



Review

Conditions at risk of pancreatic cancer: The radiology perspective

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ARTICLE INFO

Keywords:

Pancreatic Ductal Adenocarcinoma
Pancreatic Neoplasms
Computed Tomography
Magnetic Resonance Screening
Cancer Screening

ABSTRACT

Pancreatic cancer remains one of the most aggressive cancer worldwide, with pancreatic ductal adenocarcinoma being the most common malignant pancreatic lesion, associated with poor prognosis. While surgical resection is the only curative treatment, only a minority of patients is eligible for surgery due to its diagnosis at advanced stages. Therefore, strategies for early detection of pancreatic cancer are needed. This article aims to provide a state-of-the-art review of the most common conditions associated to an increased risk of pancreatic cancer. Conditions linked to risk of pancreatic cancer development include certain pancreato-biliary anatomical variants, intraductal papillary mucinous neoplasms, mucinous cystic neoplasm, and familial pancreatic cancer with specific genetic mutations. Early imaging signs of pancreatic cancer can also be incidentally encountered on CT or MRI performed for other indications and they should be promptly recognized by the radiologists in order to avoid delays in the diagnosis. The features include focal pancreatic atrophy, contour deformity, dilation of the main pancreatic duct (MPD), changes in the caliber of the MPD, abrupt interruption of the MPD, and biliary tree dilation. MRI with the adoption of abbreviated protocols has been increasingly evaluated for the follow-up of cystic lesions. Although screening of the general population is not recommended due to the low incidence and high costs, surveillance with MRI can be considered in selected high-risk individuals.

1. Introduction

Pancreatic cancer is the 14th most common cancer worldwide by incidence, but it is ranked in the 7th place of all cancer-related deaths, with an increased incidence trend in the recent years [1]. The 5-year survival rate is estimated to be 9 % in all stages, and it markedly decreases to 3 % in patients with advanced pancreatic cancer [2]. Pancreatic ductal adenocarcinoma (PDAC) is the most common malignant lesion, accounting for about 90 % of pancreatic cancers [3]. Surgical resection is the only curative treatment for pancreatic cancers, which can be combined with neoadjuvant and adjuvant chemotherapy, but only a minority of patients are eligible for surgery due to the presence of vascular infiltration or distant metastasis at the time of the diagnosis [4]. To improve survival, it is crucial to identify pancreatic cancer at early stages, ideally before the development of clinical

symptoms, which are often delayed and related to the infiltration of adjacent structures or distant metastases.

Imaging plays a crucial role in the identification of early signs of pancreatic cancer, follow-up of premalignant lesions, and surveillance of patients at high risk of developing pancreatic cancer. Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) are routinely performed in clinical practice for the diagnosis and follow-up of pancreatic lesions. Several conditions, including genetic mutations, certain pancreatobiliary anatomical variants, and lesions such as intraductal papillary mucinous neoplasms (IPMNs) or mucinous cystic neoplasm (MCNs), can be considered at risk of pancreatic cancer development. Furthermore, it is important to recognize the early imaging signs of pancreatic cancer on CT or MRI performed for other indications, in order to avoid delays in the diagnosis.

This article aims to provide a state-of-the-art review of the most

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<https://doi.org/10.1016/j.ejrad.2025.112119>

Received 10 November 2024; Received in revised form 28 March 2025; Accepted 15 April 2025

Available online 17 April 2025

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common conditions associated with an increased risk of pancreatic cancer, discussing the differential diagnosis, imaging features suggesting malignancy, future strategies for screening, and reporting recommendations.

2. Early imaging signs of pancreatic cancer

Diagnosis of pancreatic cancer is often made at advanced stages in clinical practice due to nonspecific clinical presentation, which leads to delayed diagnosis with locally advanced or metastatic lesions. Early detection and diagnosis of pancreatic cancer remains a significant challenge for the radiologists interpreting abdominal imaging. Contrast-enhanced CT and MRI are the two main imaging modalities for the diagnosis and local staging of PDAC [5]. While these two imaging

modalities have comparable performance in the detection of larger pancreatic lesions, early detection of PDAC can be particularly tricky on CT as about 5–10 % of all PDACs are isoattenuating on CT, being most commonly lesions smaller than 3 cm [5,6]. Isoattenuating pancreatic cancers have been reported more commonly in well-differentiated tumors compared to moderately-to-poorly differentiated tumors, and they were associated with better prognosis [6,7]. A study by Choi et al [8] demonstrated that MRI provided a significantly higher sensitivity in the detection of solid pancreatic lesions and better lesion conspicuity compared CT.

Secondary signs of pancreatic cancer (Fig. 1), especially PDAC, can be observed in contrast-enhanced studies and should be carefully checked by radiologists (Table 1) [7]. About 50 % of early signs can be missed in clinical practice, especially in imaging studies acquired for

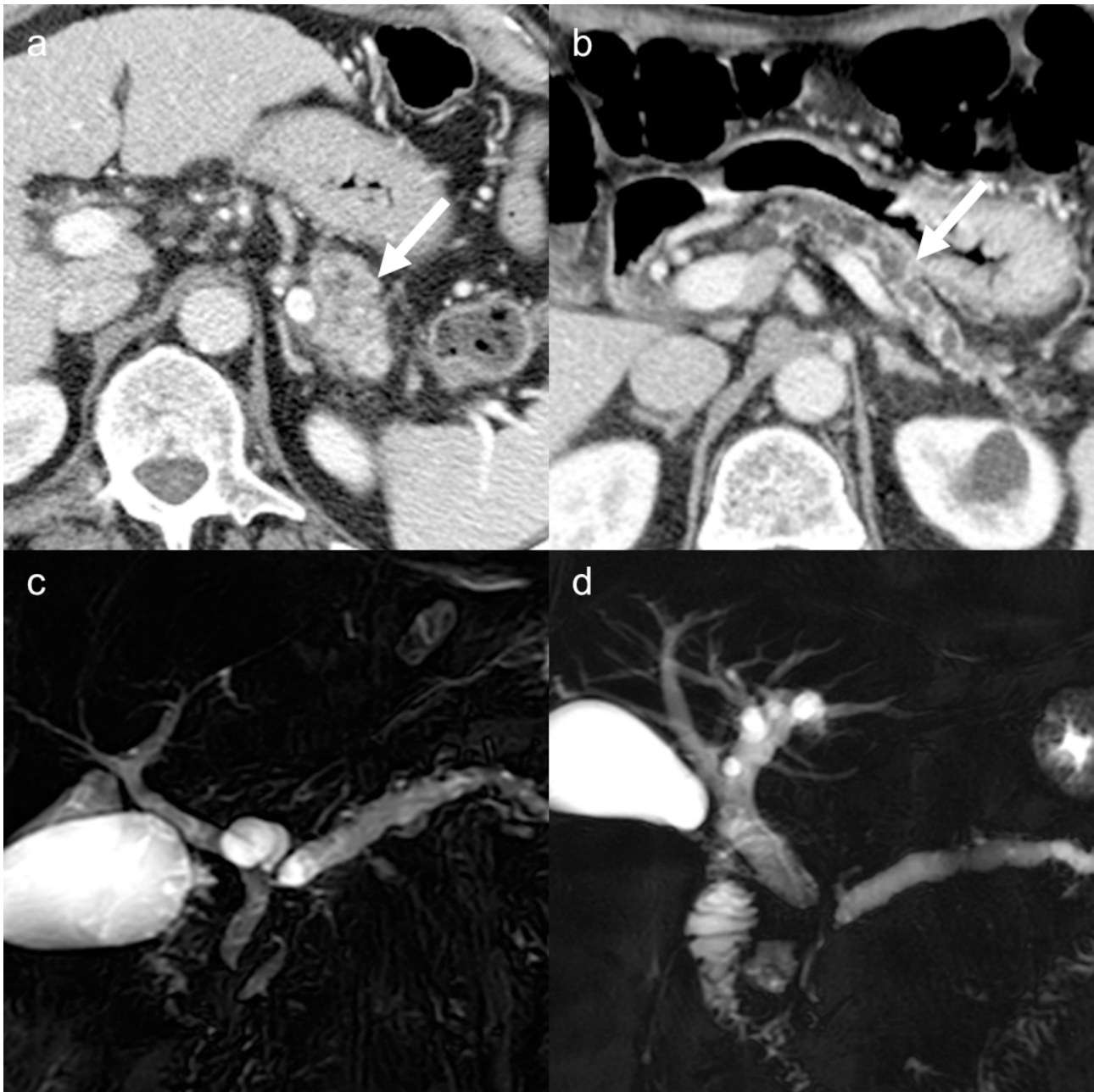


Fig. 1. (a) 70-year-old male with early pancreatic cancer in the tail showing contour deformity (arrow) with loss of the normal pancreatic lobulation. (b) 74-year-old male with pancreatic cancer manifesting with atrophy of the pancreatic body and tail (arrow) associated with dilation of the main pancreatic duct. (c) 75-year-old female with early pancreatic cancer associated with abrupt cutoff of the main pancreatic duct and upstream dilation. (d) 90-year-old male with simultaneous dilation of the main pancreatic duct and common bile duct (“double duct sign”) due to pancreatic ductal adenocarcinoma.

