Differential Diagnosis and Diagnostic Evaluation Algorithm

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Introduction

Diagnosis of a pancreatic mass has a broad differential comprising both solid and cystic lesions. The increasing utilization of cross-sectional imaging frequently leads to incidental pancreatic masses, including solid pancreatic tumors in up to 7 % and pancreatic cystic lesions in up to 16 % [1–3].

Taking into account the epidemiology of solid pancreatic lesions, the majority of incidental pancreatic solid masses are pancreatic ductal adenocarcinomas [1]. However, a thorough medical history and physical examination have to consider the differential diagnosis, including pancreatic neuroendocrine tumors (PNETs), metastasis, and other malignant and benign pancreatic conditions. Another challenge is avoiding unnecessary surgical procedures in the treatment of diseases that can mimic pancreatic cancer, such as autoimmune pancreatitis (AIP), chronic pancreatitis, and lymphoma.

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The same is true for the differential diagnosis of cystic pancreatic lesions, which encompasses benign lesions, low-grade malignant lesions, and malignant lesions, including pancreatic cancer. This chapter focuses on the differential diagnosis of solid and cystic pancreatic masses, as well as their diagnostic approach. Following the description of different etiologies of pancreatic lesions as well as their epidemiology and diagnostic hallmarks, an evidence-based diagnostic algorithm will be illustrated focusing on cross-sectional, endoscopic imaging, and laboratory testing (Table 16.1 and Fig. 16.1).

Pancreatic Adenocarcinoma

Pancreatic adenocarcinoma is the fourth leading cause of cancer death despite its relatively low incidence [25]. The average age at the time of diagnosis is 71 years, with a slight male predominance [26]. It is speculated that males have more exposure to risk factors for developing pancreatic cancer, including cigarette smoking and alcohol use. Other associated factors are chronic pancreatitis, obesity, high intake of animal fat, inherited genetic predisposition, non-"O" blood group, and occupational exposure to nickel and chlorinated hydrocarbon [27]. In addition, several studies have reported a relationship between pancreatic adenocarcinoma and diabetes mellitus. In fact, more than two thirds of patients with pancreatic adenocarcinoma have

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Table 16.1 Synopsis of differential diagnosis of most common pancreatic masses

Characteristic	Pancreatic adenocarcinoma [4]	Chronic pancreatitis [5, 6]	Autoimmune pancreatitis [7, 8]	BD-IPMN [9, 10]	MCN [9, 10]	Microcystic SCN [9, 10]	Pseudopapillary tumor [11–13]	PNET [14–18]	Pancreatic metastasis [14, 19–24]
Sex	Male (56 %)	Male (70 %)	Male (75 %)	Male (60 %)	Female (99.8 %)	Female (80 %)	Female (85 %)	Female (50 %)	Male (58 %)
Median age	70	40	Type 1: 60 Type 2: 50	65	50	60	25	60 (younger if functional tumor)	60
Location	Head (75 %)	Head	Anywhere	Uncinate	Body/Tail	Anywhere	Anywhere (predilection tail)	Anywhere	Head (45 %)
Multifocal	No	No	N/A	Yes	No	No	No	No	Localized mass (50 %–70 %), multifocal mass (15 %–44 %), diffuse enlargement of the gland (5–10 %)
Calcification	Possible, not specific	Frequent	Possible, not specific	Rare	Peripheral, rare	Central, 30 %	Yes (peripheral, 30 %)	Possible, not specific	Possible, not specific
Histologic	Adenocarcinoma with desmoplastic reaction	Destruction of acinar tissue and replacement with extensive fibrosis	Type 1: Periductal lymphoplasmacytic infiltrate, obliterative phlebitis, storiform fibrosis and abundant IgG4-positive cells Type 2: granulocytic epithelial lesion in pancreatic duct, minimal IgG4-positive cells	Subtype are gastric, intestinal, pancreatobiliary and oncocytic IPMN	Ovarian stroma	Glycogen-rich cuboidal epithelial cells	Pseudopapillae	Well Differentiated: solid, trabecular, gyriform patter of cells with “organoid” growth Poorly differentiate: sheet like, diffuse architecture, with high nuclear/cytoplasmatic ratio, necrosis	Depends on the primary tumor
Capsule	No	No	No	No	Yes	No	Yes	Possible, not specific	No
Communication with MPD	N/A	N/A	N/A	Yes	No	No	No	N/A	N/A

Malignant potential	N/A	No	No	Yes (higher if combined type)	Yes	No	None or low	Yes	N/A
Imaging (CT/MRI/EUS)	Mass (EUS) with or without indirect signs (mass effect)	Solid mass in a context of calcific chronic pancreatitis	Diffuse or segmental/focal enlargement with PD stricture or strictures without upstream dilation	Fine septated cystic lesion, grape-like appearance	Single spherical lesion (unilocular or multilocular), orange-like	Complex cystic lesion with central scar, honeycomb-like	Solid encapsulated tumor with a cystic component, possible area of hemorrhage	Thick enhancing peripheral rim, fluid with clear or hemorrhagic content	Not specific, 45–95 % of patients have metastasis in other sites
			Other organ involvement (Type 1: 60 %; Type 2: infrequent)					Sharp defined mass, lobulated borders	
Contrast enhancement	Hypoenhancing mass	Hypoenhancing area	Hypoenhancing area (delayed contrast enhancement)	Mural nodules, wall thickening (if present)	Fibrous capsule, septations and mural nodules (if present)	Fibrous septation	Peripheral mild enhancement	Hyperenhancing	Wide variability between metastases of different primary tumors, but also between metastases from the same primary tumor
Cytology	Adenocarcinoma cells	Inflammatory cell, negative for malignancies	Not diagnostic	Mucinous epithelium with/without dysplasia	Mucinous epithelium with/without dysplasia	Serous, frequently acellular, bloody fluid (not diagnostic)	Papillary structures with fibrovascular stalks	Monotonous, poorly cohesive small cells with plasmacytoid morphology	Depends on primary tumor
Miscellaneous				Cyst fluid CEA: High	Cyst fluid CEA: High	Cyst fluid CEA: Low	Immunochemistry: Vimentin, CD10, progesterone receptor, nuclear expression of beta-catenin, CD56 +	Immunochemistry : Chromogranin A, Synaptophysin	Immunochemical staining depend on primary tumor
				Cystic fluid Amylase: High	Cystic fluid Amylase: Low	Cystic fluid Amylase: Low		Prognostic evaluation: mitotic rate, Ki67	

