

# Pancreatic Cystic Lesions: New Diagnostic Strategies

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## **ABSTRACT**

*Pancreatic cystic neoplasms (PCN) are a heterogeneous group of pancreatic cysts that include intraductal papillary mucinous neoplasms, mucinous cystic neoplasms, serous cystic neoplasms and other rare cystic lesions, all with different biological behaviors and variable risk of progression to malignancy. As more pancreatic cysts are incidentally discovered on routine cross-sectional imaging, optimal surveillance for patients with PCN is becoming an increasingly common clinical problem, highlighting the need to balance cancer prevention with the risk of (surgical) overtreatment. This Review summarizes the latest developments in the diagnosis and management of PCN, including the quality of available evidence. Also discussed are the most important differences between the PCN guidelines from the American Gastroenterological Association, the International Association of Pancreatology and the European Study Group on Cystic Tumors of the Pancreas, including diagnostic and follow-up strategies and indications for surgery. Finally, new developments in the management of patients with PCN are addressed.*

**Key words:** *Pancreatic cystic neoplasms (PCN), mucinous cystic neoplasms, serous cystic neoplasms.*

## **Introduction:**

Pancreatic cystic neoplasms (PCN) are a heterogeneous group of pancreatic cysts that include intraductal papillary mucinous neoplasms (IPMN), mucinous cystic neoplasms (MCN), serous cystic neoplasms (SCN) and other rare cystic lesions, such as solid pseudopapillary neoplasms (SPN) and cystic neuroendocrine tumours (cNET), all of which have diverse clinical, radiological and pathological features<sup>1,2,3,4</sup> (Table 1). Together, these cyst types represent 90% of PCN, with IPMN being the most common<sup>2</sup>

The increased use of high-quality, cross-sectional imaging and the trend for healthy individuals to undergo preventive health check-ups, including full-body MRI, has increased the detection of PCN. The prevalence of PCN varies markedly with the type of imaging used and among studies. Whereas abdominal ultrasonography only detected PCN in 0.21% of individuals<sup>5</sup>, CT revealed PCN in 2.6%<sup>6</sup>, and MRI (with magnetic resonance cholangiopancreatography (MRCP)) revealed PCN in 2.4% to 49.1% of tested individuals<sup>7,8,9,10</sup>. In autopsy studies, PCN are detected in up to

50% of patients<sup>5,11,12</sup>. Increasing age strongly correlates with the presence of PCN, whereas gender is not correlated with the presence of PCN<sup>6,7,8,10</sup>. Additionally, there is a causative link between diabetes mellitus and IPMN. In individuals with diabetes mellitus, the risk of detecting IPMN on imaging is increased (OR 1.79, 95% CI 1.08–2.98), especially in the case of insulin use (OR 6.03, 95% CI 1.74–20.84)<sup>13</sup>. Overall, 10–45% of individuals with IPMN have diabetes mellitus<sup>14,15,16,17,18,19,20,21</sup>. Furthermore, individuals with chronic pancreatitis also have an increased risk of IPMN<sup>13,20</sup>.

**Table (1): Key demographic and clinical features of PCN**

| Characteristics                                     | SCN   | MCN   | MD/MT-IPMN   | SB-IPMN  | SPN   | cNET   |
|---|---|---|--|--|---|--|
| Age of presentation                                 | Variable, usually 5 <sup>th</sup> to 7 <sup>th</sup> decade | Variable, usually 5 <sup>th</sup> to 7 <sup>th</sup> decade | Variable, usually 5 <sup>th</sup> to 7 <sup>th</sup> decade                            | Variable, usually 5 <sup>th</sup> to 7 <sup>th</sup> decade    | 2 <sup>nd</sup> to 3 <sup>rd</sup> decade       | Variable, usually 5 <sup>th</sup> to 6 <sup>th</sup> decade              |
| Gender distribution                                 | 70% female  | 90–95% female   | Equal  | Equal  | 90% female                                      | Equal  |
| Clinical presentation                               | Incidental finding, abdominal pain, mass effect             | Incidental finding, abdominal pain or malignancy-related    | Incidental finding, jaundice, pancreatitis, exocrine insufficiency, malignancy-related | Incidental finding, jaundice, pancreatitis, malignancy-related | Incidental finding, abdominal pain, mass effect | Incidental finding (usually nonfunctioning), abdominal pain, mass effect |
| Typical imaging characteristics                     | Microcystic (honeycomb appearance)                          | Unilocular, macrocystic                                     | Dilated pancreatic duct or dilated pancreatic duct with dilated side branches          | Dilated side branches  | Solid and cystic mass                           | Solid and cystic mass, hypervascular                                     |
| Connection or involvement with main pancreatic duct | No  | No  | Yes  | Yes  | No  | No   |
| Solitary or multifocal                              | Solitary  | Solitary  | Solitary/multifocal  | Solitary/multifocal  | Solitary  | Solitary   |
| Malignant potential <sup>a</sup>                    | Negligible  | 10–39%  | 36–100%  | 11–30%   | 10–15%  | 10%  |

