).[37–39] Currently, IPMNs are the most frequently resected cystic lesion.[40] The World Health Organization defines IPMNs as follows: An intraductal papillary mucin-producing neoplasm, arises in the main pancreatic duct or its major branches. The papillary epithelium component, and the degree of mucin secretion, cystic duct dilatation, and invasiveness are variable. Intraductal papillary-mucin neoplasms are divided into benign, borderline, and malignant noninvasive or invasive lesions.[41]

Most IPMNs are in the head of the pancreas and derived from the main pancreatic duct and its branches.[41–44] Usually, IPMN lesions involve either a single cystic mass or a segmental duct; however, diffuse involvement has also been described.[41,45–47]

In general, IPMNs are subdivided into different types depending on the involvement of pancreatic ductal system microscopically and macroscopically[24,39,41]: main-duct

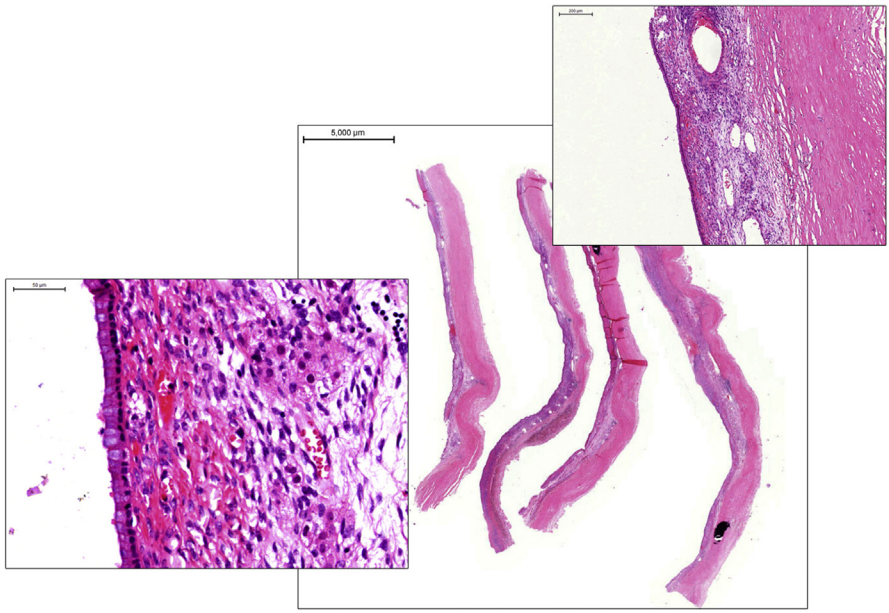

Fig. 5. Histopathologic microscopic examination reveals an MCN. Hematoxylin-eosin stain (H&E stain).

Fig. 6. Macroscopic pathologic examination of an IPMN. Macroscopic examination of an IPMN. In macroscopic examination the cystic formation might feature different shapes and colors (*left*, *right*).

IPMN (MD-IPMN) (**Figs. 7** and **8**), BD-IPMN (**Figs. 9** and **10**), and mixed-duct IPMN (XD-IPMN). For further details see **Table 1**. Generally speaking, risk factors for malignant IPMNs include solid components, main pancreatic duct dilation, cyst size greater than 3 cm, and nodules.[33,34]

Diagnostics of Incidentalomas of the Pancreas

When approaching incidental pancreatic cysts, the following aspects should be addressed:

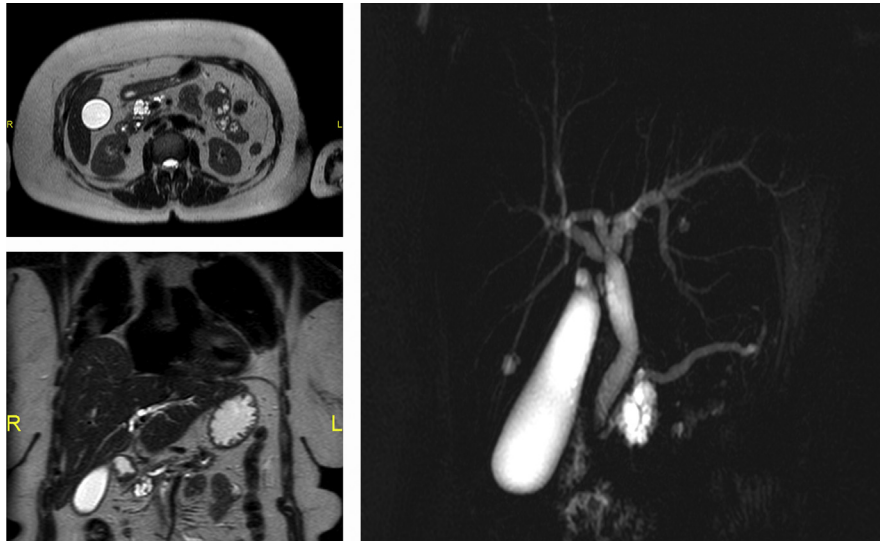

Fig. 7. MRI and MRCP scan of an incidental main-duct IPMN with a multilocular configuration. MRI and MRCP scan of an incidental main-duct IPMN with a multilocular configuration. Transversal MRI scan (*upper left*). Coronal MRI scan (*downer left*). MRCP scan (*right*).

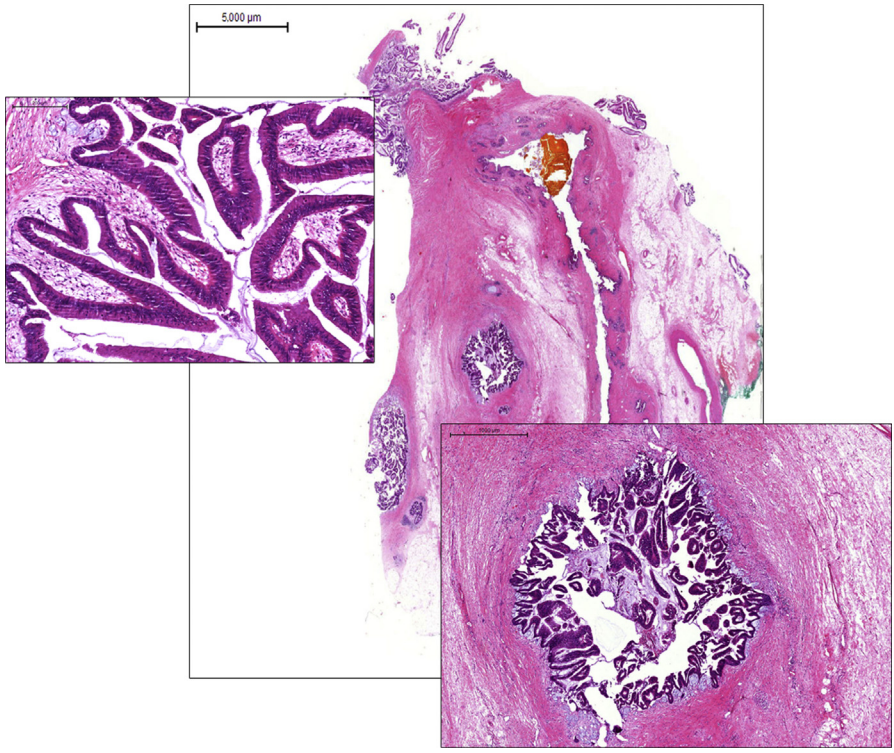

Fig. 8. Histopathologic examination reveals a main-duct IPMN with an intestinal subtype. H&E stain.

1. Type of cyst
   a. Mucinous or nonmucinous? Mucinous cysts show a much higher potential for malignancy than nonmucinous cysts; therefore, it is crucial to distinguish mucinous from nonmucinous cysts.
      i. Multidetector CT is able to identify mucinous cysts with an accuracy of 71% to 84%.[52–55] However, accuracy for diagnosing the specific type of cyst is lower (40%–70%).[52–55] SCs usually have a higher attenuation than pseudocysts, MCNs, and IPMNs; lower attenuation than insulinomas; and comparable attenuation to pancreatic adenocarcinomas.[56]

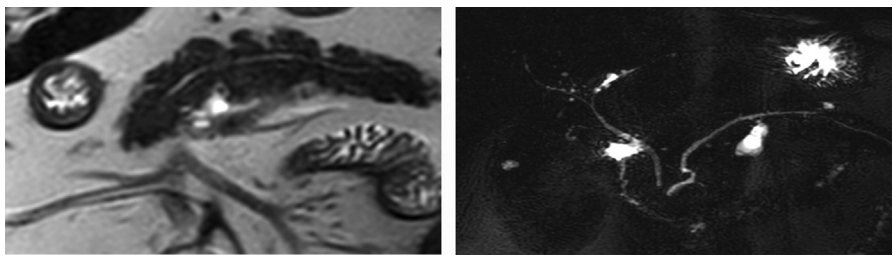

Fig. 9. Incidental cystic pancreatic lesions. MRCP scan indicates a BD-IPMN. Incidental cystic pancreatic lesions in MRI scan (*left*). MRCP scan indicates a BD-IPMN (*right*).