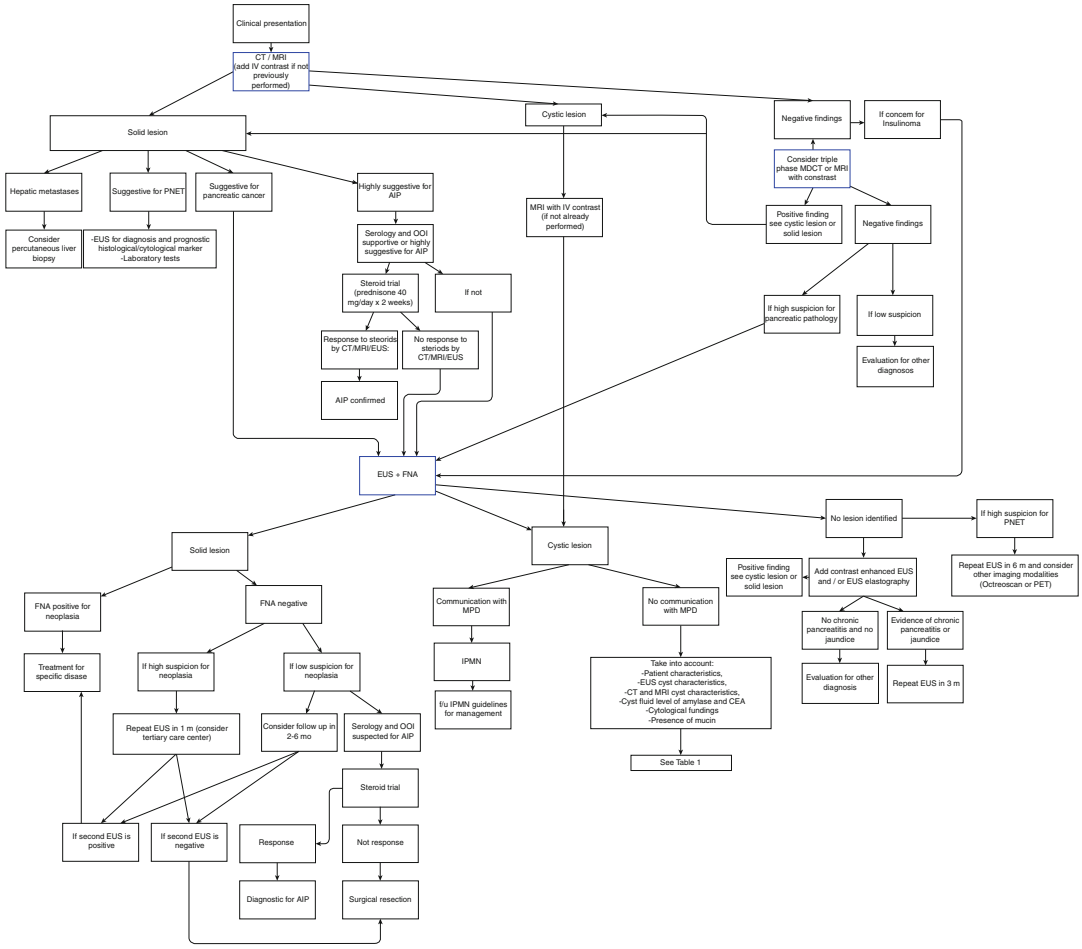

Fig. 16.1 Diagnostic algorithm for pancreatic masses

diabetes mellitus at the time of diagnosis, and more than 50 % of patients with pancreatic cancer have a new onset of diabetes mellitus preceding the cancer diagnosis by 2 years [28–31].

In most cases, pancreatic cancer is detected based on imaging, which includes both the incidental finding of a solid pancreatic mass and focused hepato-pancreato-biliary evaluation in symptomatic patients. No laboratory test with high sensitivity and specificity exists to reliably distinguish pancreatic cancer from benign pancreatic conditions [32]. The differential diagnosis is initially based on imaging findings, which emphasizes the importance of recognizing the strengths and weaknesses of the available imaging techniques.

Abdominal ultrasound has been proven to be of low yield for diagnosing pancreatic cancer, with accuracy ranging between 50–70 % [33]. Computed tomography (CT) is the preferred test to diagnose pancreatic cancer, as long as intravenous contrast is appropriately utilized (pancreas protocol). Multidetector CT (MDCT) with iodine contrast has a sensitivity of 76–92 % [34, 35]. Herein pancreatic cancer enhances poorly due to its hypovascularity, whereas 11 % of cases show isoattenuating lesions [36]. In such cases, indirect signs, including mass effect, abrupt pancreatic duct cutoff, and "double-duct sign," defined as dilation of both pancreatic and biliary ducts, can be helpful to raise the suspicion of pancreatic cancer [36, 37]. Pancreatic protocol CT scan with

imaging of both arterial and venous phases further increases the diagnostic yield of pancreatic cancer up to a sensitivity of 89–97 % [38–40].

Endoscopic ultrasound (EUS) has been a fundamental tool for the evaluation of solid pancreatic masses since the 1990s. The sensitivity of EUS to detect pancreatic cancer ranges between the mid-80s and 100 % [41–50]. An important advantage of EUS is its ability to acquire tissue samples for cytology utilizing fine-needle aspiration (FNA). Multiple authors have found that EUS-FNA provides the most definite nonoperative diagnosis of pancreatic cancer; the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were 95–98 %, 85–100 %, 98–100 %, and <85 %, respectively [51–54]. A recent meta-analysis included 4984 patients who underwent EUS-FNA for a solid pancreatic mass. Hewitt et al. found a pooled sensitivity, specificity, PPV, and NPV of 91 %, 94 %, 98 %, and 72 %, respectively, to diagnose pancreatic cancer based on EUS-acquired cytology [55]. By contrast, the absence of pancreatic solid mass on EUS in patients with clinical concern for pancreatic cancer has an NPV that approaches 100 % [56, 57]. Based on the available data, a negative or nondiagnostic FNA does not exclude pancreatic cancer. However, the absence of a pancreatic mass lesion on EUS excludes pancreatic cancer in the majority of cases. Yet, a repeat EUS within 2 months following a negative or nondiagnostic EUS needs to be considered, especially in the realm of high clinical suspicion for hepato-pancreato-biliary malignancy. This diagnostic approach is backed up by three studies. Bhutani et al. reported on 20 patients with missed pancreatic cancer by EUS. Factors contributing to false-negative EUS results were concomitant chronic pancreatitis ($n=12$), diffuse infiltrating cancer ($n=3$), ventral/dorsal split ($n=2$), and an episode of acute pancreatitis within less than 4 weeks prior to EUS ($n=1$) [58]. In another study, Eloubeidi et al. reported on 22 patients with clinical suspicion for pancreatic cancer who underwent a repeat EUS-FNA for initially suspicious (41.6 %), benign (41.6 %), or indeterminate (8.3 %) EUS-FNA. Eighty percent of patients with initially suspicious EUS-FNA were diagnosed with malignancy. Moreover, in 20 % of patients with initially benign EUS-FNA findings, the diagnosis was changed to a malignant condition [59]. Accordingly, Suzuki et al. reported on 84 patients with initially inconclusive EUS-FNA who underwent a repeat EUS-FNA at a high-volume tertiary center for evaluation of a solid pancreatic mass. The repeat EUS-FNA established a diagnosis in 82.1 %, of which all cases harbored a malignancy (mostly pancreatic adenocarcinoma, followed by PNET, metastasis, and lymphoma) [60].

Not every solid pancreatic mass harbors pancreatic adenocarcinoma. The challenge to distinguish between the differential diagnoses of solid pancreatic masses was evaluated by Tummala et al. Based on EUS, malignant neoplasms were detected in the majority (81.2 %) of patients with solid mass and dilated main pancreatic duct. Most were pancreatic ductal adenocarcinoma (71.6 %) followed by PNET, giant cell neoplasm, metastatic, nonsmall cell lung carcinoma, and spindle cell carcinoma. It was found that 18.7 % of the lesions were benign, including chronic pancreatitis and cystic neoplasms. By contrast, in patients with a nondilated pancreatic duct, most pancreatic masses (66.2 %) were benign and included chronic pancreatitis, cystic lesions, and lymph nodes. PNETs represented the majority of the 33.7 % malignant lesions, followed by pancreatic ductal adenocarcinoma and metastasis to the pancreas [61].

