Overview of Pancreatic Masses and Cystic Lesions

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1.1 Introduction

A wide spectrum of benign and malignant diseases can produce a mass in the pancreas; these diseases can be solid benign (such as mass-forming chronic pancreatitis) or, more frequently, malignant (ductal adenocarcinoma, endocrine tumors), or cystic (cystic neoplasms, true cysts, or pseudocysts). The most important question is whether or not it is a malignant or a benign tumor; whenever possible, in the majority of the cases that are fit for treatment, histological confirmation of the diagnosis of malignancy is necessary. Of course, the major interest in routine clinical practice is in diagnosing and treating benign and malignant tumors; a systematic classification of pancreatic solid and cystic masses has been recently reported by the World Health Organization (Table 1.1) [1, 2]. Pancreatic neoplasms originate from epithelial cells, neuroendocrine cells, and mesenchymal tumors, and they can be benign, premalignant, or malignant; the pancreas can also be involved in lymphomas and solid tumors of distant organs. The aim of this review was to describe the clinical signs of solid and cystic lesions as well as the imaging aspect in order to reach an appropriate diagnosis, and the respective treatment and follow-up.

1.2 Epidemiological Aspects

The incidental finding of a solid pancreatic mass is quite rare while the occasional finding of a pancreatic cystic nodule is rather common [3]. There is no doubt that the majority of the symptomatic pancreatic masses are pancreatic cancer which is an intractable malignancy and is the seventh leading cause of global cancer deaths in industrialized countries [4]. Based on GLOBOCAN 2018 estimates, pancreatic

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Table 1.1 World Health Organization (WHO) 2010 classification of solid and cystic lesion of the pancreas [1, 2]

Epithelial tumors
Benign
Acinar cell cystadenoma
Serous cystadenoma
Premalignant lesions
Pancreatic intraepithelial neoplasia, grade 3 (PanIN-3)
Intraductal papillary mucinous neoplasm (IPMN) with low- or intermediate-grade dysplasia
Intraductal papillary mucinous neoplasm (IPMN) with high-grade dysplasia
Intraductal tubulopapillary neoplasm (ITPN)
Mucinous cystic neoplasm (MCN) with low- or intermediate-grade dysplasia
Mucinous cystic neoplasm (MCN) with high-grade dysplasia
Malignant lesions
Ductal adenocarcinoma
Adenosquamous carcinoma
Mucinous adenocarcinoma
Hepatoid carcinoma
Medullary carcinoma
Signet ring cell carcinoma
Undifferentiated carcinoma
Undifferentiated carcinoma with osteoclast-like cells
Acinar cell carcinoma
Acinar cell cystadenocarcinoma
Intraductal papillary mucinous neoplasm (IPMN) with an associated invasive carcinoma
Mixed acinar ductal carcinoma
Mixed acinar neuroendocrine carcinoma
Mixed acinar neuroendocrine ductal carcinoma
Mixed ductal neuroendocrine carcinoma
Mucinous cystic neoplasm (MCN) with an associated invasive carcinoma
Pancreatoblastoma
Serous cystadenocarcinoma
Solid pseudopapillary neoplasm
Neoplasms of the neuroendocrine pancreas
Nonfunctioning (nonsyndromic) neuroendocrine tumors
Pancreatic neuroendocrine microadenoma
Nonfunctioning pancreatic neuroendocrine tumor
Insulinoma
Glucagonoma
Somatostatinoma
Gastrinoma
VIPoma
Serotonin-producing tumors with and without carcinoid syndrome

Table 1.1 (continued)

Serotonin-producing tumor
ACT-producing tumor with Cushing syndrome
ACTH-producing tumor with Cushing syndrome
Pancreatic neuroendocrine carcinoma (poorly differentiated neuroendocrine neoplasm)
Neuroendocrine carcinoma (poorly differentiated neuroendocrine neoplasm)
Small-cell neuroendocrine carcinoma
Large-cell neuroendocrine carcinoma
Mixed neuroendocrine non-neuroendocrine neoplasms
Mixed ductal neuroendocrine carcinoma
Mixed acinar neuroendocrine carcinoma
Mature teratoma
Mesenchymal tumors
Lymphangioma
Lipoma
Solitary fibrous tumor
Perivascular epithelioid cell neoplasm (PEComa)
Ewing sarcoma
Desmoplastic small round cell tumor
Lymphomas
Diffuse large B cell lymphoma (DLBCL)
Follicular lymphoma
Lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
T cell lymphomas
Secondary tumors