Table 1

Most commonly observed early imaging signs associated with pancreatic cancer diagnosis.

Imaging sign	Definition
Abrupt cutoff of the MPD	Abrupt interruption or narrowing of the MPD with or without upstream dilation
Contour deformity	Loss of the normal pancreatic lobulation
Dilation of the MPD	MPD size > 3 mm
Distal pancreatic atrophy	Atrophy of the pancreatic parenchyma distal to the tumor
Double duct sign	Simultaneous dilation of the MPD and bile duct
Focal faint parenchymal enhancement	Poorly demarcated enhancing area on portal venous phase
Focal pancreatic atrophy	Focal narrowing of the pancreatic parenchyma in comparison with the rest of the gland
Loss of fat planes	Loss of normal perivascular fat planes

Abbreviation: MPD, Main Pancreatic Duct.

other clinical indications [9,10]. Among these accessory signs, main pancreatic duct (MPD) dilation has been reported as the most common one, being observed in about 61 % of early PDAC (Fig. 2) [11]. Missed imaging findings of PDAC have been related to lesions smaller than 2 cm, isoattenuating PDAC and non-contours deforming tumors [11]. Occasionally, early PDAC can manifest with signs of acute pancreatitis due to the stenosis of the MPD or with cystic changes secondary to tumoral necrosis [12].

Recent studies investigated imaging signs and pancreatic abnormalities that can precede the diagnosis of PDAC [13–16]. A study by Toshima et al analyzed early abnormalities on CT examination performed at least one year before the diagnosis of PDAC, reporting focal pancreatic abnormalities in 53 % of patients before the diagnosis of PDAC [13]. Notably, the most common abnormalities were pancreatic atrophy, faint enhancement, and MPD caliber change [13]. Miura et al [14] observed a focal pancreatic atrophy in the location of the subsequent tumor in about 32 % of patients on CT studies acquired between 6 months and one year before the diagnosis of PDAC. Pancreatic fat infiltration on pre-diagnosis CT was also reported as an independent risk factor for the development of PDAC [15,16]. Therefore, radiologists should suggest further investigations, including MRI and endoscopic ultrasound, if any of these signs are detected on imaging, especially for newly appearing pancreatic abnormalities.

3. Pancreatic and biliary variants

Some pancreatic and biliary anatomical variants have been associated with the increased risk of developing pancreatic cancer, with variable frequency in the literature. The two most common congenital disorders of the pancreas are the *pancreas divisum* and the annular pancreas [17].

Pancreas divisum is an anatomical variant of the pancreas that occurs during fetal development, defined as a failure in fusion between the dorsal and ventral portion of the gland. During fetal life, two ducts develop: the MPD and the accessory pancreatic duct. In a typical human embryo, the pancreas forms from two separate buds, and they eventually fuse to create a single, functioning organ. In the case of *pancreas divisum*, this fusion does not occur, resulting in the pancreas remaining divided into two distinct parts with two distinct ducts, clearly recognizable, in which the dorsal duct drains the majority of the pancreas through the minor papilla (Fig. 3). This condition is relatively common and occurs in about 5–10 % of the population [18]. *Pancreas divisum* is usually asymptomatic. However, in some cases, it can lead to complications such as recurrent pancreatitis and abdominal pain [19]. The noninvasive reference standard imaging technique to diagnose *pancreas divisum* is MRI with MR cholangiopancreatography (MRCP) sequences, while the invasive one is endoscopic retrograde cholangiopancreatography (ERCP). Both techniques can demonstrate the typical crossing duct sign. A study published in 2014 [18] enrolled 995 healthy subjects who

underwent MRCP to evaluate pancreatic abnormalities. The Authors found that normal pancreatic duct variants were observed in 90.4 %, while *pancreas divisum* in 9.6 %. They also concluded that morphological signs of chronic pancreatitis or restriction of pancreatic exocrine function were not associated with pancreatic duct variants, and no increased risk of pancreatic cancer was reported.

The second most important pancreatic abnormality that needs to be recognized at imaging is the annular pancreas, a rare congenital condition. In this case, a ring or band of pancreatic tissue develops around the duodenum, partially or completely encircling it. This abnormality occurs during fetal development when the pancreas does not rotate properly and does not coalesce in its normal position [20]. The presence of a ring-shaped pancreas may be associated with duodenal obstruction, pancreatitis, and endocrine or exocrine insufficiency, but there is no evidence supporting an association with PDAC. CT and MRI can demonstrate an enlarged pancreatic head encasing the second duodenal segment (Fig. 4). Moreover, MRI can help solve the differential diagnosis of ectopic pancreatic tissue thanks to its intrinsic evaluation of tissue signals. The ectopic pancreas encircling the duodenal wall should present a signal analogous to the other portions of the pancreas, without diffusion restriction and homogeneous enhancement during dynamic imaging [21].

Other important variants regarding the pancreaticobiliary junction include 1) pancreaticobiliary maljunction (PBM), 2) congenital dilations of the bile ducts (i.e. choledochal cysts and choledochal diverticulum), and 3) low insertion of the cystic duct into the common hepatic duct.

PBM is a congenital malformation in which the bile duct and pancreatic duct converge outside the duodenal wall with a common channel length > 8 mm in adults [22]. It has been suggested that this anomaly may lead to the reflux of pancreatic enzymes into the common bile duct, increasing the risk of cancer [22]. Although CT may raise suspicion of PBM, the most accurate noninvasive imaging technique is MRI with MRCP (Fig. 5) [23]. The Japanese Study Group on Pancreaticobiliary Maljunction proposed a new PBM classification based on the formation of the pancreatic-biliary junction [24]. This new classification divides PBM into the following four types: (a) stenotic type, in which the distal common bile duct with stenosis joins the common channel; (b) non-stenotic type, in which the distal common bile duct without stenosis joins the common channel, (c) dilated channel type, in which the common channel is dilated, and (d) complex type, in which the PBJ has formed in a complicated configuration [24].

Anomalous dilations of the bile ducts can occur as a result of different congenital or acquired conditions. After ruling out the potential of a tumor, stone, or inflammation as the source of the dilation, a choledochal cyst can be diagnosed based on the disproportional dilation of the extrahepatic bile ducts. Todani classification [25] is widely used in the case of congenital dilations of the bile ducts. In particular, bile duct cysts are classified into 5 types, based on the site: Type I: a fusiform dilation of a portion or entire common bile duct; Type II: isolated diverticulum of the common bile duct; Type III (choledochocoele): dilation of duodenal portion of common bile duct; Type IV: multiple dilations of the intrahepatic and extrahepatic biliary tree (a) or only the extrahepatic bile ducts (b); Type V (Caroli's disease): cystic dilations of intrahepatic biliary ducts. MRCP is a useful, noninvasive tool that shows good overall accuracy in the detection and classification of choledochal cysts [26]. Furthermore, whereas the ERCP may not be able to delineate these structures in patients with choledochal cysts due to the likelihood of the tight structure in the distal region of the cyst, the MRCP can concurrently and easily delineate both the biliary and pancreatic duct structure.