Additionally, EUS is important for evaluating nonspecific pancreatic changes seen on CT and MRI, such as pancreatic ductal dilation and diffuse pancreatic head enlargement. Sixty-five percent of patients with those findings were diagnosed with pancreatic cancer based on EUS imaging [62, 63].

When compared with CT, EUS was found to be superior for detecting pancreatic cancer, which was reflected by a higher sensitivity of 94–99 % vs. 57–86 % [64–66]. This was especially true for pancreatic cancer under 3 cm in size [46]. Likewise, a systematic review of 678 patients confirmed the higher sensitivity of EUS to detect pancreatic cancer than CT (93–100 % vs.

50–89 %) [67]. However, those studies are limited by their partially outdated CT techniques.

Despite the superior sensitivity of EUS to detect pancreatic cancer, as of now MDCT scan with IV contrast is the initial, preferred diagnostic imaging test to detect pancreatic cancer. This is mostly based on limited EUS availability. Also, MDCT is interchangeable with MRI [68].

Chronic Pancreatitis

Chronic pancreatitis is an inflammatory condition resulting in permanent structural changes in the pancreas leading to exocrine and endocrine pancreatic insufficiency. It can be complicated by inflammatory mass formation, especially in focal chronic pancreatitis leading to bile duct or pancreatic duct obstruction, which can resemble pancreatic cancer. Additionally, chronic pancreatitis is a risk factor for pancreatic cancer, which was confirmed by a recent meta-analysis in which 5 % of patients with chronic pancreatitis developed pancreatic cancer over 20 years [69].

Historically, cross-sectional imaging has poor sensitivity and specificity for differentiating chronic pancreatitis from pancreatic cancer. However, recent progress in CT and MRI techniques improved the diagnostic yield. Triple-phase CT scan was shown to differentiate between pancreatic cancer and chronic pancreatitis with a sensitivity, specificity, PPV, and NPV of 94.1 %, 83.6 %, 91.4 %, and 88.2 %, respectively [70]. In terms of MRI, Sandrasegaran et al. showed that a distinct mass was helpful in distinguishing between chronic pancreatitis and pancreatic cancer; however, the diagnostic yield remained low [71]. Fewer data are available for EUS. A small study revealed the sensitivity, specificity, and accuracy of EUS to distinguish between cancer and focal pancreatitis to be 73 %, 100 %, and 83 %, respectively [72]. The combination of EUS and FNA for solid pancreatic masses was shown to improve the sensitivity, specificity, PPV, and accuracy to 89.5 %, 98.4 %, 99.5 %, and 91.5 %, respectively. The additional value of EUS elastography to distinguish between pancreatic inflammatory masses and pancreatic cancer was reflected in a meta-analysis showing a pooled sensitivity and specificity of 92 % and 68 %, respectively [73].

Apart from imaging, pancreatic juice analysis of DNA methylation markers appears to be a promising approach to distinguish between chronic pancreatitis and pancreatic cancer with high sensitivity and specificity [74].

Groove pancreatitis is postulated to be a subtype of chronic segmental pancreatitis localized between the pancreatic head, duodenum, and bile duct. It is a particular challenge to distinguish groove pancreatitis from pancreatic cancer. Insufficient data are available for CT, MRI, and EUS imaging to distinguish between both disease identities. Pancreaticoduodenectomy remains the mainstay of treatment, achieving both resolution of obstructive symptoms caused by the inflammation and tissue diagnosis to exclude pancreatic cancer [75].

Acute Pancreatitis

Acute pancreatitis was shown to be the presenting diagnosis of patients with pancreatic cancer in 1.3 %. Therefore, pancreatic cancer needs to be excluded by imaging in all patients above the age of 40 years who are diagnosed with new-onset acute pancreatitis, despite the absence of gallstone disease, alcohol use, and hyperlipidemia [76]. Imaging is also indicated for patients with new-onset acute pancreatitis suspected to be secondary to alcohol or tobacco abuse, as both are also risk factors for pancreatic cancer [27, 76].

Local complications of acute pancreatitis, such as acute necrotic collection and walled-off necrosis, could mimic or mask pancreatic cancer; however, no literature exists on this topic.

Autoimmune Pancreatitis

Autoimmune pancreatitis (AIP) is a well-recognized differential diagnosis for pancreatic cancer. To date, two types of AIP are described: AIP type 1 and AIP type 2. This is described in detail in Chap. 5 in this book.

Sausage-shaped enlargement of the pancreas with a peripheral rim of hypoattenuation is the hallmark presentation of AIP based on contrast-enhanced CT (CECT) imaging. Similarly, MRI reveals diffuse enlargement of the pancreas with a hypointense capsule-like rim. In addition, cross-sectional imaging adds the advantage of assessing for extrapancreatic other organ involvement [77].

Both AIP types can present with focal features, including a pancreatic inflammatory mass and pancreatic duct stricture, resembling pancreatic cancer. This occurs more frequently in AIP type 2 (85 %) [78]. A frequent diagnostic challenge is a common bile duct (CBD) stenosis, which can be present in both AIP and pancreatic cancer. Yet the CBD wall thickening of the stenotic area is smoother in AIP than it is in pancreatic cancer.

EUS-FNA increases the diagnostic yield of AIP in comparison with CT and MRI. Hypoechoic enlargement of the pancreas with hyperechoic spots and the absence of a discrete mass are typical features of AIP seen on EUS exam [7, 79]. The addition of an EUS-guided 19-gauge biopsy can be diagnostic for AIP type 1 in up to 94 % of patients, but only 42 % with AIP type 2 [80].

Chari et al. compared both imaging and laboratory findings of patients with AIP and pancreatic cancer. According to their published algorithm, only 30 % of patients with mainly AIP type 1 required either a steroid trial or a pancreatic specimen, which also included two pancreatic resections, for the diagnosis of AIP [81]. However, the nonoperative diagnosis of AIP type 2 lacks both sensitivity and specificity. According to HISORt criteria, the diagnosis of AIP type 2 cannot be made unless histology is available, although robust data on diagnostic accuracy are lacking [77]. Therefore, close follow-up is recommended when nonoperative workup is consistent for AIP type 2 and excludes pancreatic cancer [82].

Cystic Pancreatic Tumors

Cystic tumors of the pancreas encompass mainly three different tumor identities, including serous cystic neoplasm, mucinous cystic neoplasm, and intraductal papillary mucinous neoplasm (IPMN). These types are described in detail elsewhere in this book.

Rare Pancreatic Tumors

Pseudopapillary tumor is a rare benign or low-grade malignant neoplasm predominantly in young women located mostly in the pancreatic tail [83–86]. MRI was shown to be superior to CT to identify characteristic features such as a well-demarcated cystic or solid mass with fibrous capsule as well as possible peripheral calcification and hemorrhagic areas [87]. Accordingly, EUS reveals a well-defined, hypovascular, hypoechoic mass, with solid, cystic, or mixed solid and cystic pancreatic component [88].