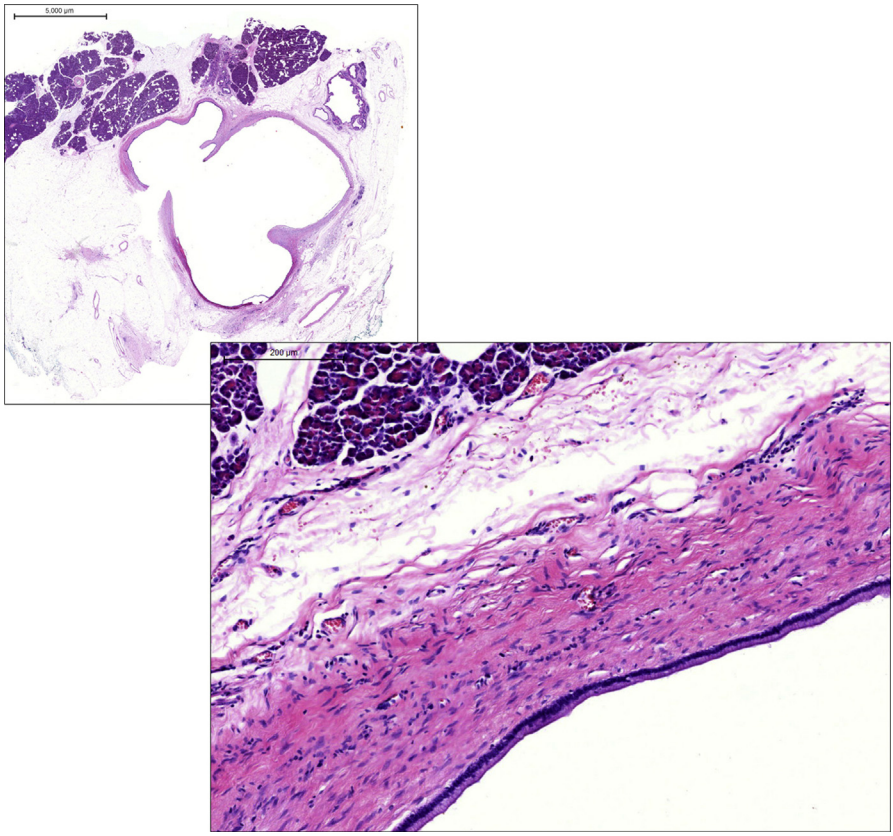

Fig. 10. Histopathologic examination reveals a BD-IPMN with a gastric epithelial subtype. H&E stain.

Table 1
Types of intraductal papillary mucinous neoplasm

MD-IPMN	BD-IPMN	XD-IPMN
• Cystic tumor that involves only the main pancreatic duct which features diffuse or segmental dilatation to >5 mm[24,33]	• Tumor involves only branch-ducts, no dilatation of main pancreatic duct[7]	• Tumor involves both the main pancreatic duct and its side branches[24]
• *Histologic characteristics: mostly intestinal epithelial subtype*[48]	• *Histologic characteristics: mostly gastric epithelial subtype*[48]	• *Histologic characteristics: both gastric and intestinal epithelial subtype, depending on ratio MD-IPMN to BD-IPMN*[48]
• *High frequency of malignancy (>60%)*[24,33,49,50]	• Lower frequency of malignancy (26%)[24]	• XD-IPMN has a comparable malignant potential to MD-IPMN[33,48]
	• 20% to 30% of BD-IPMN ultimately turn out to be mixed type IPMN on histopathologic examination after surgical pathologic assessment[33,51]	

ii. Compared with multidetector CT, MRI is superior in identifying mucinous cysts with an accuracy of 79% to 82%; however, for diagnosing specific types of cysts it is comparable to multidetector CT.[52,55] Therefore, MRI or magnetic resonance cholangiopancreatography (MRCP) is the preferred imaging technique because it better detects septa, nodules, and duct communication.[6,20,52]
iii. High-resolution imaging of pancreatic cystic lesions can be provided by EUS[21,22] and allows cytologic and biochemical fluid analysis of the cystic fluid when combined with EUS-guided fine-needle aspiration.[22,57] However, EUS imaging alone is insufficient for mucinous cysts with only 56% sensitivity, 45% specificity, and 51% accuracy.[52,57]