Finally, the anatomy of the cystic duct should be studied, especially in case of low insertion into the common hepatic duct. In these cases, MRCP shows the cystic duct joining the common hepatic duct at its lower third [27]. An important study published in the literature aimed to evaluate the risk of cancer in patients with low insertion of the cystic duct [28]. The Authors, by evaluating 860 pre-operative MRI

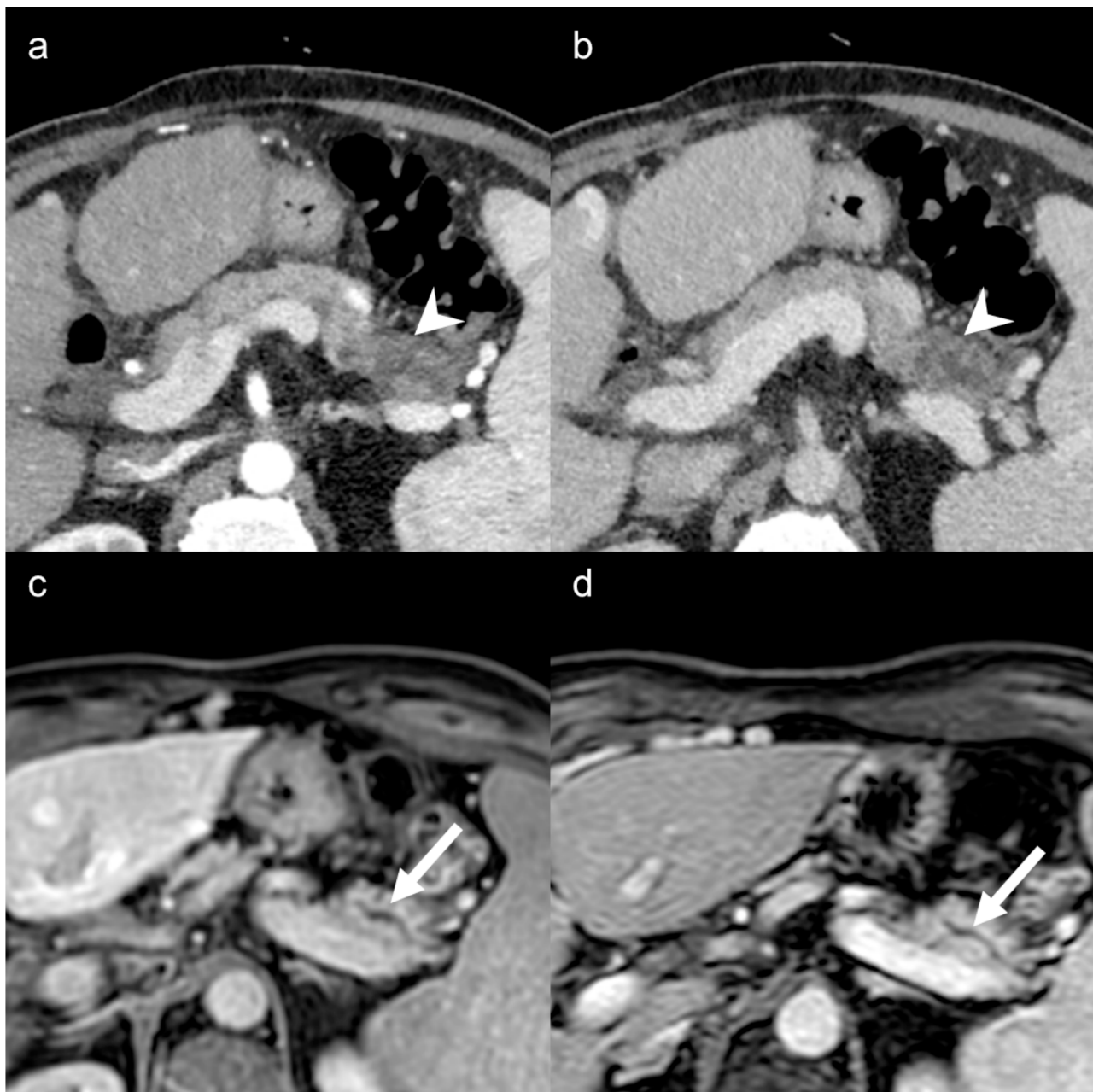


Fig. 2. 75-year-old male with pancreatic ductal adenocarcinoma in the tail. Contrast-enhanced CT on arterial (a) and portal-venous (b) phases show a hypovascular pancreatic lesion in the tail (arrowheads). Contrast-enhanced MRI acquired 12 months (c) and 18 months (d) before demonstrated focal dilation of the main pancreatic duct (arrows).

examinations, demonstrated that the low-union, seen < 10 % of the population, was present in 44 % of *peri*-ampullary cancers (73 % distal bile duct/cholangiocarcinoma, 42 % pancreatic head, and 34 % ampullary) [28].

4. Intraductal papillary mucinous neoplasms

IPMNs are the most frequently identified pancreatic cystic lesions, representing up to 82 % of pancreatic cystic lesions in cohort studies [29,30]. They are characterized by cystic dilation of the MPD and/or secondary ducts, papillary growth within the pancreatic ductal system and thick mucus secretion. In the 1970 s and the 1980 s, the first few cases of IPMN were described. However, in the 1990 s the term IPMN was coined and the tumor was defined as a specific entity among the cystic pancreatic tumors [31]. The incidence of IPMN has progressively

increased all over the world since the initial reports, but this may reflect the combination of the widespread use of cross-sectional imaging, its classification, and the progress in confidence of recognition of the pathology.

The majority of patients with IPMN with inactive mucin production or involvement of the body/tail of the pancreas are asymptomatic, representing an incidental finding in abdominal imaging. Nevertheless, some patients can present with abdominal symptoms, obstructive jaundice, acute pancreatitis, or new onset of diabetes.

The risk of IPMN for undergoing malignant transformation is well known since they will follow the dysplasia-carcinoma sequence [32]. Histologically, IPMNs can present low-grade dysplasia (adenoma), intermediate-grade dysplasia (borderline), high-grade dysplasia (carcinoma in situ), and associated infiltrating carcinoma [33]. Morphological subtypes include gastric, intestinal and pancreatobiliary subtypes, with

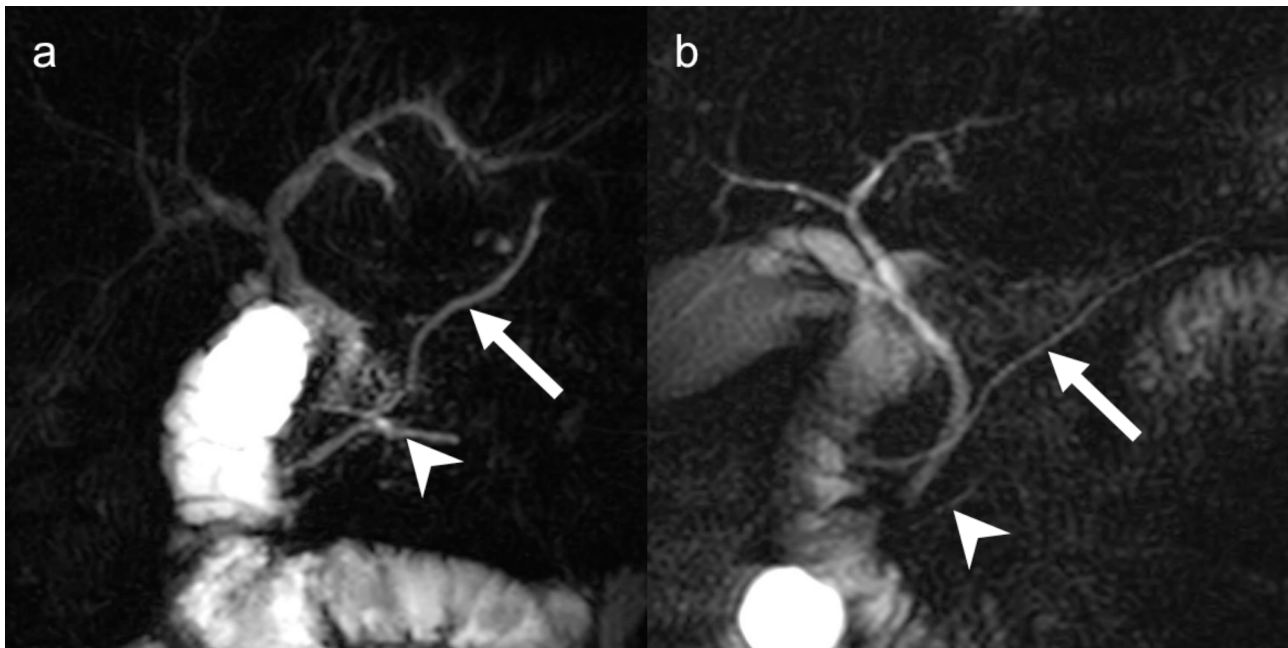


Fig. 3. Examples of variants of pancreas divisum depicted on MRCP. In both types, the main pancreatic duct drains into the minor papilla. Incomplete pancreas divisum (a) is characterized by a connection between the accessory (arrowhead) and the main pancreatic duct (arrow). In contrast, in complete pancreas divisum (b) there is no connection between the accessory (arrowhead) and the main pancreatic duct (arrow).