cancer has been ranked as the 11th most common cancer in the world counting 458,918 new cases and causing 432,242 deaths (4.5% of all deaths caused by cancer) in 2018 [4]. The worldwide incidence of and mortality from pancreatic cancer correlate with increasing age and are slightly more common in men than in women [4]. Its incidence is estimated to increase and will include 355,317 new cases by 2040. A slight difference in pancreatic cancer incidence among genders as well as a significantly different geographic distribution has been observed [4]; it is more common in men (5.5 per 100,000; 243,033 cases) than in women (4.0 per 100,000; 215,885 cases). Finally, the incidence rate for both genders increases with age [4]. The mortality rate is also high; in 2018, the highest mortality rates were recorded in Western Europe (7.6 per 100,000 people), Central and Eastern Europe (7.3 per 100,000 people), and followed by Northern Europe and North America (equally 6.5 per 100,000 people) [4]; a trend towards an increase in pancreatic cancer incidence (+77.7% with 356,358 new cases) and mortality (+79.9%, 345,181 deaths) has been predicted from 2018 to 2040 [4]. Even if the mortality/incidence ratio from 2014 to 2018 was 94%, the five-year survival rate for pancreatic cancer increased from 6% to 9% which shows that some progress has been made [4].

The prevalence of incidentally discovered pancreatic cysts detected by computed tomography (CT) or magnetic resonance imaging (MRI) is approximately 3% [5, 6], increasing up to 9% when using high-resolution MRI [7]; this rate can be as high as 20–40% when considering only elderly people. The most represented incidentalomas are intraductal papillary mucinous neoplasia (IPMNs) and serous cystadenomas, although very small cystic lesions are difficult to characterize and small cysts may also disappear [8]. For a cystic mass or in the case of a cystic component, the most informative imaging technique is MRI; whereas, for a solid pancreatic mass, the in-depth imaging technique is CT. The prevalence of a solid pancreatic mass occasionally found at CT scan is quite low, ranging from 0.5 [9, 10] to 6% [11]. Correct diagnostic management is important for the diagnosis of a pancreatic solid nodule to assure the appropriate treatment of the patient in order to avoid over- and undertreatment. Therefore, the physician plays a pivotal role in coordinating the different specialists involved in the diagnostic process, such as endoscopists, pathologists, and radiologists. The differential diagnosis of a pancreatic solid nodule includes two different pathogenic etiologies: neoplastic or inflammatory/autoimmune. Neoplastic pancreatic nodules present great histological variability, and the likelihood of a diagnosis depends, for the most part, on the presence of symptoms rather than an incidental diagnosis. A diagnosis of malignancy is more probable in symptomatic rather than in asymptomatic cases [3]. The finding of a pancreatic mass associated with symptoms such as jaundice, weight loss, and back pain suggests a diagnosis of malignancy, with an incidence of pancreatic cancer in up to 80% of cases [12]. Conversely, in the case of the incidental diagnosis of a solid pancreatic nodule, the most common diagnoses are pancreatic neuroendocrine tumors (NENs), followed by pancreatic ductal adenocarcinoma, solid pseudopapillary tumors, and focal chronic pancreatitis (0–11%) [13].

1.3 Clinical Presentation

The size and anatomic location of the mass are crucial when determining the presence of clinical symptoms. A mass located in the head of the pancreas typically results in the obstruction of the biliary duct, leading to jaundice or pancreatic duct obstruction, with consequent pain and impairment in exocrine function; a mass in the body and tail of the pancreas is more often asymptomatic [14, 15]. If the pancreatic mass is a pancreatic NEN, in particular if it is functional, the symptoms are related to the hormone released (more often insulinomas and gastrinomas), making them usually easily recognizable [16]. An uncommon presentation of pancreatic nodules includes acute pancreatitis due to obstruction of the pancreatic duct, new onset or worsening diabetes in healthy adults, and incidental finding on abdominal imaging for unrelated diseases [17, 18]. On the contrary, the majority of cystic pancreatic neoplasms are usually asymptomatic [19, 20], and the appearance of symptoms similar to those of a solid mass may indicate malignant transformation [21].