PNETs are a heterogeneous group representing less than 10 % of all pancreatic neoplasms. They occur in equal frequency in men and women, most often between the sixth and seventh decades. Between 5–10 % have a cystic appearance, whereas the remaining tumors are solid [89]. Further, PNETs can be divided into nonfunctional and functional PNETs. Functional PNETs include insulinoma, glucagonoma, gastrinoma, and VIPoma tumors and are associated with a variety of clinical syndromes caused by respective hormones secreted by the tumor [90, 91]. Nonfunctional PNETs are not associated with a particular clinical syndrome. However, these neoplasms also secret tumor-specific peptides like Chromogranin A (CgA). In addition to imaging and FNA of the tumor mass, CgA is currently utilized as a biomarker providing both additional evidence for diagnosis as well as a marker for surveillance of PNETs [92–95].

Pancreatic Metastasis

The pancreas is rarely a site of metastasis. In this context, renal cell carcinoma is the most common metastasizing cancer followed by lung (both small cell and non-small cell cancer), melanoma, breast, colon, and other cancers (hepatocellular carcinoma, ovarian cancer, carcinoid, liposarcoma).

In the majority of cases, patients already have evidence of the primary cancer as well as metastasis to other organs. The exception is renal cell carcinoma, which can present up to a decade following the treatment of the primary tumor [96].

Metastatic disease is most commonly detected as a localized solitary mass. However, multifocal metastases as well as diffuse enlargement of the pancreas due to metastasis were previously reported [14, 19, 20]. EUS-FNA was shown to be diagnostic for renal cell cancer, lung cancer, and melanoma. Additionally, renal cell cancer can be distinguished from pancreatic adenocarcinoma by its hypervascularity [21, 97].

Other Diseases

An intrapancreatic accessory spleen is a congenital abnormality with an estimated prevalence of 1:500. Hereby, the pancreatic tail is the second most common site of an accessory spleen [98]. Contrast-enhanced cross-sectional imaging reveals a hypervascular mass which enhances similarly as the spleen [98, 99].

Further rare solid pancreatic masses include acinar cell carcinoma, benign fibrous tumor, giant cell osteoclastoma, adenosquamous carcinoma, lymphoma, and teratoma with substantial overlap with rare cystic tumors. Those include metastatic disease, teratoma, pancreatoblastoma, lymphangioma, and lymphoepithelial cyst [9, 14]. A specific diagnosis of those uncommon tumors is rarely made by sole imaging. Accordingly, a tissue diagnosis is required and usually obtained by EUS-FNA or by pancreatectomy, which is also the definitive therapy in most cases.

Diagnostic Algorithm for a Pancreatic Mass

Each patient with a new pancreatic mass requires a thorough anamnesis, which should at best predate the index abdominal imaging. Thus, a delay of diagnosis of unusual causes of a pancreatic mass (e.g., PNET or metastasis) can be avoided. Most patients will have an incidental pancreatic mass found during evaluation for nonspecific symptoms, whereas only a minority of patients will have painless jaundice, which is a hallmark for pancreatic cancer. Any unexplained acute pancreatitis after the age of 40 years as well as a worsening course of chronic pancreatitis should include pancreatic cancer in the differential diagnosis [27, 76].

Following the anamnesis, the attention is drawn to the imaging study. Given the limitation of transabdominal ultrasound as well as noncontrast CT, each patient should undergo a cross-sectional imaging study utilizing intravenous contrast [33]. Alternatively, EUS can be offered for patients with contrast allergy or contrast intolerance (e.g., due to renal failure).

Any new solid pancreatic lesion raises the concern for pancreatic malignancy, with pancreatic adenocarcinoma being the most common one. Depending on the contrast enhancement pattern as well as the evaluation of a possible local and distant spreading, pancreatic carcinoma can be distinguished from PNET and metastasis as well as from benign conditions most of the time [34–36]. According to local surgical preference and availability of neoadjuvant therapy, EUS can be offered to obtain a tissue diagnosis. Hereby, the presence of a dilated pancreatic duct shifts the likelihood from a benign condition to a malignant condition [61].

The workup of a pancreatic mass in patients with underlying chronic pancreatitis is challenging. Neither cross-sectional imaging nor EUS-FNA reaches a sufficient sensitivity and specificity to distinguish benign from malignant masses, which implicates the frequent need for pancreatic surgery [100].

Patients with no risk factors for chronic pancreatitis or pancreatic cancer who are diagnosed with a new pancreatic mass or a diffuse pancreatic duct stricture without typical features of a pancreatic adenocarcinoma require additional workup. This requires the measurement of serum IgG4 level as well as a focused review of cross-sectional imaging for rim enhancement and the so-called other-organ involvement to evaluate for AIP. Hereby, most cases of AIP type 1 can be diagnosed noninvasively [78, 81, 101, 102].

EUS-FNA adds additional diagnostic information for both AIP type 1 and type 2 although that approach has low yield for AIP type 2 [80]. A steroid trial for suspected AIP requires a repeat imaging test to document resolution of pancreatic mass or pancreatic duct stricture. The absence of improvement raises the concern for a malignant process necessitating a surgical resection in patients with resectable disease.

A solid pancreatic mass visualized on both cross-sectional imaging followed by a nondiagnostic EUS-FNA remains of high concern for pancreatic cancer [103]. Therefore, indeterminate imaging studies of a solid pancreatic mass in conjunction with a negative, indeterminate, and/or benign FNA require close follow-up. As EUS-FNA is limited by an NPV of approximately 80 %, a repeat FNA is indicated within 1–2 months, preferably at a high-volume tertiary center [51–53, 58, 60]. Concomitantly, evaluation for AIP needs to be performed as delineated above.

The absence of a visualized mass on EUS despite a documented pancreatic solid lesion on initial cross-sectional imaging requires further attention. When available, contrast-enhanced EUS and EUS elastography add valuable information to identify a target lesion for FNA [51, 73, 104, 105]. This applies particularly for patients with underlying chronic pancreatitis which is associated with false-negative EUS results [58, 72, 100]. The presence of chronic pancreatitis or dilation of the pancreatic duct, in the absence of a distinct pancreatic mass on EUS, needs to be followed by a repeat EUS exam within 2 months [58, 61, 72, 100]. Contrary, a pristine pancreas on EUS virtually excludes pancreatic cancer [56, 57].

Negative cross-sectional imaging studies in the context of a high clinical concern for pancreatic malignancy require a high-quality contrast CT if not already performed initially. Depending on local preference, CT is interchangeable with MRI [68]. Insulinoma is an exemption, as EUS was shown to be superior compared with contrast-enhanced cross-sectional imaging for its detection [106]. Following a negative or nondiagnostic high-quality CT study, EUS adds further information. A normal pancreatic EUS exam excludes pancreatic cancer as described above with a high NPV, and an alternative diagnosis needs to be considered [56, 57]. In selected cases with substantial concern for pancreatic cancer, EUS can be repeated within 1–2 months to reevaluate for pancreatic mass lesion given the small chance of an initially false-negative test [58].