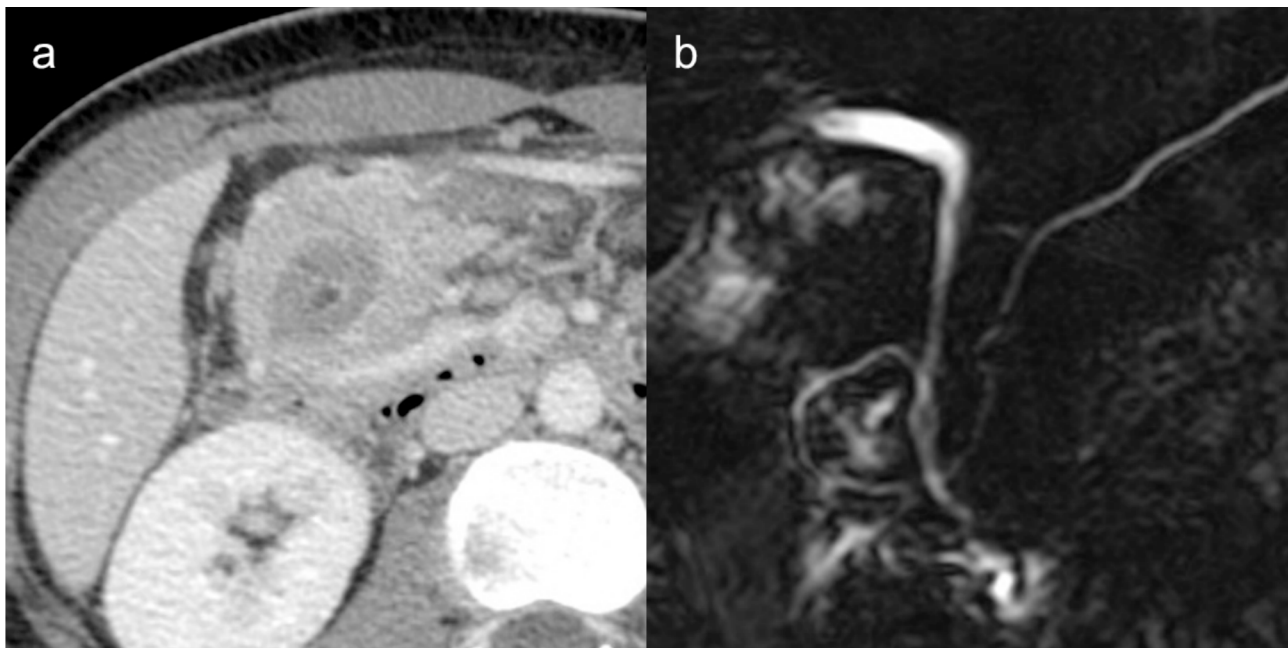


Fig. 4. 48-year-old male with annular pancreas. Contrast-enhanced CT (a) show the pancreatic parenchyma surrounding the second segment of the duodenum. MRCP (b) demonstrates the main pancreatic duct encircling the duodenum.

the latter being associated with highest risk of malignancy [33].

On the basis of the type of pancreatic ductal system involvement, IPMNs are classified into three main types: branch duct type (BD-IPMN), when a cystic dilation of the branch duct is present (Fig. 6); main duct type (MD-IPMN), when there is progressive dilation of the MPD, that can be diffuse or focal; and combined type (MIXED-IPMN), in presence of dilation of both branch and main pancreatic ducts (Fig. 7). Main duct and mixed-type IPMNs have a higher malignant potential than BD-IPMNs, which usually have a more indolent benign course [34,35]. In a recent review by Tanaka et al, noninvasive and invasive carcinomas

were reported in about 20 % and 40 % of MD-IPMNs as compared with 10 % and 13 % in BD-IPMNs, respectively [36]. Main-duct and mixed-type IPMNs had an approximately 80 % malignancy rate at a 10-year follow-up in a retrospective study by Han et al. [37].

MRI with MRCP is considered as the primary imaging modality in detecting and evaluating IPMNs. The ductal system and its communication with cystic lesions are better appreciated on MRI [38]. Furthermore, pancreatic MRI with MRCP is the preferred method for follow-up of IPMNs and, in particular, for BD-IPMNs [38].

In a retrospective study, Boraschi et al evaluated the long-term



Fig. 5. 43-year-old female affected by choledochocoele. MRI (a, b) shows a well-circumscribed round-shaped dilation of the main biliary duct consistent with choledochocoele complicated by choledocholithiasis. On MRCP (c) it is possible to evaluate the presence of a pancreaticobiliary maljunction with the common bile duct draining into the main pancreatic duct (arrow).

outcome of MRI in assessing the evolution of individuals with BD-IPMN without worrisome features and/or high-risk stigmata at the time of the diagnosis with a follow-up of at least 10 years [39]. Their data confirmed the low risk of pancreatic cancer development in patients with BD-IPMN with a 2.9 % incidence of pancreatic cancer; moreover, worrisome features and high-risk stigmata were promptly identified during the follow-up, supporting the utility of surveillance MRI protocol [39]. In a large long-term study of 1404 consecutive patients with a diagnosis of BD-IPMN, the authors found a 5-year incidence rate of pancreatic malignancy of 3.3 %, reaching 6.6 % at 10 years, and 15.0 % at 15 years [40]. These data highlight a low, but concrete risk of developing malignancy of BD-IPMN that increases over the time.

Current international consensus guidelines for management and follow-up of IPMNs have been continuously modified and revised [38,41–43], with some disagreements among them [44]. According to the most recent Kyoto guidelines, high-risk stigmata and worrisome features have been updated [43]. High-risk stigmata are: jaundice in a patient with cystic lesion; enhancing mural nodule ≥ 5 mm or solid component; MPD ≥ 10 mm; and suspicious or positive results on cytology. Worrisome features on imaging are: cyst ≥ 30 mm; enhancing mural nodule < 5 mm; thickened/enhancing walls; MPD of 5–9 mm; MPD abrupt interruption; lymphadenopathies; cyst growth ≥ 2.5 mm per year.

According to the most recent European Guidelines, MRI with MRCP should be used for diagnosis and follow-up, whereas endoscopic ultrasound should be performed in selected cases (IPMN with possible surgical indication) [38,43]. The presence of jaundice, positive cytological specimen for high-grade dysplasia or cancer, the presence of a contrast-enhancing mural nodule (≥ 5 mm) or solid mass, and MPD ≥ 10 mm are considered absolute indications for surgery in the European Guidelines [38]. Growth rate ≥ 5 mm/year, increased serum CA 19.9 level, MPD diameter between 5 and 9.9 mm, cyst diameter ≥ 4 cm, symptoms (new-onset of diabetes mellitus or acute pancreatitis), and contrast-enhancing mural nodules are reported as relative indications for surgical resection in European Guidelines [38]. Cyst < 4 cm without absolute/relative surgical indications can undergo surveillance.

Overall, independently from different guidelines, suspicious radiological signs for a malignant transformation can be considered the presence of mural nodules (> 5 mm), the size of the lesion (greater than 30–40 mm), MPD dilation (> 10 mm), MPD abrupt interruption, and enlargement of the lymph nodes.

In agreement with current IPMN management guidelines, Del Chiaro et al. found MPD dilation, even between 5 mm and 9.9 mm, as the single best predictor of high-grade dysplasia or invasion, highlighting the

critical role that MPD plays in the selection of surgical candidates [45].

Various authors have also focused on the diagnostic performance of diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) values in the differentiation of benign and malignant IPMNs [46,47]. In a recent meta-analysis of 307 patients, Xu et al demonstrated that DWI had a considerable potential and value in this differential diagnosis, with DWI section thickness and imaging parameters influencing diagnostic specificity [46]. ADC value may also be useful for identifying malignant transformation of IPMNs since the ADC of benign IPMNs (mean $2.79 \times 10^{-3} \text{ mm}^2/\text{s}$) was significantly higher than that of malignant ones (mean $1.83 \times 10^{-3} \text{ mm}^2/\text{s}$) [47].