A distinction between the different types of PCN is essential, as the malignant potential of PCN varies between the various types. SCN are mostly benign without the need for surveillance, whereas IPMN, MCN, SPN and cNET are considered premalignant and require either surveillance or surgical resection<sup>3,4</sup>. Notably, the risk of malignancy of PCN has mainly been established from surgical cohorts. Information on the longitudinal risk of malignancy of IPMN, MCN, SPN and cNET is limited, owing to a lack of reports on the natural history of PCN. Advanced neoplasia in the pancreas (high-grade dysplasia (HGD) or invasive cancer) has been reported in 11–30% of patients who received resection for side-branch (SB)-IPMN<sup>15,22,23,24,25</sup>.

The risk of advanced neoplasia in IPMN is increased predominantly by main duct involvement, with a mean frequency of 62% (range 36–100%) in resected specimens.<sup>26,27,28,29,30,31,32</sup> In addition, individuals with IPMN are at increased risk (1–8%) of developing conventional pancreatic ductal adenocarcinoma (PDAC) elsewhere in the pancreas<sup>33,34,35,36</sup>. The risk of advanced neoplasia in patients with resected MCN has been reported at 10–39%<sup>37,38,39,40,41,42</sup>.

Invasive cancer has been reported in up to 15% of those with resected SPN<sup>43</sup> and 10% of those with resected cNET<sup>44</sup>.

PCN are known precursors for invasive pancreatic cancer<sup>45</sup> and, without a breakthrough in prevention and treatment, PDAC is projected to become the second most common cause of cancer death in 2030 (ref.<sup>46</sup>). Surgical resection combined with chemotherapy is the only treatment option for long-term survival. Due to the late onset of symptoms, only 15–20% of patients are resectable at the time of diagnosis<sup>47</sup>.

PDAC arises from noninvasive precursor lesions, including PCN, which take several years to progress to invasive cancer. Thus, opportunities for early detection and (surgical) cure do exist. Owing to the potential for progression to invasive pancreatic cancer, patients with premalignant PCN are routinely monitored. The primary goal is to prevent malignancy and/or alleviate symptoms, while avoiding unnecessary surgery. Surgical resection is generally considered justifiable in patients with advanced neoplasia (that is, HGD or invasive cancer).

Currently, three guidelines provide recommendations on PCN surveillance and surgical resection on the basis of symptoms and (perceived) risk of malignancy: the 2015 American Gastroenterological Association (AGA)<sup>48</sup>; the International Association of Pancreatology (IAP)<sup>3</sup>; and the European Study Group on Cystic Tumors of the Pancreas (European)<sup>4</sup>. The IAP<sup>3</sup> and the European<sup>4</sup> guidelines were revised in 2017 and 2018, respectively.

As more PCN are incidentally discovered on routine cross-sectional imaging, optimal surveillance for patients with PCN is becoming an increasingly common clinical problem, highlighting the need to balance cancer prevention with the risk of (surgical) overtreatment. This Review covers the latest developments in diagnostic modalities, revised guidelines and treatment options for PCN.

### **Classification and pathology of PCN**

A pancreatic cyst is defined as a unilocular or multilocular cavity-forming neoplasm or non-neoplastic tumor-like change of the pancreas<sup>49</sup>. PCN are classified as either mucinous (IPMN or MCN) or nonmucinous cystic neoplasms (SCN, SPN and cNET)<sup>49</sup>. Mucinous PCN are lined by endoderm-derived columnar epithelium, whereas nonmucinous PCN are lined by simple cuboidal epithelium. The key demographic and clinical features of the different types of PCN are outlined in Table 1.