1.3.1 Pain

Present in the majority of patients, pain is often the symptom which prompts the patient to seek medical attention. Typically, it arises as pain in the upper abdomen which radiates to the back or vague discomfort similar to indigestion which, however, does not respond to common drugs [22, 23]. Abdominal pain is present even if the mass is small (<2 cm), regardless of its location, although it has been reported by more patients having a mass in the body and/or tail of the pancreas (90%) as compared with those having cancer in the head of the pancreas (70%) [24]. The origin of the pain can be multifactorial; stretching of the pancreatic capsule and/or ductal stenosis or obstruction may contribute to its onset [25] as does liver capsule pain from metastatic liver disease. If the mass is a cancer, perineural invasion is the main cause of pain [26]. Interestingly, pain helps to predict a poor outcome in pancreatic adenocarcinoma while, in all other pancreatic malignancies in which neural invasion of cancer cells is not a key pathomorphological phenomenon, no association of pain and survival has been reported [27, 28].

1.3.2 Jaundice

Jaundice is caused by the extrinsic obstruction of the bile duct with excessively increased levels of conjugated bilirubin and alkaline phosphatase in the blood. The absence of urobilinogen and stercobilinogen determines the pale stools and dark urine. Approximately 82% of patients with a mass in the head of the pancreas have so-called “painless jaundice” as a marked feature, and rising bilirubin levels can cause pruritus. When the tumor is in the head of the pancreas, it occurs in 80% to 90% of patients, while when the lesion arises in the body and tail, it is observed in approximately 6% of patients.

1.3.3 Weight Loss

The association of a pancreatic mass and weight loss is typical of pancreatic adenocarcinoma, and it may occur in the absence of jaundice or distant localization of the disease [29]. Among the numerous factors affecting normal nutritional support, patients may experience the onset of exocrine pancreatic insufficiency (EPI) before diagnosis, during nonsurgical treatment, and/or following surgery. Since testing is cumbersome, EPI is often recognized clinically and treated empirically [30].

In the end, malnutrition can lead to skeletal muscle wasting and fat degradation, longer hospital stays, and an increased risk of complications; it reduces response to the treatment and patient well-being while increasing the risk of morbidity and mortality in operated and non-operated patients [31–33].

1.3.4 Diabetes

Diabetes of new onset in patients with a pancreatic nodule should alert the physician to the possibility of a diagnosis of cancer, since almost 80% of pancreatic cancer patients have glucose intolerance or frank diabetes. The majority of cases of diabetes associated with pancreatic cancer are diagnosed either concomitantly with the cancer or during the 2 years before the cancer is found; 71% of the glucose intolerance found in pancreatic cancer patients is unknown before the cancer is diagnosed [34, 35]. Several studies have demonstrated that diabetes in pancreatic cancer patients is characterized by peripheral insulin resistance and that insulin sensitivity in patients who undergo tumor resection is markedly improved 3 months after surgery. Nonetheless, diabetes or impaired glucose tolerance often occurs in pancreatic NEN patients due to the tumor mass effect or because the hormones secreted by the tumor interfere with the glucose metabolism [36].

1.3.5 Nausea and Vomiting

Early satiety, nausea, and vomiting often occur in the case of a large mass, and they are usually related to compression on the second portion of the duodenum creating partial or complete obstruction [29], or to the delayed gastric emptying which often accompanies pancreatic nodules [37].

1.3.6 Signs of Malignant Transformation of Cystic Pancreatic Neoplasms

Assessing the following risk features is helpful in decision-making between the options of watchful waiting versus surgery. Patients with at least two of the following risk factors (such as lesion size greater than 3 cm which involves a threefold increase in malignancy risk, the presence of a mural nodule, and dilation of the main pancreatic duct) appear to be at risk for malignant progression, although the data supported by retrospective studies have demonstrated approximately a 15% chance of developing a pancreatic malignancy [38, 39]. Other factors may also be predictive of a higher risk of malignancy, such as a family history of pancreatic cancer (increases the risk of IPMN), mutations which predispose to pancreatic cancer (*BRCA2*), abnormal blood levels of carbohydrate antigen 19-9 (CA-19-9), unexplained acute pancreatitis (especially in patients over 50 years of age), recent onset diabetes mellitus, excess weight, and coarse calcification [40–46].