In daily clinical practice, the management of IPMNs, and in particular of BD-type, is particularly challenging because of the need to balance the low but concrete risk of developing malignancy over time versus the costs and discomfort of prolonged follow-ups as well as the risk of overdiagnosis and overtreatment in patients with low grade dysplasia manifesting with worrisome features. Abbreviated MRI protocols have been proposed and seem to be effective in the surveillance of IPMNs. Potential advantages include shorter imaging time, no need for intravenous injection of contrast media, decreased cost, and better patient tolerance [48–50]. In a recent study, Morelli et al. have also proposed a follow-up strategy of image-based surveillance with ultrasound and restricted use of MRI [51]. Despite the known limitations of ultrasound examination of the pancreas, ultrasound could be a safe complementary approach to MRI in selected cases, delaying and reducing the numbers of second-level examinations and therefore reducing the costs.

5. Mucinous cystic neoplasms

Pancreatic mucinous cystic neoplasms (also reported as mucinous cystadenomas) are rare and encountered almost exclusively in women, with a peak in the fifth decade of life and account for around 8 % of cystic pancreatic lesions in pathologically proven cohorts [43,52].

MCNs are characterized by the presence of mucinous secreting columnar epithelium surrounded by ovarian stroma, which differentiates it from IPMN [53]. MCN may be discovered fortuitously on imaging or may be associated with symptoms mainly including abdominal pain and rarely fatigue, weight loss, or pancreatitis [54].

The main radiological features of MCN include a round solitary cystic lesion, typically located in the posteroinferior portion of the body-tail junction [55]. The cyst shows a thick peripheral wall that can also present contrast enhancement, especially on MRI [56]. The radiological appearance of the cyst depends on its content. Most commonly, the

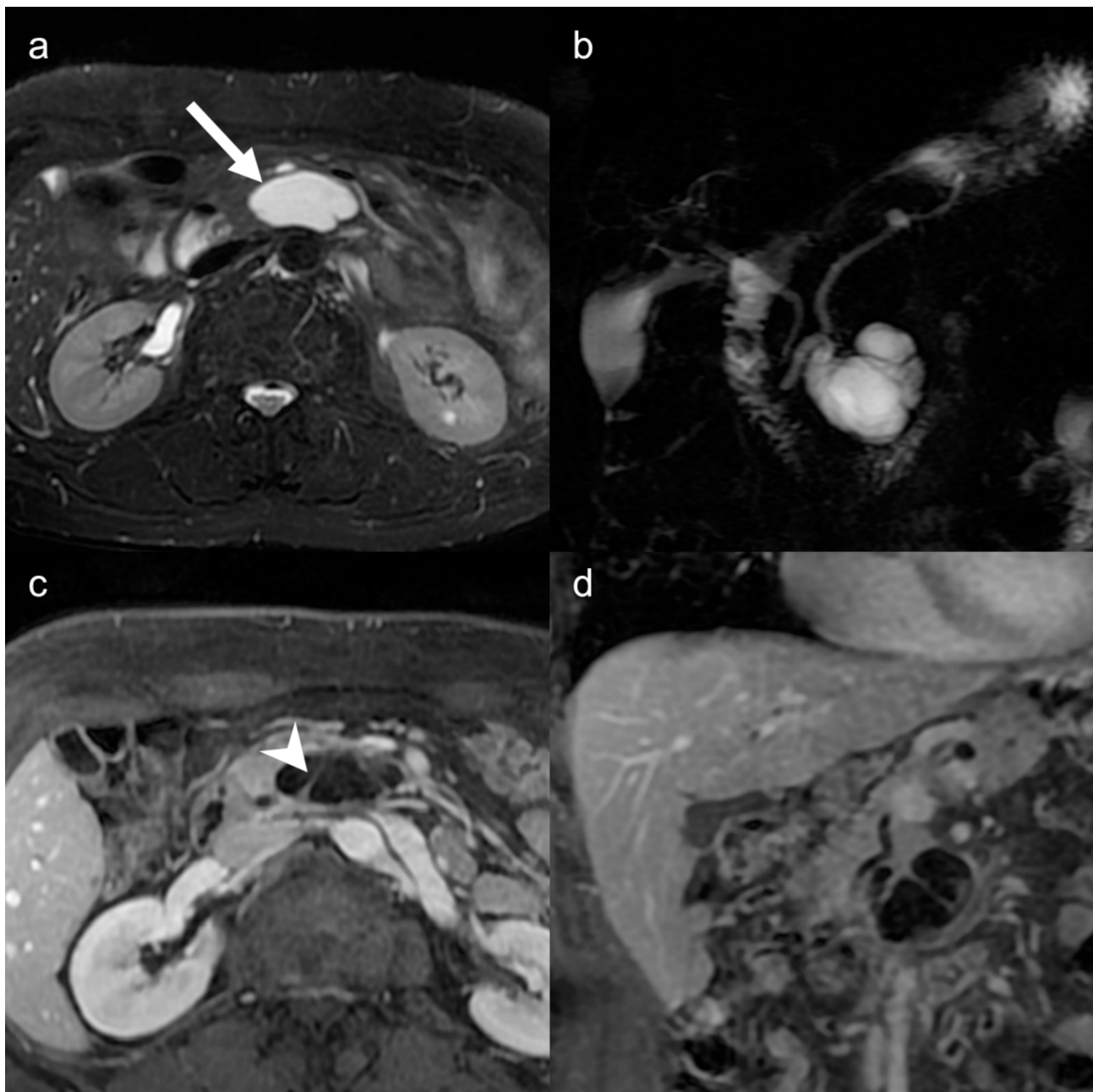


Fig. 6. Branch-duct IPMN in a male patient. MRI on axial T2-weighted image (a) and MRCP (b) show a cystic lesion in the pancreatic head (arrow) in connection with the main pancreatic duct. Internal enhancing septa are observed on axial (c) and coronal (d) post-contrast images (arrowhead).

appearance is of simple fluid, with a homogenous hypoattenuation on CT, homogeneous low T1 signal intensity, and homogeneous high T2 signal intensity on MRI. Nevertheless, the T1 signal may be modified by the proteinaceous content of the mucin or intralesional hemorrhage thus frequently leading to an iso- or hyperintense T1 signal [56]. The MCN can also have internal septa, giving the lesion a multilocular appearance, while peripheral wall or septal calcifications, which can be identified on CT, may be seen in up to 25 % of cases [57].

The combination of typical location, radiological appearance, and demographic features usually allows the radiologists to suggest the diagnosis of MCN, but some differential diagnoses should be considered. The absence of communication with the MPD as well as the solitary appearance of the cyst are the main features that allow the differential diagnosis with a BD-IPMN. The history of acute pancreatitis, as well as the cyst localization, are important features in distinguish MCN from

pancreatic pseudocyst or walled-off necrosis. In some cases, the noninvasive differential diagnosis between MCN and other solitary cystic lesions of the pancreas including oligocystic serous cystadenoma, cystic neuroendocrine tumor, and solid pseudopapillary tumor may be challenging [58]. The predominant enhancement in the arterial phase and positivity to somatostatin targeting PET-CT usually allows to differentiate MCNs from cystic neuroendocrine tumors [59]. The presence of a fibrous thick hypointense T2-weighted signal and prominent extensive calcifications on CT can suggest the diagnosis of solid pseudopapillary neoplasm over MCN [60].