The WHO classification of tumours of the digestive system recommend a three-tiered system for grading dysplasia in PCN: low-grade dysplasia (LGD); borderline-grade dysplasia; and HGD<sup>50</sup>. In LGD, the neoplastic cells show minimal pleomorphism, and mitosis is rare. In borderline-grade dysplasia, nuclear pleomorphism and stratification are more pronounced, and some nuclei may begin to lose polarity<sup>50</sup>. HGD is characterized by marked architectural and cytological atypia, as well as substantial mitotic activity<sup>50</sup>. The grade of dysplasia should be determined by the highest grade of focus in the tumour, regardless of size. To improve concordance in reporting and alignment with practical consequences, a two-tiered grading system has been proposed (LGD versus HGD)<sup>51</sup>.

### Symptoms of PCN

Most PCN are incidentally discovered on cross-sectional imaging, as typical pancreatic symptoms (that is pancreatitis, jaundice and new-onset diabetes mellitus) are absent in the majority of patients with PCN. The onset of acute pancreatitis can be related to the massive production of mucin in patients with IPMN with main duct involvement. In these patients, mucin plugs can occlude the main pancreatic duct, leading to acute pancreatitis with epigastric discomfort, acute abdominal pain referred to the back and high levels of serum amylase. Of patients with IPMN, 13–35% are reported to present with (secondary) acute pancreatitis, although this incidence is based on surgical series and is likely to be overestimated<sup>17,56,57,58</sup>

Progressive inflammatory changes in the pancreas can also result in permanent structural damage, which can lead to impairment in endocrine and exocrine function. Atrophy of the pancreas secondary to main pancreatic duct obstruction and fibrosis can also lead to endocrine and exocrine pancreatic insufficiency. Extrinsic compression of the common bile duct by PCN might cause biliary outflow obstruction, leading to the onset of jaundice. In addition, jaundice can be secondary to mucin plugs in the common bile duct or direct tumor invasion. Jaundice and pancreatitis are mostly associated with advanced neoplasia, but can also occur in patients with PCN but without advanced neoplasia.

### Diagnosis of PCN

As management of PCN varies according to its type, the distinction between the different subtypes is crucial. The current work-up of newly diagnosed PCN consists of a pancreatic protocol CT or gadolinium-enhanced MRI with MRCP and, if indicated, endoscopic ultrasonography (EUS)<sup>1,2,3,4,48</sup>. The indication for EUS is implied as an adjunct to other imaging modalities if the PCN has either clinical or radiological features of concern (that is, nodules, dilatation of the pancreatic duct or a thickened enhancing wall), or to obtain cyst fluid for cytology and biochemical analysis if a more precise diagnosis might change patient management. MRI with MRCP is the preferred method for follow-up of PCN as studies have shown that repeated exposure to ionizing radiation following CT increases the risk of malignancy<sup>59,60</sup>. Although most patients accrue low radiation-induced cancer risks from cumulative CT exposures, incremental risks are estimated to exceed 1% above baseline in 7% of the scanned patients<sup>59</sup>. Furthermore, MRI with MRCP is more sensitive than CT for identifying a connection with the pancreatic duct and the presence of an enhancing mural nodule (solid component within a cyst) or internal septations<sup>26,61</sup>.

### Imaging characteristics

IPMN can be morphologically classified according to their location and extension with the ductal system as main duct (MD), side branch (SB) and mixed type (MT) (Fig. 1). MD-IPMN can be recognized by the abrupt dilation of the main pancreatic duct. In some cases, a bulging ampulla extruding thick mucin (referred to as a ‘fish-eye’ ampulla) is seen during endoscopic examination, which is virtually pathognomonic for MD-IPMN. SB-IPMN can be recognized by the dilation of side branches of the main pancreatic duct, or by a ‘grape-like’ cystic lesion that associates with the main pancreatic duct. MT-IPMN meet both criteria for MD-IPMN and SB-IPMN. IPMN occur most commonly in the head of the pancreas (70%), but 20% occur in the body or tail and 5–10% of the IPMN are multifocal<sup>62</sup>.