2. Is the cyst currently malignant?
   a. Unfortunately, diagnostic differentiation between benign and premalignant lesions can be tricky.[26,58,59] In addition, cystic fluid analysis studies currently fail to clearly distinguish among the different pancreatic cyst types or to predict the behavior of these lesions.[14,58,59] Overall accuracy of preoperative diagnosis of pancreatic cysts is currently only 68% compared with surgical histopathologic assesment.[59,60] One study suggested a preoperative diagnostic accuracy of only 47%.[59,61] Malignant pancreatic lesions are lethal in most cases. Therefore, the following principle should be obeyed: if in doubt take it out! Especially considering that a tailored surgical approach, for example, segmental resection. Duodenum-preserving pancreatic head resection, also done by laparoscopy, can be offered to the patient.
3. If not, what is the malignant potential of the cyst?[52,59] If it is high or if there is doubt about it being benign, it should be treated with oncological intent.
4. Important considerations include a patient's biological age, comorbidities, fitness, tumor localization, and the planned surgical approach; what is the benefit-risk ratio? Young, surgically fit patients with long life expectancies will most likely benefit from a surgical approach, whereas biologically old patients with serious life-limiting comorbidities will most likely not benefit.

Treatment of Intraductal Papillary Mucinous Neoplasms

Surgical decisions for IPNM must be based on the type of IPMN diagnosed.[49] The risk of malignancy in MD-IPMN and XD-IPMN is 60% to 90%, therefore these 2 entities represent major indications for oncological surgical treatment that includes a formal pancreatic resection and lymphadenectomy.[24,49,50] However, for BD-IPMN, indications for surgery should be more balanced because malignancy occurs in approximately 20% to 25% (**Figs. 11** and **12**).[7,49,62,63]

Surgical Treatment of Main-Duct and Mixed-Duct Intraductal Papillary Mucinous Neoplasm Lesions

Because MD-IPMN and XD-IPMN are highly associated with malignant transformation, they both should be treated with surgical-oncologic intent. The type of surgical procedure will vary and depends on the localization of the lesions. The surgical standard procedures include partial, distal, and total pancreatectomy.[39,49,64]

Treatment of Branch-Duct Intraductal Papillary Mucinous Neoplasm

Currently, the guidelines recommend resection of BD-IPMN with a diameter of more than 3 cm. Smaller BD-IPMN should only be resected when high-risk stigmata, including mural nodules, positive cytology, symptoms, or a synchronously dilated main duct, are evident.[49] Recent studies, however, show that the incidence of