MCN has the potential for malignant transformation (Fig. 8). In a surgical cohort of 163 patients with MCN (defined by the presence of ovarian stroma), 12 % had invasive carcinoma and 5.5 % had carcinoma in situ [54]. Besides the invasion of adjacent structures, the presence of enlarged lymph nodes and the presence of distant metastases that are

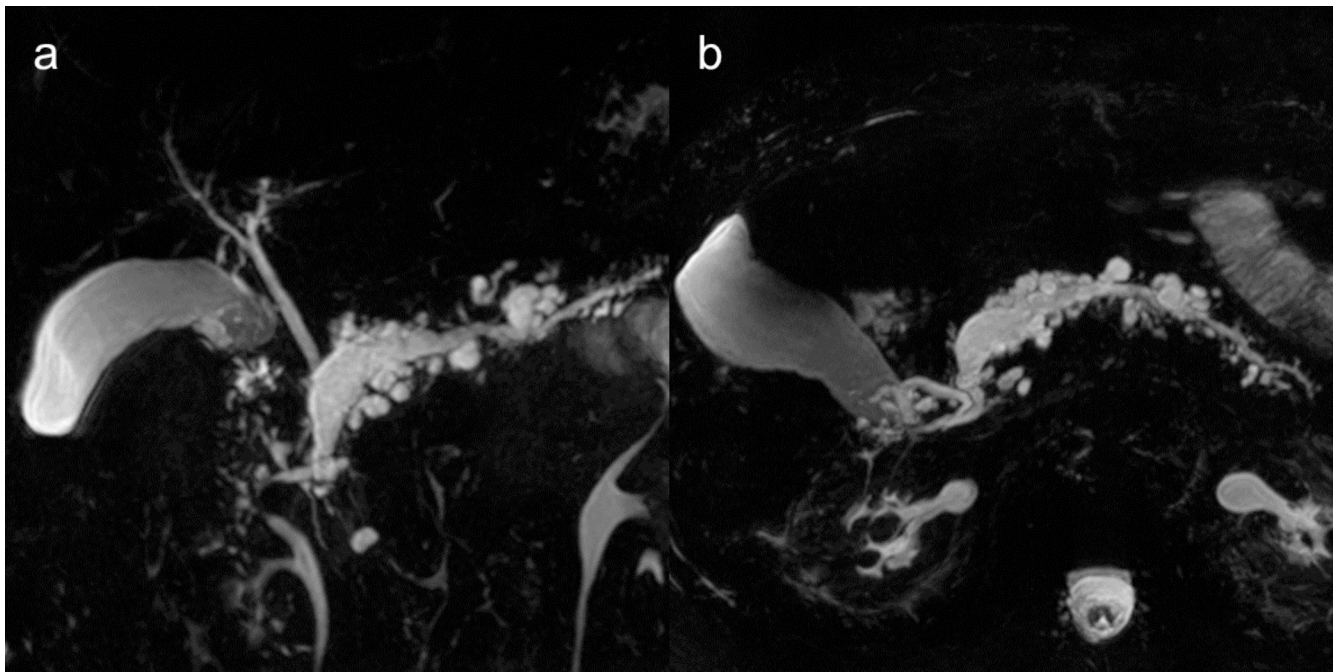


Fig. 7. 68-year-old male with mixed-type IPMN. MRI with 3D-MRCP reconstructed images on coronal (a) and axial (b) planes show dilation of the main pancreatic duct up to 10 mm and branch ducts. Histopathological analysis after pancreaticoduodenectomy confirmed the diagnosis of main pancreatic duct IPMN with mild-to-moderate dysplasia.

clear signs of aggressiveness, the cyst size (>4 cm), and the presence of enhancing solid components (thick enhancing septa) or mural nodules are the main radiological features that are associated with malignant transformation [56,57].

Considering the potential for malignant transformation, surgical resection should be considered as the reference treatment. The outcome in resected patients is excellent, and the prognosis is strongly related to the presence of invasive adenocarcinoma and metastatic lymph nodes [61].

6. Non-mucinous cystic neoplasms

Serous cystadenomas are most commonly encountered in women in the 5th–7th decade [57]. The typical imaging features include the microcystic or honeycombing appearance with lobulated contours, with high signal intensity on T2-weighted images (Fig. 9). The oligocystic pattern is rarely observed, and it can pose challenges for the differential diagnosis with other pancreatic cystic lesions [57]. A micro-lobulated appearance of the lesion wall, related to the presence of multiple clustered cysts, may help in suggesting the diagnosis of oligocystic serous cystadenoma [62]. Serous cystadenomas are most commonly asymptomatic and discovered incidentally. They tend to grow over time with a reported growth rate of about 2–4 mm per year [63,64]. This can lead to complications related to the compression of the adjacent structure such as the main pancreatic duct or the bile duct with possible chronic pancreatitis or bile duct obstruction [62]. Malignant transformation of serous cystadenoma has been exceptionally reported in the literature; therefore, asymptomatic serous cystadenomas should not undergo surgical resection [65].

Solid pseudopapillary neoplasm (SPN) is a rare pancreatic neoplasm most commonly occurring in young women [66]. The typical radiological appearance is that of a well-demarcated lesion with mixed cystic and solid components showing progressive enhancement on post-contrast phases [60]. Intraleisional hemorrhage and calcifications can be present [60]. SPNs have a potential of malignant and invasive behavior: in fact, 11–16 % of the lesions presents aggressive histopathological features (Fig. 10) [67,68]. Therefore, surgical resection is recommended by

the European guidelines and it is associated with a good long-term prognosis, with a reported recurrence rate of about 2 % [38,68].

7. Familial pancreatic cancer

Less than 5 % of all pancreatic cancers have a hereditary and familial background [69]. The criteria for identifying high-risk patients with familial pancreatic cancer have changed over time and now consider the extent of the familial involvement and the identified mutations. The PRECEDE consortium define patients at high risk of familial pancreatic cancer the individuals two or more relatives with PDAC, including at least one first- or second-degree relative [70]. Furthermore, other genetic conditions are included in the high-risk individuals including familial atypical multiple mole and melanoma, Peutz-Jeghers syndrome, hereditary pancreatitis, and confirmed germline variants the most common being BRCA1, BRCA2 and ATM [70]. These individuals should undergo regular screening due to the greater lifetime risk of developing PDAC. The Cancer of Pancreas Screening (CAPS) consortium recommends screening all BRCA1/2 carriers with an affected first-degree relative or BRCA2 carriers with two affected second-degree relatives [71]. The American College of Gastroenterology (ACG) recommends surveillance for all BRCA1/2 carriers with at least one first-degree or second-degree relative [72]. The 2022 American Society for Gastrointestinal Endoscopy (ASGE) guidelines have broader inclusion criteria, suggesting that screening is appropriate for BRCA patients even in the absence of family history [73].

There is currently no consensus on the best imaging modality for screening high-risk individuals. The two typically involved modalities are MRI with MRCP and endoscopic ultrasound, which are often alternated. Small sample sizes and lack of standardization in inclusion criteria and follow-up have limited outcome studies for screening high-risk individuals. Paiella et al [74] performed a metaanalysis of 16 studies, showing that pancreatic adenocarcinoma or high-grade precursor lesions were found in up to 2 % of high-risk individuals. Paiella and Capurso, in 2019, reported the results from the first round of surveillance in high-risk individuals included in the Italian Registry of Families at Risk of Pancreatic Cancer, with a 2.6 % prevalence of malignant