In contrast to IPMN, MCN typically arise in the body and tail of the pancreas and they are mostly unilocular or septated macrocystic cysts<sup>38,63,64</sup> (Fig. 1). The morphological varieties of SCN

include microcystic, macrocystic (or oligocystic), mixed microcystic and macrocystic, and solid SCN<sup>65,66</sup>. Microcystic SCN are composed of multiple small cystic spaces with a honeycomb-like appearance (Fig. 1).

A central calcification or scar can be present in SCN. Macrocystic (or oligocystic) SCN are composed of fewer, larger cysts. SCN can be unilocular; however, this variant is rare<sup>67</sup>. The appearance of macrocystic SCN can be difficult to distinguish from MCN or SB-IPMN, and solid SCN might be difficult to distinguish from SPN. SPN most commonly appear as a mixed cystic and solid mass in the pancreas, but they can also appear as a cystic mass or a calcified cystic mass<sup>68</sup>. cNET most commonly appear as a mixed cystic and solid mass in the pancreas, but they can also appear completely cystic. On imaging, heterogeneous enhancement is commonly seen in cNET owing to necrotic and hemorrhagic changes<sup>69,70</sup>.

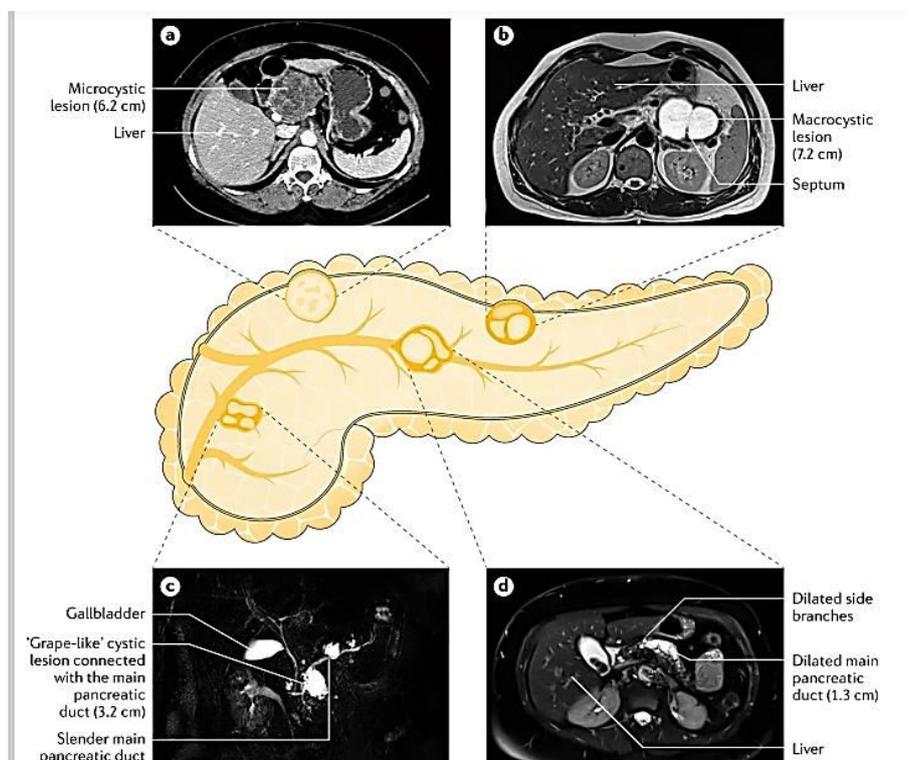


Fig (1) Examples of different types of PCN

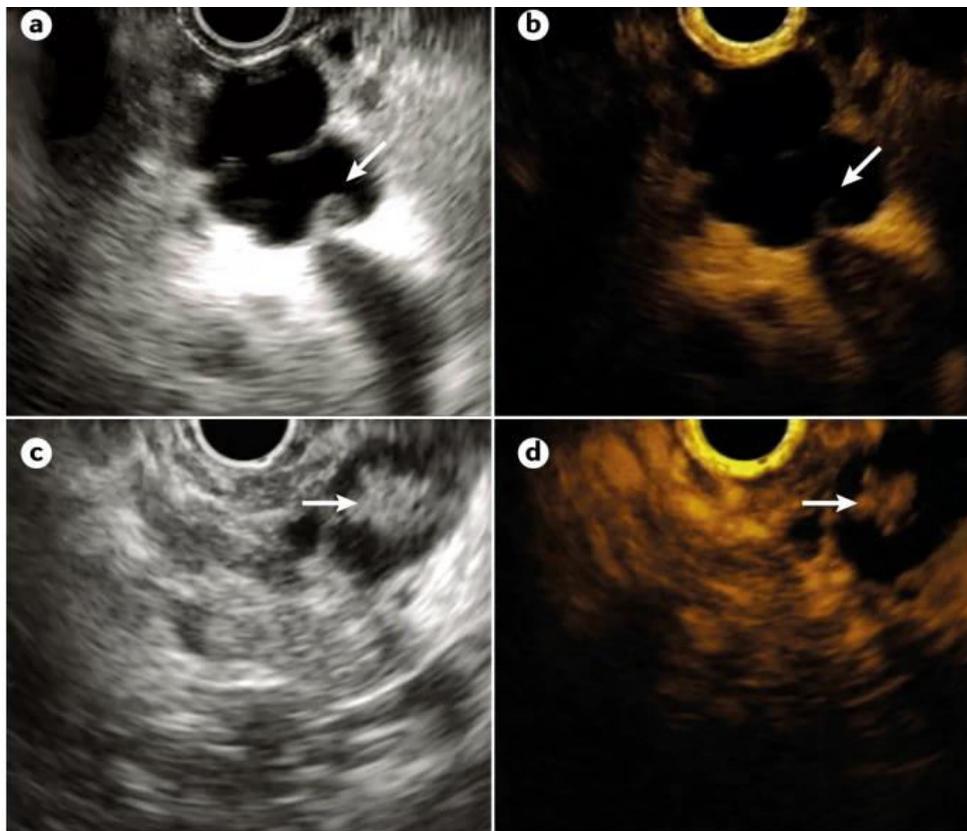
**a** | CT image showing a microcystic lesion with a diameter of 6.2 cm in the body of the pancreas. The image suggests a typical serous cystic neoplasm. **b** | MRI image showing a macrocystic lesion with a thickened wall and a septum, with a diameter of 7.2 cm in the body and tail of the pancreas. The image is suggestive of a mucinous cystic neoplasm. **c** | A magnetic resonance cholangiopancreatography image of a multifocal side branch-intraductal papillary mucinous neoplasm (IPMN). The largest cystic lesion in the pancreatic head has a diameter of 3.2 cm. No thickened wall or enhancing nodule is seen with a slender main pancreatic duct. **d** | MRI image of a dilated main pancreatic duct of 1.3 cm, with small dilated side branches and no intraductal enhancing nodules. Image suggests a mixed-type IPMN. PCN, pancreatic cystic neoplasms.