1.4 Genetic Mutations and Laboratory Markers

In the diagnostic workup of a pancreatic nodule, laboratory tests are useful in guiding the diagnosis and for a general evaluation of the patient. Laboratory tests can diagnose subclinical jaundice or signs of inflammation, guiding the subsequent

workup. In recent years, the genetic evaluation of patient status has been emphasized; for example, the most importance has been ascribed to the possibility of associated familial pancreatic cancer or a gene mutation capable of leading to the development of pancreatic cancer [47, 48]. Germline mutations of BRAC1/2 are present in 1–4.6% of pancreatic ductal carcinoma patients as compared to a prevalence of BRAC1/2 mutations in the general population of 1:400; it should be noted that a BRAC2 mutation is a common hereditary risk factor in outpatients with pancreatic tumors. Other mutations are related to the PALB2, CDKN2A, ATM, p53, MSH1, MSH2, and MSH6 genes. These mutations are rare but they have high penetrance; for example, the presence of CDKN2A increases the risk of developing a pancreatic ductal carcinoma 38-fold [49]. The distinction between neuroendocrine tumors (NETs) and neuroendocrine carcinomas (NECs) is also linked to their genetic background, as TP53 and RB1 inactivation in NECs sets them apart from NETs. A large number of genetic and epigenetic alterations have been reported, and recurrent changes have been traced back to a reduced number of core pathways, including DNA damage repair, cell cycle regulation, and the phosphatidylinositol 3-kinase/mammalian target of rapamycin signaling [50]. Finally, the presence of familial pancreatic cancer in cystic lesions of the pancreas suggests performing a resection due to the increased risk of developing a malignant transformation [21].

From a practical point of view, a wide variety of tumor markers derived from serum, pancreatic tissue, saliva, and/or stool and of different natures (tumor-associated antigens, hormones, enzymes, and immunoglobulins) have been evaluated during the diagnostic workup of a pancreatic nodule. Tumor markers have no utility in screening but could be an important tool during the differential diagnosis, staging, and prognosis of pancreatic neoplastic masses. In pancreatic cancer, the most used and validated serum marker of a pancreatic mass is CA 19-9 which has a reported sensitivity and specificity of 80–90%; CA19-9 is a mucinous glycoprotein normally present in glandular secretions of a mucous type. It is synthesized by pancreatic and biliary ductal cells and by gastric, colon, endometrial, and salivary epithelia. It is not found at high levels in normal tissues but can be detected at elevated levels in patients with pancreatic, hepatobiliary, gastric, hepatocellular, colorectal, and breast cancer. With a cutoff value of 37 kU/L, CA19-9 has poor sensitivity and specificity for diagnosing pancreatic cancer [51]. In the same manner, CA 19-9 is also of no value in diagnosing the malignant transformation of pancreatic cystic neoplasms [52]. However, CA19-9 levels are correlated with tumor size and small tumors may be missed; moreover, 5–10% of the population lacks the glycosyl-transferase Lewis blood group antigen required for the expression of CA 19-9 [53–55]. According to the American Society of Clinical Oncology (ASCO) guidelines, CA 19-9 should not be used as a screening marker in asymptomatic individuals due to its low-positive predictive value [56], but they recommend its use in guiding the therapeutic strategy [57]. The clinical importance of CA 19-9 is not limited only to the diagnosis; establishing serum CA 19-9 levels can provide information regarding prognosis, patient stratification (survival groups), and resectability of the disease. On multivariate analysis, preoperative CA 19-9 levels and lymph node ratio emerged as independent predictors of survival in patients with resected pancreatic ductal adenocarcinoma (PDAC) [58]. Other studies

have demonstrated that a lower value of preoperative CA 19-9 correlates with tumor resectability [59] and a better prognosis [60]. Moreover, it is useful for monitoring patients after surgery and during chemotherapy. In the case of a functioning pancreatic NEN, hormone secretion is important in determining symptoms and guiding the diagnosis. In nonfunctioning NENs, the symptoms could be absent or aspecific. Many serum markers have been proposed to guide to and sustain a diagnosis. The most important is chromogranin A (CGA) [61, 62] and, in the same way as CA 19-9, it should not be used as a screening tool for PDAC; the aforementioned markers should not be used with a screening intent but only in cases of clinical or imaging suspicion of an NEN.

1.5 Imaging: What the Clinician Should Know?

The imaging tests which best recognize pancreatic lesions include ultrasound, transabdominal (US), or endoscopic (EUS); CT, MRI, and positron emission tomography (PET), usually in combination with CT (i.e., PET-CT). As reported in Table 1.2, physicians should know what each single examination could add to defining the pancreatic mass as solid or cystic, and what they should expect from the various imaging modalities available (Fig. 1.1).