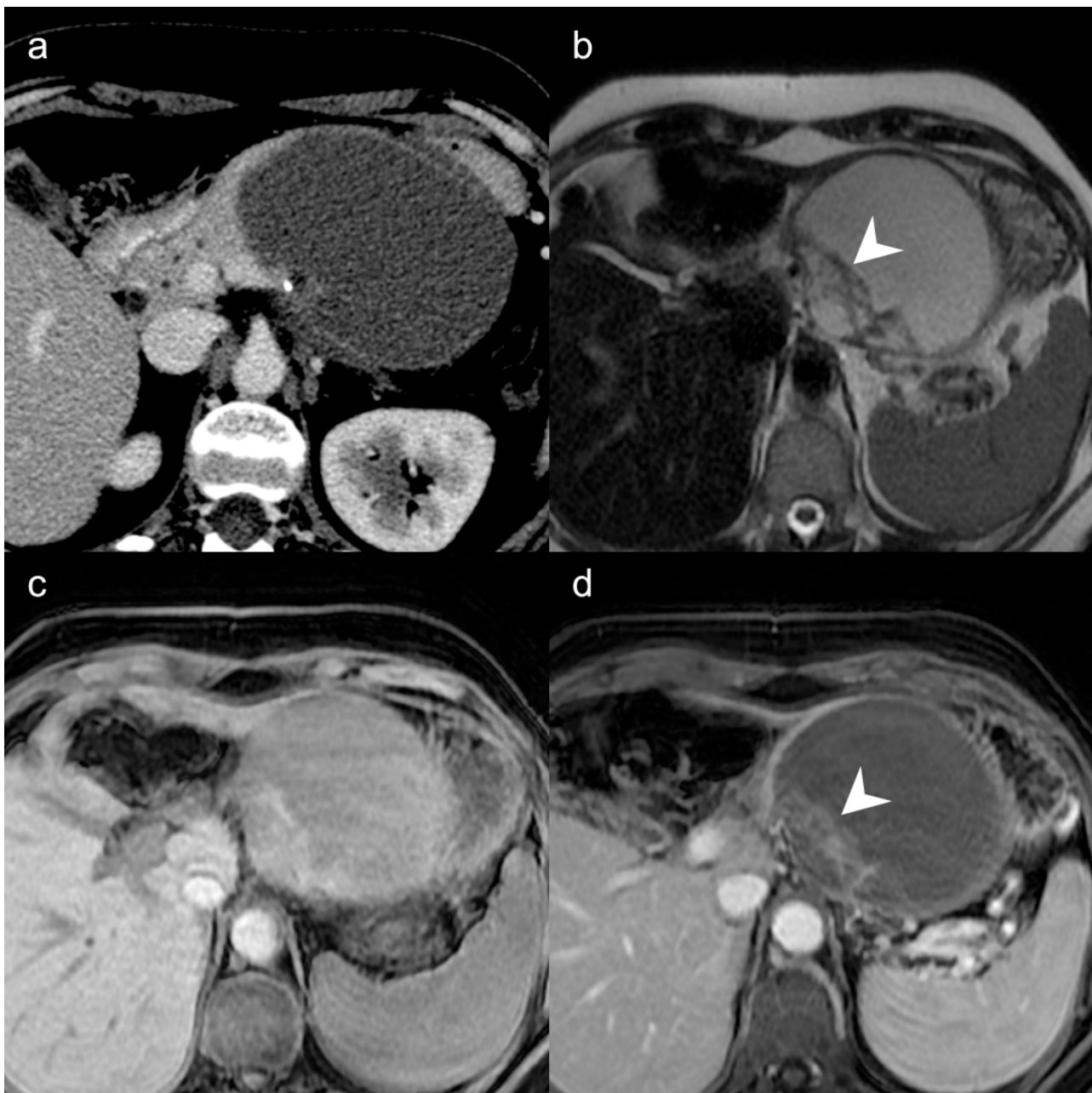


Fig. 8. 59-year-old female with malignant degeneration of mucinous cystic neoplasm. Contrast-enhanced CT (a) shows a large cystic lesion in the pancreatic body and tail with peripheral calcification. On MRI, the lesion demonstrates T2 hyperintensity with internal septa (b, arrowhead), iso-to-hyperintense T1 signal (c), and septa enhancement on post-contrast venous phase (d, arrowhead).

lesions, mainly advanced at presentation [75]. The recently published update on the same cohort showed a 1-, 2-, and 3-year cumulative hazard of pancreatic cancer of 1.7 %, 2.5 %, and 3 %, respectively [76].

Canto et al [77] followed 354 high-risk individuals reporting a detection rate of 7 % for pancreatic cancer and high-grade dysplasia over a median follow-up of 5.6 years; particularly, in 9/10 of the diagnosed pancreatic cancers were resectable, resulting in a 3-year survival of 85 % in the surgically treated group. Overbeek et al [78] reported a cumulative risk of PDAC of 3.1 % in high-risk subjects undergoing surveillance for 5 years and 4.7 % at 10 years.

More recently, a 20-year surveillance study conducted by the Dutch Pancreatic Cancer Group in patients with a CDKN2A/p16 pathogenic variant, demonstrated that 5.8 % of the patients outside surveillance had stage I PDAC, as compared with 38.7 % of surveillance patients who developed PDAC; and patients in surveillance had a better prognosis,

reflected by a 5-year survival of 32.4 % and a median overall survival of 26.8 months vs 4.3 % 5-year survival and 5.2 months median overall survival in non-surveillance patients [79].

Overall, considering the clinical benefit, an imaging screening program for PDAC should be routinely implemented in the population at high risk of PDAC [79]. However, there is a clear need to identify the appropriate high-risk population that would mostly benefit from a surveillance programme.

8. Future imaging strategies for screening

The main goal of a PDAC screening strategy is the early detection of asymptomatic high-grade precursor lesions and noninvasive PDAC. Screening the general population for PDAC is not recommended due to the low disease incidence and high costs. In 2019, the US Preventive

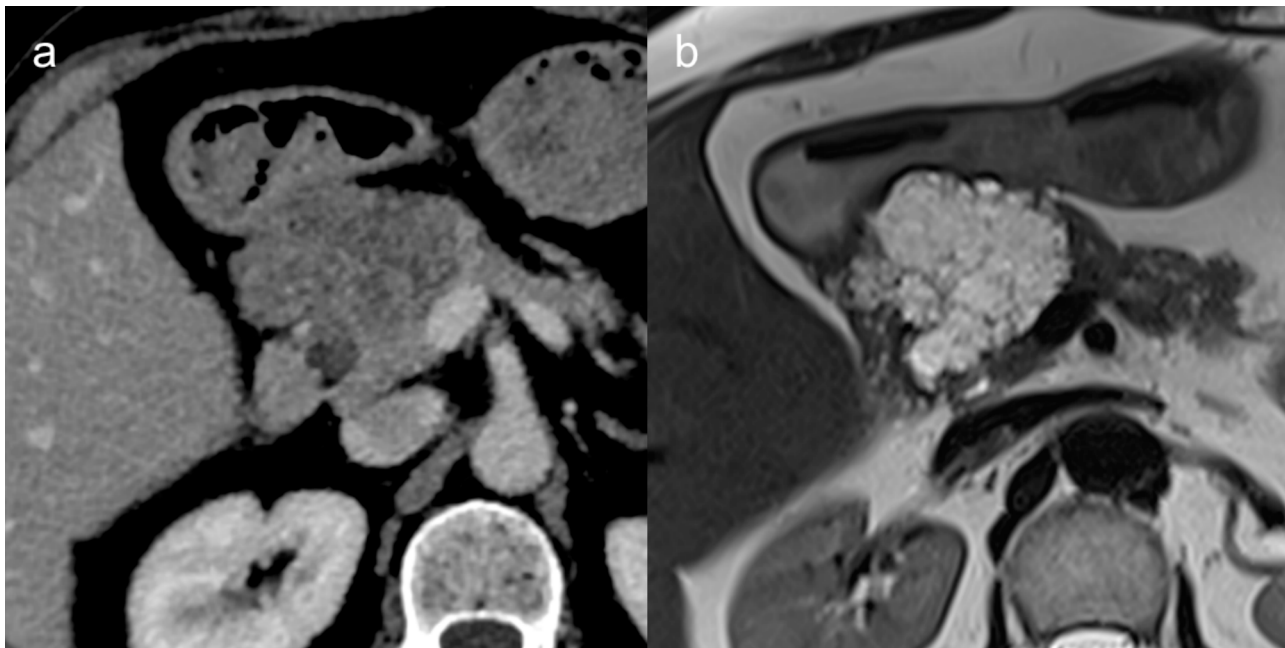


Fig. 9. 59-year-old female with serous cystadenoma. Contrast-enhanced CT (a) and MRI on T2-weighted image (b) show a lobulated lesion in the pancreatic head with microcystic appearance and high signal intensity of T2-weighted image.

Services Task Force reaffirmed its statement on screening the general population for PDAC, attesting that there is no evidence that screening for PDAC or treatment of PDAC detected at screening improves disease-specific morbidity or mortality, with benefits that can be defined small coupled with at least moderate harms [80]. The routine application of an imaging-based screening strategy needs to fit in the already overwhelmed imaging schedules and needs to be sensitive enough to promptly identify those individuals requiring further assessment [81].