### New developments in imaging techniques

The increasing demand to improve the visualization of a connection between a pancreatic cyst and the pancreatic duct has resulted in the introduction of secretin-enhanced MRCP<sup>71</sup>. Secretin is a 27-amino acid polypeptide hormone that stimulates the release of pancreatic juice from acinar cells in the exocrine pancreas into the pancreatic ducts, leading to an increase in size and visibility of the duct<sup>72</sup>. Secretin is now available as a synthetic agent and, when given intravenously, it can improve visualization of the pancreatic duct by increasing its diameter. Several studies have suggested improved visualization of the pancreatic duct with secretin-enhanced MRCP compared with conventional MRCP<sup>71,73,74</sup>; however, more studies are needed to determine whether the addition of secretin outweighs its cost and prolonged scanning time (an extra 5–10 min).

Contrast-enhanced EUS seems the most accurate diagnostic modality for the discrimination between mural nodules and mucin clots, producing a very low rate of false negatives compared with other imaging modalities<sup>75,76,77,78,79</sup>.

Distinction between mural nodules and mucin clots or debris is clinically relevant. One meta-analysis including 70 studies with 2,297 resected IPMN reported a positive predictive value of an enhancing mural nodule on contrast-enhanced EUS of 62% for the presence of advanced neoplasia at final pathology<sup>80</sup>. To distinguish mural nodules from mucin clots, determining the presence of vascularity in mural nodules seems helpful. Contrast-enhanced EUS can characterize vascularity by detecting signals from microbubbles in vessels produced by intravenously administered contrast agents (Fig. 2). Nevertheless, EUS is an operator-dependent procedure that relies on specialist experience and ability<sup>81,82</sup>.