Correct identification of a cystic lesion on cross-sectional imaging is particularly challenging. The majority of cystic lesions encompass serous cystic neoplasm, mucinous cystic neoplasm, and IPMN, which can be best distinguished by their characteristic epidemiologic profile in combination with typical features on contrast-enhanced cross-sectional imaging and cystic fluid evaluation (cytology, CEA, and amylase level). Management of cystic neoplasms depends on their type, size, main pancreatic duct involvement in case of IPMN, presence of concerning EUS features (mural nodules), interval tumor growth, and the presence of symptoms which eventually leads to the decision to perform surgery [107–111].

Atypical features of solid and cystic pancreatic masses on cross-sectional imaging, which can include atypical contrast enhancement pattern of the mass, require evaluation with EUS-FNA. In the setting of a broad differential diagnosis, including malignant tumors like PNET, metastatic disease, lymphoma, teratoma, pancreatoblastoma, solid pseudopapillary tumor, as well as benign findings such as accessory spleen, EUS-FNA is of particular interest to provide a nonoperative diagnosis [9, 14, 21, 97–99].

References

1. Goodman M, Willmann JK, Jeffrey RB. Incidentally discovered solid pancreatic masses: imaging and clinical observations. Abdom Imaging. 2012;37:91–7.
2. de Jong K, Nio CY, Hermans JJ, Dijkgraaf MG, Gouma DJ, van Eijck CH, van Heel E, Klass G, Fockens P, Bruno MJ. High prevalence of pancreatic cysts detected by screening magnetic resonance imaging examinations. Clin Gastroenterol Hepatol. 2010;8:806–11.

3. Lee KS, Sekhar A, Rofsky NM, Pedrosa I. Prevalence of incidental pancreatic cysts in the adult population on MR imaging. Am J Gastroenterol. 2010;105: 2079–84.
4. Rosch T, Lorenz R, Braig C, Feuerbach S, Siewert JR, Schusdziarra V, Classen M. Endoscopic ultrasound in pancreatic tumor diagnosis. Gastrointest Endosc. 1991;37:347–52.
5. Perumal S, Palaniappan R, Pillai SA, Velayutham V, Sathyanesan J. Predictors of malignancy in chronic calcific pancreatitis with head mass. World J Gastrointest Surg. 2013;5:97–103.
6. Yadav D, Notahara K, Smyrk TC, Clain JE, Pearson RK, Farnell MB, Chari ST. Idiopathic tumefactive chronic pancreatitis: clinical profile, histology, and natural history after resection. Clin Gastroenterol Hepatol. 2003;1:129–35.
7. Farrell JJ, Garber J, Sahani D, Brugge WR. EUS findings in patients with autoimmune pancreatitis. Gastrointest Endosc. 2004;60:927–36.
8. Hoki N, Mizuno N, Sawaki A, Tajika M, Takayama R, Shimizu Y, Bhatia V, Yamao K. Diagnosis of autoimmune pancreatitis using endoscopic ultrasonography. J Gastroenterol. 2009;44:154–9.
9. Dewhurst CE, Mortele KJ. Cystic tumors of the pancreas: imaging and management. Radiol Clin North Am. 2012;50:467–86.
10. Yoon WJ, Brugge WR. Pancreatic cystic neoplasms: diagnosis and management. Gastroenterol Clin North Am. 2012;41:103–18.
11. Butte JM, Brennan MF, Gonen M, Tang LH, D'Angelica MI, Fong Y, Dematteo RP, Jarnagin WR, Allen PJ. Solid pseudopapillary tumors of the pancreas. Clinical features, surgical outcomes, and long-term survival in 45 consecutive patients from a single center. J Gastrointest Surg. 2011;15: 350–7.
12. Buetow PC, Buck JL, Pantongrag-Brown L, Beck KG, Ros PR, Adair CF. Solid and papillary epithelial neoplasm of the pancreas: imaging-pathologic correlation on 56 cases. Radiology. 1996;199:707–11.
13. Yao X, Ji Y, Zeng M, Rao S, Yang B. Solid pseudopapillary tumor of the pancreas: cross-sectional imaging and pathologic correlation. Pancreas. 2010;39:486–91.
14. Megibow AJ. Unusual solid pancreatic tumors. Radiol Clin North Am. 2012;50:499–513.
15. Byrne MF, Jowell PS. Gastrointestinal imaging: endoscopic ultrasound. Gastroenterology. 2002;122:1631–48.
16. Anderson MA, Carpenter S, Thompson NW, Nostrant TT, Elta GH, Scheiman JM. Endoscopic ultrasound is highly accurate and directs management in patients with neuroendocrine tumors of the pancreas. Am J Gastroenterol. 2000;95:2271–7.
17. Tenner SM, Banks PA, Wiersema MJ, Van Dam J. Evaluation of pancreatic disease by endoscopic ultrasonography. Am J Gastroenterol. 1997;92:18–26.
18. Chatzipantelis P, Salla C, Konstantinou P, Karoumpalis I, Sakellariou S, Doumani I. Endoscopic ultrasound-guided fine-needle aspiration cytology of pancreatic neuroendocrine tumors: a study of 48 cases. Cancer. 2008;114:255–62.
19. Scatarige JC, Horton KM, Sheth S, Fishman EK. Pancreatic parenchymal metastases: observations on helical CT. Am J Roentgenol. 2001;176:695–9.
20. Merkle EM, Boaz T, Kolokythas O, Haaga JR, Lewin JS, Brambs HJ. Metastases to the pancreas. Br J Radiol. 1998;71:1208–14.
21. Waters L, Si Q, Caraway N, Mody D, Staerkel G, Sneige N. Secondary tumors of the pancreas diagnosed by endoscopic ultrasound-guided fine-needle aspiration: A 10-year experience. Diagn Cytopathol. 2014;42(9):738–43.
22. Klein KA, Stephens DH, Welch TJ. CT characteristics of metastatic disease of the pancreas. Radiographics. 1998;18:369–78.
23. Ferrozzi F, Bova D, Campodonico F, Chiara FD, Passari A, Bassi P. Pancreatic metastases: CT assessment. Eur Radiol. 1997;7:241–5.
24. Palmowski M, Hacke N, Satzl S, Klauss M, Wente MN, Neukamm M, Kleeff J, Hallscheidt P. Metastasis to the pancreas: characterization by morphology and contrast enhancement features on CT and MRI. Pancreatology. 2008;8:199–203.
25. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin. 2014;64:9–29.
26. http://seer.cancer.gov/statfacts/html/pancreas.html. SEER 18 2007–2011, Age-Adjusted, pancreas
27. Muniraj T, Jamidar PA, Aslanian HR. Pancreatic cancer: a comprehensive review and update. Dis Mon. 2013;59:368–402.
28. Ben Q, Xu M, Ning X, Liu J, Hong S, Huang W, Zhang H, Li Z. Diabetes mellitus and risk of pancreatic cancer: a meta-analysis of cohort studies. Eur J Cancer. 2011;47:1928–37.
29. Pannala R, Leirness JB, Bamlet WR, Basu A, Petersen GM, Chari ST. Prevalence and clinical profile of pancreatic cancer-associated diabetes mellitus. Gastroenterology. 2008;134:981–7.
30. Permert J, Ihse I, Jorfeldt L, von Schenck H, Arnqvist HJ, Larsson J. Pancreatic cancer is associated with impaired glucose metabolism. Eur J Surg. 1993;159:101–7.
31. Batabyal P, Vander Hoorn S, Christophi C, Nikfarjam M. Association of diabetes mellitus and pancreatic adenocarcinoma: a meta-analysis of 88 studies. Ann Surg Oncol. 2014;21(7):2453–62.
32. Duffy MJ, Sturgeon C, Lamerz R, Haglund C, Holubec VL, Klapdor R, Nicolini A, Topolcan O, Heinemann V. Tumor markers in pancreatic cancer: a European group on tumor markers (EGTM) status report. Ann Oncol. 2010;21:441–7.
33. Rickes S, Unkrodt K, Neye H, Ocran KW, Wermke W. Differentiation of pancreatic tumours by conventional ultrasound, unenhanced and echo-enhanced power Doppler sonography. Scand J Gastroenterol. 2002;37:1313–20.
34. Amin Z, Theis B, Russell RC, House C, Novelli M, Lees WR. Diagnosing pancreatic cancer: the role of