1.5.1 Transabdominal Ultrasound (US)

Ultrasound is a ubiquitous and radiation-free imaging test used worldwide, having ever-evolving applications and devices; it has the potential of displaying the pancreas, pancreatic duct, and associated lesions. The challenge with US in pancreatic disease is the structures that the US beam has to pass before it gets to the pancreas itself. Frequently, the stomach and any other bowel is filled with gas and obscures the pancreas as can excess abdominal wall adipose tissue. An experienced physician can avoid some of these pitfalls using water to distend the stomach or with varied positioning, but their use is limited. In addition, it is difficult to ensure that the entire gland was imaged on any given examination. Contrast-enhanced ultrasound has valuable diagnostic accuracy in differentiating exocrine from endocrine pancreatic tumors, a fundamental step in addressing appropriate histological evaluation, therapeutic approach, and follow-up [63]. In the case of the presence of pancreatic cystic neoplasms, three-dimensional contrast-enhanced EUS can be safely used to follow patients with IPMNs of less than 1 cm [64].

1.5.2 Computed Tomography (CT)

Computed tomography scanning is the workhorse for diagnosing pancreatic abnormalities; it provides excellent anatomic detail and does so consistently. Computed tomography scanning requires ionizing radiation, and typical pancreas protocol CT

Table 1.2 Characteristics of common pancreatic cysts

Type of cyst	Age at onset	Location	Imaging (CT/MRI)	Imaging (EUS)	Cytology	Cyst fluid analyses	Confocal endomicroscopy
IPMN (main pancreatic duct and branch-duct)	Middle-aged and older individuals	Common in the pancreatic head, may be incidental and multifocal	MD: Diffuse or focal involvement of the MPD; BD: Cyst or cluster of cysts, may be multifocal, ductal communication	MD: Dilation of the MPD, hyperechoic nodules arising from the ductal wall; BD: Small cluster of grape-like dilations of the BD, mural nodules	Colloid-like mucin, mucin stains positive, mucinous epithelial cells with varying degrees of atypia, sparsely cellular	Thick, viscous mucus, CEA concentration usually high, amylase concentration may be high, KRAS mutation	Epithelial villous structures; no vascular networking
MCN	Middle-aged women	Body and tail, incidental, single lesion	Large cysts with thick septae, peripheral calcification, wall thickening	Macrocystic lesion with few septae. Sometimes focal, peripheral, calcification. No ductal dilation. Sometimes atypical papillary projections may be present	Mucinous epithelial cells with varying degrees of atypia, colloid-like mucin, mucin stains positive	Thick, viscous mucus, CEA concentration usually high, KRAS mutation, GNAS mutation	Epithelial villous structures; no vascular networking
SCN	Usually in older women	Entire pancreas, many small cysts or oligo/macrocystic	Microcystic multiple small cysts, central fibrous scar with calcification, sometimes oligocystic	Multiple, small, anechoic cystic areas and "honeycomb" appearance, sometimes central fibrosis or calcification	Usually acellular and nondiagnostic, small cluster of cells with bland cuboidal morphology, glycogen stain positive, mucin negative	Clear and thin, may be hemorrhagic, CEA and amylase concentrations very low	Thickened cyst wall; unilocular vascular networking; fibrous bands

IPMN intraductal papillary mucinous neoplasm, *MD* main duct, *MPD* main pancreatic duct, *BD* branch duct, *MCN* mucinous cystic neoplasm, *SCN* serous cystic neoplasm, *CT* computed tomography, *MRI* magnetic resonance imaging, *EUS* endoscopic ultrasonography, *CEA* carcinoembryonic antigen