**Fig (2):** Contrast-enhanced EUS for discrimination between mural nodules and mucin clots. Parts **a** and **b** are representative of mucus clots. **a** | Endoscopic ultrasound (EUS) revealed a hyperechoic mural lesion in the cyst (arrow). **b** | Contrast-enhanced EUS showed no vascularity in the mural lesion (arrow). Parts **c** and **d** are representative of mural nodules. **c** | EUS revealed a hyperechoic mural lesion in the cyst (arrow). **d** | Contrast-enhanced EUS showed vascularity in the mural lesion (arrow).

**Confocal laser endomicroscopy (CLE)** is a promising modality to show differentiation between the PCN types. CLE enables real-time visualization of the PCN with microscopic detail using an endoscopic probe introduced through a 19-gauge needle used for fine-needle aspiration (FNA)<sup>83,84</sup>. The findings highly specific for SCN are a ‘superficial vascular network’ or ‘fern pattern’<sup>85,86</sup>. For IPMN, characteristic findings include finger-like papillae, whereas for MCN characteristic findings include single or multiple layers of epithelium without a papillary configuration (epithelial bands)<sup>87,88,89</sup>.

Although the interpretation of CLE is challenging, clinical trials have reported promising results with respect to its diagnostic accuracy for the differentiation between PCN types (71–94%)<sup>83,84,85,87,89</sup>. However, the reported rates (3.2–9.0%) of adverse events (for example, pancreatitis or intracystic hemorrhage) remain a concern<sup>83,84,85,87</sup>.

### Cyst fluid analysis

In PCN, EUS–FNA enables cytopathological examination, identification of extracellular mucin, biochemical analyses and analysis of molecular biomarkers<sup>90</sup>. EUS–FNA is a safe procedure with a low risk of complications of 2–3%<sup>4,91</sup>. Potential complications are abdominal pain, infection, intracystic bleeding or pancreatitis. Antibiotic prophylaxis is commonly used for EUS–FNA of pancreatic cystic neoplasms; however, this approach is based on longstanding clinical practice and is not evidence based<sup>91</sup>. Needle tract seeding is extremely rare with EUS-guided sampling; therefore, the risk of peritoneal metastases is not increased<sup>92</sup>.

At the macroscopic level, the string sign is the most informative indicator to differentiate between mucinous and nonmucinous PCN, as mucinous PCN usually contain highly viscous cyst fluid<sup>93,94,95,96</sup>. The string sign consists of placing a drop of cyst fluid aspirate between the thumb and index finger and stretching it; a string length >3.5 mm indicates a mucinous PCN<sup>94</sup>, with pooled sensitivity and specificity of 58% and 95%, respectively<sup>94,95</sup>. Limitations of the string sign include the subjective assessment of the test results.

Cyst fluid obtained during EUS–FNA is often acellular and, therefore, not particularly useful for cytopathological examination. One meta-analysis of cytopathological cyst fluid analyses for differentiation between mucinous and nonmucinous PCN reported a sensitivity of 54% and specificity of 93%<sup>35</sup>. However, when able to detect mucin-containing advanced neoplasia by FNA, cyst fluid cytology adds to the specificity and negative predictive value of EUS–FNA and can be of considerable value<sup>97,98,99</sup>.

Over the past 5 years, a through-the-needle forceps device has been introduced as a novel approach for EUS-guided tissue acquisition<sup>100</sup>. These microforceps, with an outer diameter of <1 mm, can be passed through a standard 19-gauge EUS needle to obtain samples of the cyst wall and/or mural nodule for histological assessment, which might improve diagnostic accuracy.

However, experience with this sampling technique is limited to case reports and small pilot studies, and therefore this technique remains investigational<sup>100,101,102,103</sup>.