percutaneous biopsy and CT. Clin Radiol. 2006;61: 996–1002.
35. Ahn SS, Kim MJ, Choi JY, Hong HS, Chung YE, Lim JS. Indicative findings of pancreatic cancer in prediagnostic CT. Eur Radiol. 2009;19:2448–55.
36. Prokesch RW, Chow LC, Beaulieu CF, Bammer R, Jeffrey Jr RB. Isoattenuating pancreatic adenocarcinoma at multi-detector row CT: secondary signs. Radiology. 2002;224:764–8.
37. Ahualli J. The double duct sign. Radiology. 2007; 244:314–5.
38. Valls C, Andia E, Sanchez A, Fabregat J, Pozuelo O, Quintero JC, Serrano T, Garcia-Borobia F, Jorba R. Dual-phase helical CT of pancreatic adenocarcinoma: assessment of resectability before surgery. Am J Roentgenol. 2002;178:821–6.
39. Bronstein YL, Loyer EM, Kaur H, Choi H, David C, DuBrow RA, Broemeling LD, Cleary KR, Charnsangavej C. Detection of small pancreatic tumors with multiphasic helical CT. Am J Roentgenol. 2004;182:619–23.
40. Karmazanovsky G, Fedorov V, Kubyshkin V, Kotchatkov A. Pancreatic head cancer: accuracy of CT in determination of resectability. Abdom Imaging. 2005;30:488–500.
41. Palazzo L, Roseau G, Gayet B, Vilgrain V, Belghiti J, Fekete F, Paolaggi JA. Endoscopic ultrasonography in the diagnosis and staging of pancreatic adenocarcinoma. Results of a prospective study with comparison to ultrasonography and CT scan. Endoscopy. 1993;25:143–50.
42. Muller MF, Meyenberger C, Bertschinger P, Schaer R, Marincek B. Pancreatic tumors: evaluation with endoscopic US, CT, and MR imaging. Radiology. 1994;190:745–51.
43. Melzer E, Avidan B, Heyman Z, Coret A, Bar-Meir S. Preoperative assessment of blood vessel involvement in patients with pancreatic cancer. Isr J Med Sci. 1996;32:1086–8.
44. Marty O, Aubertin JM, Bouillot JL, Hernigou A, Bloch F, Petite JP. Prospective comparison of ultrasound endoscopy and computed tomography in the assessment of locoregional invasiveness of malignant ampullar and pancreatic tumors verified surgically. Gastroenterol Clin Biol. 1995;19:197–203.
45. Dufour B, Zins M, Vilgrain V, Levy P, Bernades P, Menu Y. Comparison between spiral x-ray computed tomography and endosonography in the diagnosis and staging of adenocarcinoma of the pancreas. Clinical preliminary study. Gastroenterol Clin Biol. 1997;21:124–30.
46. Legmann P, Vignaux O, Dousset B, Baraza AJ, Palazzo L, Dumontier I, Coste J, Louvel A, Roseau G, Couturier D, Bonnin A. Pancreatic tumors: comparison of dual-phase helical CT and endoscopic sonography. Am J Roentgenol. 1998;170:1315–22.
47. Akahoshi K, Chijiiwa Y, Nakano I, Nawata H, Ogawa Y, Tanaka M, Nagai E, Tsuneyoshi M. Diagnosis and staging of pancreatic cancer by endoscopic ultrasound. Br J Radiol. 1998;71:492–6.
48. Gress FG, Hawes RH, Savides TJ, Ikenberry SO, Cummings O, Kopecky K, Sherman S, Wiersema M, Lehman GA. Role of EUS in the preoperative staging of pancreatic cancer: a large single-center experience. Gastrointest Endosc. 1999;50:786–91.
49. Ainsworth AP, Rafaelsen SR, Wamberg PA, Durup J, Pless TK, Mortensen MB. Is there a difference in diagnostic accuracy and clinical impact between endoscopic ultrasonography and magnetic resonance cholangiopancreatography? Endoscopy. 2003; 35:1029–32.
50. Harrison JL, Millikan KW, Prinz RA, Zaidi S. Endoscopic ultrasound for diagnosis and staging of pancreatic tumors. Am Surg. 1999;65:659–64; discussion 664–5.
51. Giovannini M, Thomas B, Erwan B, Christian P, Fabrice C, Benjamin E, Genevieve M, Paolo A, Pierre D, Robert Y, Walter S, Hanz S, Carl S, Christoph D, Pierre E, Jean-Luc VL, Jacques D, Peter V, Andrian S. Endoscopic ultrasound elastography for evaluation of lymph nodes and pancreatic masses: a multicenter study. World J Gastroenterol. 2009;15:1587–93.
52. Eloubeidi MA, Varadarajulu S, Desai S, Shirley R, Heslin MJ, Mehra M, Arnoletti JP, Eltoum I, Wilcox CM, Vickers SM. A prospective evaluation of an algorithm incorporating routine preoperative endoscopic ultrasound-guided fine needle aspiration in suspected pancreatic cancer. J Gastrointest Surg. 2007;11:813–9.
53. Eloubeidi MA, Jhala D, Chhieng DC, Chen VK, Eltoum I, Vickers S, Mel Wilcox C, Jhala N. Yield of endoscopic ultrasound-guided fine-needle aspiration biopsy in patients with suspected pancreatic carcinoma. Cancer. 2003;99:285–92.
54. Buscail L, Faure P, Bournet B, Selves J, Escourrou J. Interventional endoscopic ultrasound in pancreatic diseases. Pancreatology. 2006;6:7–16.
55. Hewitt MJ, McPhail MJ, Possamai L, Dhar A, Vlavianos P, Monahan KJ. EUS-guided FNA for diagnosis of solid pancreatic neoplasms: a meta-analysis. Gastrointest Endosc. 2012;75:319–31.
56. Klapman JB, Chang KJ, Lee JG, Nguyen P. Negative predictive value of endoscopic ultrasound in a large series of patients with a clinical suspicion of pancreatic cancer. Am J Gastroenterol. 2005;100:2658–61.
57. Catanzaro A, Richardson S, Veloso H, Isenberg GA, Wong RC, Sivak Jr MV, Chak A. Long-term follow-up of patients with clinically indeterminate suspicion of pancreatic cancer and normal EUS. Gastrointest Endosc. 2003;58:836–40.
58. Bhutani MS, Gress FG, Giovannini M, Erickson RA, Catalano MF, Chak A, Deprez PH, Faigel DO, Nguyen CC. The No Endosonographic Detection of Tumor (NEST) Study: a case series of pancreatic cancers missed on endoscopic ultrasonography. Endoscopy. 2004;36:385–9.
59. Eloubeidi MA, Varadarajulu S, Desai S, Wilcox CM. Value of repeat endoscopic ultrasound-guided fine needle aspiration for suspected pancreatic cancer. J Gastroenterol Hepatol. 2008;23:567–70.