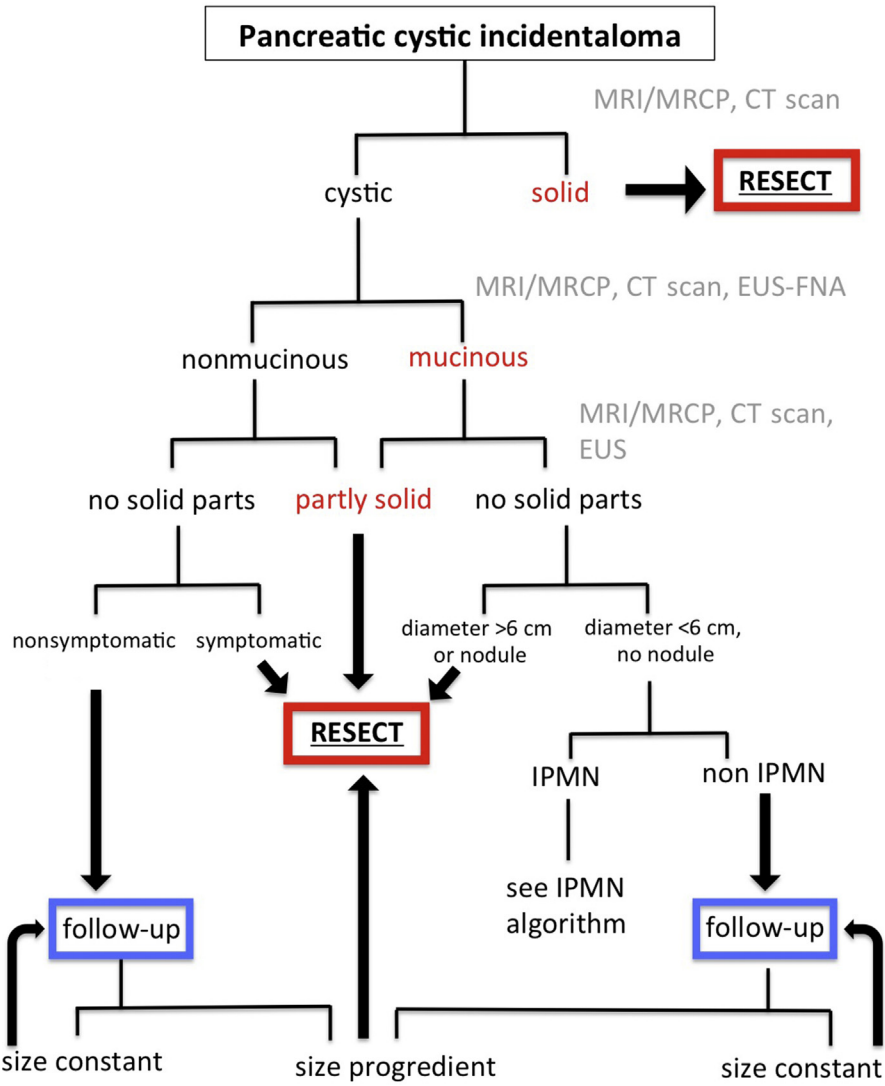

Fig. 11. Decision-making algorithm for pancreatic cystic incidentalomas. FNA, fine-needle aspiration.

malignancy is approximately 25% in BD-IPMN less than 3 cm[49,62,65–67] and neither the existence of mural nodules nor clinical symptoms correlated with malignancy.[49,67]

According to the Sendai guidelines,[24,68] BD-IPMNs have been treated according to risk stratification. However, several large series have implied that even small and asymptomatic side-branch IPMNs without suspicious radiologic features contain a risk of invasive carcinoma that may be as high as 20%.[51,65,66,69] Also, cyst size may be inaccurate for predicting malignant risk.[69] In fact, so-called Sendai-negative IPMNs have a malignant findings in 14% to 25.5% of final histologic examination of the resected pancreatic specimen.[24,51,60,62]

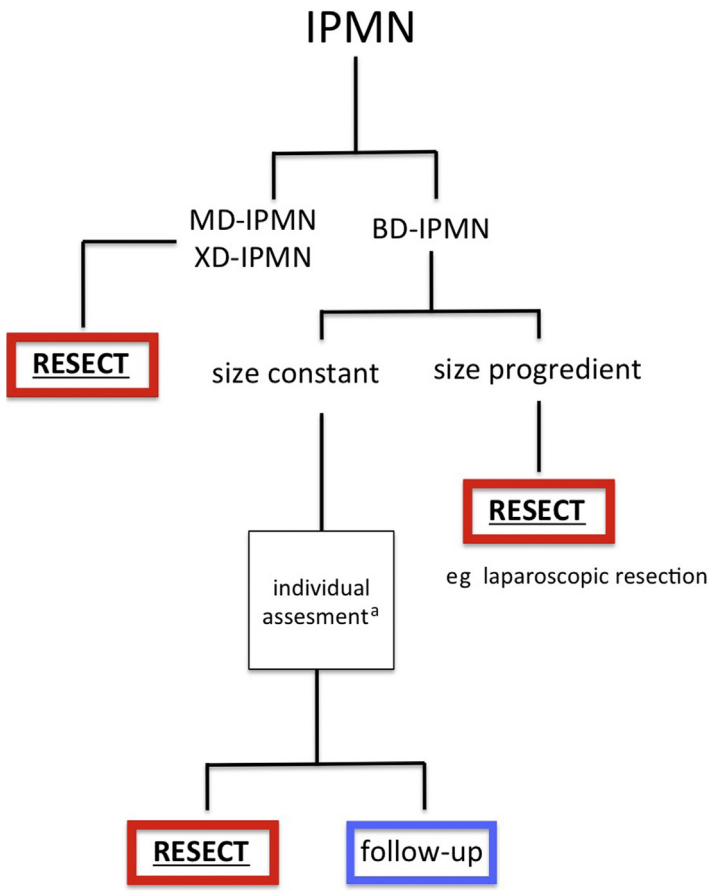

Fig. 12. Decision-making algorithm for IPMNs. [a] Assessment of all morphological and clinical factors, including imaging, tumor markers, symptoms, progression, and prior patient history.

Currently, diagnostic and prognostic markers fail to be sufficiently reliable to distinguish between cysts at risk of malignant transformation and those with no risk. Therefore, surgery for BD-IPMNs should be considered in all fit patients.[51,62] Preferably, the surgery should be performed in specialized high-volume centers with high operative and clinical experience in pancreatic surgery.

Suspected malignant BD-IPMN should be treated similarly to the location-based approach of MD-IPMN. Depending on the location of the lesion, either a partial pancreaticoduodenectomy or distal pancreatectomy should be performed.[49] Because the surgical treatment of BD-IPMN is also focused on prevention of malignancy, less extensive surgical approaches may be considered, for example, laparoscopic enucleations or central pancreatectomies.[49,70–75]

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