Among all noninvasive imaging techniques, MRI is considered the most accurate with sensitivity, specificity and diagnostic accuracy of 93 %, 89 % and 90 %, respectively [82]. MRI is, however, time consuming, with the full pancreatic MRI protocol requiring about 30–50 min of total scan time. In the context of already long waiting lists for MRI exams, the routine application of the full pancreatic MRI protocol in a screening program seems unfeasible. Therefore, many studies have focused their attention to the adoption of abbreviated pancreatic MRI protocols or novel sequences as well as the use of radiomics [83–85]. Abbreviated MRI protocols suggested in different studies indicate the omission of contrast-enhanced or DWI sequences, or an ultrashort protocol with only axial T2-weighted and MRCP sequences as potential time-saving examination; however, these studies were mostly focused on cystic rather than solid lesions [85–87]. For this reason, the PRECEDE consortium recommends routine adoption of dynamic T1-weighted contrast-enhanced sequences on surveillance MRI/MRCP in the screening population [70]. A recent prospective study by Yoon JH et al investigated an accelerated MRI protocol including axial and coronal heavily T2-weighted imaging with breath hold, 3D MRCP using compressed sensing (and 2D MRCP in non-cooperative patients), DWI using two b values (0, 800 sec/mm²), dynamic extracellular T1-weighted imaging, two-point Dixon on a 3 T MRI scanner [88]. The total in-room time for accelerated MRI ranged from 13.7 min to 24.9 min with a mean of 18.5 min for all participants, and was longer in non-cooperative patients. The sensitivity and specificity of the accelerated MRI protocol in patients undergoing follow-up for IPMN or newly diagnosed pancreatic cysts were 75 % and 95 %, respectively. With regard to the adoption of novel sequences, Boekstijn et al suggested the adoption of an inversion recovery pre-pulse T1-turbo field echo sequences to increase the contrast between normal and abnormal pancreatic tissue, with some potential benefit for early identification of PDAC in their very small cohort of nine

patients with PDAC [89]. Further studies are warranted before implementation of this sequence in clinical routine.

The application of machine learning and artificial intelligence could provide future tools for large-scale opportunistic screening on CT and MRI exams acquired for other clinical indication in various clinical setting, although robust studies for pancreatic cancer screening are nowadays lacking [90,91].

9. Standardized MRI reporting in high-risk individuals

With increased identification of high-risk individuals eligible for pancreatic screening, standardization of imaging and reporting is needed. The current landscape of International Society Guidelines provides practical recommendations for MRI protocol and standardized reporting of pancreatic key findings in high-risk individuals, to guide uniformity of performance and interpretation of surveillance imaging studies, and to improve communication with clinicians by providing a standardized lexicon and reporting template [42,92–95].

A detailed spectrum of imaging key findings should be included in the imaging reports when an incidental pancreatic lesion is detected on MRI.

Main pancreatic duct.

- **Diameter:** if larger than 5 mm, either diffusely or segmentally, without an obstructing stone, mass, acute or chronic pancreatitis, a diagnosis of MD-IPMN should be considered [42];
- **Wall thickening, enhancement, and internal enhancing solid components:** those are signs of more aggressive biology such as high-grade dysplasia or invasive carcinoma [42,93–95];
- **Focal or multifocal strictures of the MPD without a visible mass:** multifocal strictures or isolated strictures that display narrowing without abrupt cutoff may reflect benign etiology (such as chronic pancreatitis), whereas abrupt cutoff is more suggestive of malignancy [96]. Benign strictures tend to be shorter than malignant ones (mean length of malignant strictures > 6 mm) and are less commonly associated with upstream parenchymal atrophy [97,98]. The “duct penetrating sign” (defined as a normal appearing main pancreatic duct passing through the lesion) and the “icicle sign” (referred to the appearance of the main pancreatic duct adjacent to the stenosis) can



Fig. 10. 30-year-old female with solid pseudopapillary neoplasm in the pancreatic tail and liver metastases. On MRI, the pancreatic lesion shows heterogeneous signal intensity on T1-weighted (a) and T2-weighted (b) images with enhancement of portal-venous phase (c). Hepatic metastases are detected at the time of the initial diagnosis (d, arrows).

help to differentiate pancreatic cancer from focal autoimmune pancreatitis. Any solitary pancreatic duct stricture without a visible mass should be carefully recorded in the report.

Pancreatic Parenchyma Atrophy.

Both partial and diffuse parenchymal atrophy accompanied by MPD dilation upstream from an obstruction is a well-recognized finding for PDAC [96].

Cystic Lesions.

- *Solitary versus multiple:* multiple cysts abutting the MPD increase diagnostic confidence of BD-IPMNs [42,53]. In the setting of multiple cysts, several studies recommend reporting the dominant (largest) cyst or the cyst that has the most worrisome features or high-risk

stigmata which is the most likely to progress to malignancy [93,94,99].

- *Duct communication:* it may be reported as present, likely, absent, or indeterminate. Establishing communication between the MPD and a cystic lesion, typically via a narrow neck, allows confident diagnosis of a BD-IPMN [93,94].
- *Worrisome features and high-risk stigmata:*
 - o *Size:* cyst diameter measured from outer wall to outer wall on either axial or coronal T2-weighted sequences or MRCP images is currently one of the most important predictors of malignancy, as larger cysts are associated with increased risk of high-grade dysplasia and invasive cancer [93,94].
 - o *Growth:* a rate of cyst growth of more than 2.5 mm per year should be considered a worrisome feature [43], whereas European Guidelines use a threshold of ≥ 5 mm in 1 year as indicating

significant growth [38]. The ACR white paper on incidental pancreatic cyst management recommends defining cyst growth according to baseline cyst size, with cysts smaller than 5 mm requiring a 100 % increase in longest dimension and cysts larger than 1.5 cm requiring a 20 % increase in longest dimension [93]. In addition, cyst size must also be compared with the measurement made on more remote prior studies, including the baseline study if possible.

- o *MPD diameter*: a cutoff of 5–9 mm or 7–9 mm is currently considered to be a worrisome feature [42,43].
- o *A thickened enhanced cyst wall*: defined as anything more than a thin and imperceptible wall or walls 2 mm thick or thicker [42,93,94].
- o *Mural nodules*: enhancing nodules or a solid component is the most predictive finding for development of malignancy within a cyst [42,93,94]. Enhancing mural nodules larger than 5 mm are identified as high-risk stigmata by the 2024 Kyoto guidelines [43], whereas the 2017 ACR incidental pancreatic cyst management white paper classifies an enhancing mural nodule of any size as a high-risk stigma and a not enhancing mural nodule as a worrisome feature [92,93]. For cysts smaller than 2 cm in diameter, distinguishing small enhancing mural nodules from confluent septa may be difficult [42,93,94,100].

Solid Lesions.

In case of any solid lesions with high suspicious of PDAC, dual-phase CT with pancreatic protocol is the preferred method for initial imaging evaluation (sensitivity of up to 96 %) and in the assessment of tumor resectability (accuracy rates of up to 86.8 %) [92,101,102]. According to the consensus statement of the Society of Abdominal Radiology and the American Pancreatic Association Standardized, reporting of solid lesions should include morphological assessment (size, attenuation, associated findings), vascular involvement (abutment or encasement of upper abdominal arteries and veins), and extrahepatic findings (including lymph node and distant metastases) [92,103,104].

10. Conclusion

Conditions at risk of pancreatic cancer can be frequently encountered on CT or MRI and they should be promptly recognized by the radiologists to avoid delays in the diagnosis of pancreatic cancer and increase the number of lesions diagnosed in resectable stages. MRI with MRCP is the recommended imaging method for the follow-up of pancreatic cystic lesions; the follow-up interval and length should be tailored based on the cyst size and presence of worrisome features. Screening the general population is not recommended due to the low incidence and costs. However, surveillance with MRI should be considered in selected high-risk individuals.

Funding: Roberto Cannella received co-funding by the European Union – FESR or FSE, PON Research and Innovation 2014–2020 – DM 1062/2021.

Editor Conflict of Interest: Given its role as Section Editor, Piero Boraschi had no involvement in the peer-review of this article and has no access to information regarding its peer-review.

CRedit authorship contribution statement

Roberto Cannella: Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Marco Dioguardi Burgio:** Writing – review & editing, Writing – original draft. **Cesare Maino:** Writing – review & editing, Writing – original draft. **Francesco Matteini:** Writing – review & editing, Writing – original draft. **Davide Ippolito:** Writing – review & editing, Writing – original draft. **Piero Boraschi:** Writing – review & editing, Writing – original draft. **Giulia A. Zamboni:** Writing – review & editing, Writing – original draft. **Federica Vernuccio:** Writing – review & editing, Writing – original draft,

Methodology.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Disclosures: R.C.: Disclosures: research collaboration with Siemens Healthineers; support for attending meetings from Bracco and Bayer. M. D.B.: Consulting fee from General Electric and Guerbet; support for attending meetings from Guerbet.

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