60. Suzuki R, Lee JH, Krishna SG, Ramireddy S, Qiao W, Weston B, Ross WA, Bhutani MS. Repeat endoscopic ultrasound-guided fine needle aspiration for solid pancreatic lesions at a tertiary referral center will alter the initial inconclusive result. J Gastrointestin Liver Dis. 2013;22:183–7.
61. Tummala Md P, Rao Md S, Agarwal MB. Differential diagnosis of focal non-cystic pancreatic lesions with and without proximal dilation of pancreatic duct noted on CT scan. Clin Transl Gastroenterol. 2013;4, e42.
62. Singh S, Reddymasu S, Waheed S, Vail M, He J, Talapaneni J, Olyaee M. Endoscopic ultrasonography findings in patients with non-specific changes of the pancreas on computed tomography: a single-center experience. Dig Dis Sci. 2008;53:2799–804.
63. Agarwal B, Krishna NB, Labundy JL, Safdar R, Akduman EI. EUS and/or EUS-guided FNA in patients with CT and/or magnetic resonance imaging findings of enlarged pancreatic head or dilated pancreatic duct with or without a dilated common bile duct. Gastrointest Endosc. 2008;68:237–42; quiz 334, 335.
64. DeWitt J, Devereaux B, Chriswell M, McGreevy K, Howard T, Imperiale TF, Ciaccia D, Lane KA, Maglinte D, Kopecky K, LeBlanc J, McHenry L, Madura J, Aisen A, Cramer H, Cummings O, Sherman S. Comparison of endoscopic ultrasonography and multidetector computed tomography for detecting and staging pancreatic cancer. Ann Intern Med. 2004;141:753–63.
65. Agarwal B, Abu-Hamda E, Molke KL, Correa AM, Ho L. Endoscopic ultrasound-guided fine needle aspiration and multidetector spiral CT in the diagnosis of pancreatic cancer. Am J Gastroenterol. 2004;99:844–50.
66. Harewood GC, Wiersema MJ. Endosonography-guided fine needle aspiration biopsy in the evaluation of pancreatic masses. Am J Gastroenterol. 2002;97:1386–91.
67. Dewitt J, Devereaux BM, Lehman GA, Sherman S, Imperiale TF. Comparison of endoscopic ultrasound and computed tomography for the preoperative evaluation of pancreatic cancer: a systematic review. Clin Gastroenterol Hepatol. 2006;4:717–25. quiz 664.
68. Tummala P, Junaidi O, Agarwal B. Imaging of pancreatic cancer: an overview. J Gastrointest Oncol. 2011;2:168–74.
69. Raimondi S, Lowenfels AB, Morselli-Labate AM, Maisonneuve P, Pezzilli R. Pancreatic cancer in chronic pancreatitis; aetiology, incidence, and early detection. Best practice & research. Clin Gastroenterol. 2010;24:349–58.
70. Yamada Y, Mori H, Matsumoto S, Kiyosue H, Hori Y, Hongo N. Pancreatic adenocarcinoma versus chronic pancreatitis: differentiation with triple-phase helical CT. Abdom Imaging. 2010;35:163–71.
71. Sandrasegaran K, Nutakki K, Tahir B, Dhanabal A, Tann M, Cote GA. Use of diffusion-weighted MRI to differentiate chronic pancreatitis from pancreatic cancer. Am J Roentgenol. 2013;201:1002–8.
72. Norton ID, Zheng Y, Wiersema MS, Greenleaf J, Clain JE, Dimagno EP. Neural network analysis of EUS images to differentiate between pancreatic malignancy and pancreatitis. Gastrointest Endosc. 2001;54:625–9.
73. Li X, Xu W, Shi J, Lin Y, Zeng X. Endoscopic ultrasound elastography for differentiating between pancreatic adenocarcinoma and inflammatory masses: a meta-analysis. World J Gastroenterol. 2013;19:6284–91.
74. Raimondo MY, Yab TC, Mahoney DW, Taylor WR, Anderson KS, Ahlquist DA. Methylated DNA markers in pancreatic juice discriminate pancreatic cancer from chronic pancreatitis and normal controls. Gastroenterology. 2013;144:S-90.
75. Latham J, Sanjay P, Watt DG, Walsh SV, Tait IS. Groove pancreatitis: a case series and review of the literature. Scott Med J. 2013;58:e28–31.
76. Munigala S, Kanwal F, Xian H, Scherrer JF, Agarwal B. Increased risk of pancreatic adenocarcinoma after acute pancreatitis. Clin Gastroenterol Hepatol. 2014;12(7):1143–1150.e1.
77. Shimosegawa T, Chari ST, Frulloni L, Kamisawa T, Kawa S, Mino-Kenudson M, Kim MH, Kloppel G, Lerch MM, Lohr M, Notohara K, Okazaki K, Schneider A, Zhang L. International consensus diagnostic criteria for autoimmune pancreatitis: guidelines of the International Association of Pancreatology. Pancreas. 2011;40:352–8.
78. Sah RP, Chari ST. Autoimmune pancreatitis: an update on classification, diagnosis, natural history and management. Curr Gastroenterol Rep. 2012;14:95–105.
79. Mizuno N, Bhatia V, Hosoda W, Sawaki A, Hoki N, Hara K, Takagi T, Ko SB, Yatabe Y, Goto H, Yamao K. Histological diagnosis of autoimmune pancreatitis using EUS-guided Trucut biopsy: a comparison study with EUS-FNA. J Gastroenterol. 2009;44:742–50.
80. Zhang L, Notohara K, Levy MJ, Chari ST, Smyrk TC. IgG4-positive plasma cell infiltration in the diagnosis of autoimmune pancreatitis. Mod Pathol. 2007;20:23–8.
81. Chari ST, Takahashi N, Levy MJ, Smyrk TC, Clain JE, Pearson RK, Petersen BT, Topazian MA, Vege SS. A diagnostic strategy to distinguish autoimmune pancreatitis from pancreatic cancer. Clin Gastroenterol Hepatol. 2009;7:1097–103.
82. Kamisawa T, Chari ST, Lerch MM, Kim MH, Gress TM, Shimosegawa T. Recent advances in autoimmune pancreatitis: type 1 and type 2. Gut. 2013;62:1373–80.
83. Yoon WJ, Lee JK, Lee KH, Ryu JK, Kim YT, Yoon YB. Cystic neoplasms of the exocrine pancreas: an