Among biochemical analyses performed on pancreatic cystic fluid, the quantification of levels of the tumor marker carcinoembryonic antigen (CEA) is the most useful for differentiation between mucinous and nonmucinous PCN<sup>35,90</sup>. CEA is a glycoprotein found in the embryonic endodermal epithelium. The rationale for using CEA levels to differentiate mucinous and nonmucinous cysts is that mucinous cysts are lined by endoderm-derived columnar epithelial cells capable of secreting CEA, whereas nonmucinous cysts are lined by simple cuboidal epithelium (not derived from endoderm) and should contain little or no CEA<sup>104</sup>. The internationally accepted cut-off value of CEA, as advised in the current 2017 IAP<sup>3</sup>, 2017 European Society of Gastrointestinal Endoscopy<sup>90</sup> and 2018 European<sup>4</sup> guidelines, is 192 ng/ml. This cut-off value is based on a prospective study with only 112 patients<sup>105</sup>. A systematic review published as an Abstract in 2018 with individual patient data meta-analysis, however, showed an optimal cut-off value of 20 ng/ml with sensitivity and specificity of 91% and 93%, respectively<sup>106</sup>.

An additional biomarker in the differentiation of PCN subtypes is amylase. An elevated level of amylase in cyst fluid strongly suggests a connection between the cyst and the pancreatic ductal system (that is, IPMN and pseudocysts); however, amylase levels can also be elevated in MCN<sup>107,108</sup>.

Pancreatic cyst fluid glucose levels have also been described as a potential biomarker for mucinous PCN, with similar diagnostic accuracy to the standard CEA, amylase and cytology tests but with improved efficiency<sup>109,110,111</sup>.

Glucose testing might have several distinct advantages in that it is simple, rapid, inexpensive and requires minimal cyst fluid. Confirmatory evidence is lacking; hence, this marker should be further investigated in large, prospective, multicenter trials.

DNA testing of pancreatic cyst fluid seems a promising adjunct for the differentiation between mucinous and nonmucinous PCN, between mucinous PCN subtypes (IPMN versus MCN) and between premalignant PCN and advanced neoplasia<sup>112</sup>.

Mutated genes are released into pancreatic cyst fluid after cell death and have high potential to serve as biomarkers. Mutations detected in *KRAS* and/or *GNAS* are highly sensitive and specific for IPMN, but not for MCN<sup>113</sup>. A prospective study including 102 patients with surgical pathology reported 89% sensitivity and 100% specificity for the detection of *KRAS* and/or *GNAS* mutations in IPMN and MCN<sup>113</sup>. *KRAS* and/or *GNAS* mutations were detected in 100% of the patients with IPMN and in 30% of the patients with MCN. Although mutations in *KRAS* are common in MCN, the prevalence of these mutations is reported to increase with the severity of dysplasia<sup>113,114</sup>.

Among the 102 patients in the earlier mentioned study, *KRAS* mutations were detected in 13% of the patients with LGD MCN and 100% of those with HGD MCN<sup>113</sup>. Mutations in *GNAS* are not detected in MCN and, if present, could be useful to discriminate between IPMN and MCN. *VHL* mutations or deletions are associated with SCN<sup>112,114,115,116</sup>. Mutations or deletions in *SMAD4*, *CDKN2A*, *TP53*, *PIK3CA* and/or *PTEN* are associated with advanced neoplasia<sup>117,118,119,120,121,122,123</sup>. A prospective study including 102 patients with surgical pathology found the combination of *KRAS* or *GNAS* mutations and alterations in *TP53*, *PIK3CA* or *PTEN* had 89% sensitivity and 100% specificity for advanced pancreatic neoplasia<sup>113</sup>. Further studies, however, are still required to explore the integration of DNA-based molecular testing in pancreatic cyst fluid into current management guidelines.

## Conclusion

Despite the promising results of numerous experimental and clinical studies, no definitive strategy for the differentiation between the various types of PCN and for neoplastic grading is available. Thus, patients should be discussed by a multidisciplinary team in centers with expertise in diagnosis (imaging, endoscopy, pathology) and surgical treatment of PCN. Future studies should examine the optimal diagnostic strategy for PCN (cyst type and neoplastic grade), appropriate selection criteria for surgery (absolute and relative indications), surgical strategy (for example, partial or total pancreatectomy), and follow-up strategy (modality and interval) for both operated and nonoperated IPMN and other PCN. **Conflict of Interest:** No conflict of interest.

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