update of a nationwide survey in Korea. Pancreas. 2008;37:254–8.
84. Tipton SG, Smyrk TC, Sarr MG, Thompson GB. Malignant potential of solid pseudopapillary neoplasm of the pancreas. Br J Surg. 2006;93: 733–7.
85. Estrella JS, Li L, Rashid A, Wang H, Katz MH, Fleming JB, Abbruzzese JL. Solid pseudopapillary neoplasm of the pancreas: clinicopathologic and survival analyses of 64 cases from a single institution. Am J Surg Pathol. 2014;38:147–57.
86. Kloppel G, Hruban RH, Klimstra DS, Maitra A, Morohoshi T, Notohara K, Shimizu M, Terris B Solid-pseudopapillary neoplasm of the pancreas. In: Bosman FT, Carneiro F, Hruban RH, Theise ND, editors. WHO Classification of Tumors of the Digestive System. 4th ed. WHO; 2010. p. 327–330.
87. Cantisani V, Mortele KJ, Levy A, Glickman JN, Ricci P, Passariello R, Ros PR, Silverman SG. MR imaging features of solid pseudopapillary tumor of the pancreas in adult and pediatric patients. Am J Roentgenol. 2003;181:395–401.
88. Jani N, Dewitt J, Eloubeidi M, Varadarajulu S, Appalaneni V, Hoffman B, Brugge W, Lee K, Khalid A, McGrath K. Endoscopic ultrasound-guided fine-needle aspiration for diagnosis of solid pseudopapillary tumors of the pancreas: a multicenter experience. Endoscopy. 2008;40:200–3.
89. Lewis RB, Lattin Jr GE, Paal E. Pancreatic endocrine tumors: radiologic-clinicopathologic correlation. Radiographics. 2010;30:1445–64.
90. Metz DC, Jensen RT. Gastrointestinal neuroendocrine tumors: pancreatic endocrine tumors. Gastroenterology. 2008;135:1469–92.
91. Kulke MH, Anthony LB, Bushnell DL, de Herder WW, Goldsmith SJ, Klimstra DS, Marx SJ, Pasieka JL, Pommier RF, Yao JC, Jensen RT. NANETS treatment guidelines: well-differentiated neuroendocrine tumors of the stomach and pancreas. Pancreas. 2010;39:735–52.
92. Seregni E, Ferrari L, Bajetta E, Martinetti A, Bombardieri E. Clinical significance of blood chromogranin A measurement in neuroendocrine tumours. Ann Oncol. 2001;12 Suppl 2:S69–72.
93. Dickson PV, Behrman SW. Management of pancreatic neuroendocrine tumors. Surg Clin North Am. 2013;93:675–91.
94. Campana D, Nori F, Piscitelli L, Morselli-Labate AM, Pezzilli R, Corinaldesi R, Tomassetti P. Chromogranin A: is it a useful marker of neuroendocrine tumors? J Clin Oncol. 2007;25:1967–73.
95. Stivanello M, Berruti A, Torta M, Termine A, Tampellini M, Gorzegno G, Angeli A, Dogliotti L. Circulating chromogranin A in the assessment of patients with neuroendocrine tumours. A single institution experience. Ann Oncol. 2001;12 Suppl 2:S73–7.
96. Sohn TA, Yeo CJ, Cameron JL, Nakeeb A, Lillemoe KD. Renal cell carcinoma metastatic to the pancreas: results of surgical management. J Gastrointest Surg. 2001;5:346–51.
97. Ascenti G, Visalli C, Genitori A, Certo A, Pitrone A, Mazziotti S. Multiple hypervascular pancreatic metastases from renal cell carcinoma: dynamic MR and spiral CT in three cases. Clin Imaging. 2004;28:349–52.
98. Mortele KJ, Mortele B, Silverman SG. CT features of the accessory spleen. Am J Roentgenol. 2004;183:1653–7.
99. Spencer LA, Spizarny DL, Williams TR. Imaging features of intrapancreatic accessory spleen. Br J Radiol. 2010;83:668–73.
100. Varadarajulu S, Tamhane A, Eloubeidi MA. Yield of EUS-guided FNA of pancreatic masses in the presence or the absence of chronic pancreatitis. Gastrointest Endosc. 2005;62:728–36; quiz 751, 753.
101. Chari ST, Kloeppel G, Zhang L, Notohara K, Lerch MM, Shimosegawa T. Histopathologic and clinical subtypes of autoimmune pancreatitis: the Honolulu consensus document. Pancreas. 2010;39: 549–54.
102. Kamisawa T, Chari ST, Giday SA, Kim MH, Chung JB, Lee KT, Werner J, Bergmann F, Lerch MM, Mayerle J, Pickartz T, Lohr M, Schneider A, Frulloni L, Webster GJ, Reddy DN, Liao WC, Wang HP, Okazaki K, Shimosegawa T, Kloeppel G, Go VL. Clinical profile of autoimmune pancreatitis and its histological subtypes: an international multicenter survey. Pancreas. 2011;40:809–14.
103. Maker AV, Lee LS, Raut CP, Clancy TE, Swanson RS. Cytology from pancreatic cysts has marginal utility in surgical decision-making. Ann Surg Oncol. 2008;15:3187–92.
104. Kitano M, Sakamoto H, Kudo M. Contrast-enhanced endoscopic ultrasound. Dig Endosc. 2014;26 Suppl 1:79–85.
105. Park JS, Kim HK, Bang BW, Kim SG, Jeong S, Lee DH. Effectiveness of contrast-enhanced harmonic endoscopic ultrasound for the evaluation of solid pancreatic masses. World J Gastroenterol. 2014;20:518–24.
106. Cirillo F, Falconi M, Bettini R. Clinical manifestations and therapeutic management of hyperfunctioning endocrine tumors. In: Procacci C, Megibow AJ, editors. Imaging of the pancreas: cystic and rare tumors. Berlin; New York: Springer; 2003. p. 141–52.
107. Zamboni GFN, Hruban RH, et al. Mucinous cystic neoplasms of the pancreas. In: Bosman FT, Carneiro F, Hruban RH, et al., editors. World Health Organization classification of tumours of the digestive system. 4th ed. Lyon (France): IARC; 2010. p. 300–3.
108. Tanaka M, Fernandez-del Castillo C, Adsay V, Chari S, Falconi M, Jang JY, Kimura W, Levy P, Pitman MB, Schmidt CM, Shimizu M, Wolfgang CL, Yamaguchi K, Yamao K. International consensus guidelines 2012

for the management of IPMN and MCN of the pancreas. Pancreatology. 2012;12:183–97.
109. Wu BU, Sampath K, Berberian CE, Kwok KK, Lim BS, Kao KT, Giap AQ, Kosco AE, Akmal YM, Difronzo AL, Yu W, Ngor EW. Prediction of malignancy in cystic neoplasms of the pancreas: a population-based cohort study. Am J Gastroenterol. 2014;109:121–9. quiz 130.
110. Khalid A, Brugge W. ACG practice guidelines for the diagnosis and management of neoplastic pancreatic cysts. Am J Gastroenterol. 2007;102:2339–49.
111. Grobmyer SR, Cance WG, Copeland EM, Vogel SB, Hochwald SN. Is there an indication for initial conservative management of pancreatic cystic lesions? J Surg Oncol. 2009;100:372–4.