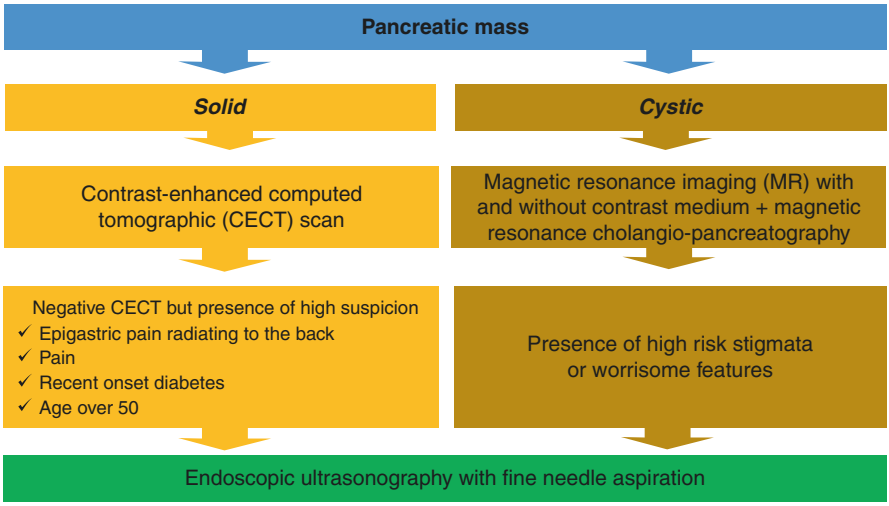

Fig. 1.1 Imaging workup for solid versus cystic pancreatic masses

scans are three-phase studies (precontrast, arterial phase, and portal venous phase imaging). In addition, iodinated intravenous contrast is required in nearly all pancreatic protocols and may be contraindicated in the setting of moderate to severe allergy or renal failure. The sensitivity and specificity of CT in diagnosing a solid pancreatic mass is high and is of paramount importance in evaluating vascular involvement; in fact, the sensitivity of CT in diagnosing vascular involvement is 98%, specificity 79%, and overall accuracy 80% having a positive predictive value of 87.5% and a negative predictive value of 96% [65].

1.5.3 Endoscopic Ultrasound and Tissue Acquisition

Endoscopic ultrasound has become the primary imaging technique for investigating patients with pancreatic lesions. Although minimally invasive, EUS does require deep sedation, and thus, patients must be appropriately evaluated with a preoperative medical assessment. It provides the option of fine-needle aspiration (FNA), and it is especially useful if the cyst morphology changes or the patient develops symptoms so that a repeat FNA can be performed. The level of carcinoembryonic antigen in the cyst fluid can be examined, and the cytological identification of lesions with a high risk of malignancy is possible. However, at present, there are limited data regarding the evaluation of molecular markers in the cystic fluid for evaluating cancer transformation. Confocal laser endomicroscopy (CLE) is a novel imaging technology which uses low-power laser to obtain in vivo histology of the gastrointestinal mucosa, and recently, a CLE miniprobe has been developed to use during EUS-FNA to visualize the cyst wall and epithelium directly through a 19-gauge FNA needle. The technical feasibility of this probe has been demonstrated, and

preliminary studies of pancreatic cystic lesions have revealed that the presence of epithelial villous structures is associated with IPMNs, having 59% sensitivity and 100% specificity [66]. Prospective studies for confirming the above are ongoing [67].

1.5.4 MRI with MR Cholangiopancreatography (MRCP)

The most comprehensive abdominal examination is MRI [68]; it offers a strong and complete pancreas examination, especially in younger patients. As opposed to CT, MRI obtains multiple complimentary sequences in addition to multiple phases of contrast enhancement. Diffusion-weighted imaging, a sequence which capitalizes on the decreased random motion of water molecules to show highly cellular tumors, is helpful in detecting otherwise occult tumors. Magnetic resonance cholangiopancreatography is useful in establishing the relationship between cystic lesions and the biliary and pancreatic ducts. However, the disadvantages of MRI are: (1) it is probably more expensive, (2) it is not universally available, and (3) it cannot be carried out in patients who have any metal implants in the body.

1.6 Treatment and Follow-Up of Patients with Solid and Cystic Lesions of the Pancreas

Solid lesions of the pancreas should be resected if the patient is fit for surgery. However, it is necessary to obtain a pathological diagnosis in order to prescribe appropriate medical therapy [69].

Cyst malignancy should be established on clinical and imaging data since a serous cystadenoma is not subject to malignant transformation [70] while an IPMN of the main duct and a mucinous cystadenoma must be removed surgically, if this is not contraindicated due to severe comorbidities. An IPMN of the secondary ducts can become malignant and, therefore, needs adequate follow-up, preferably with MRI associated with MR pancreatography or in selected cases with EUS (Fig. 1.2) [21]. The patients who should undergo EUS are therefore those with indeterminate cystic lesions, IPMNs of the secondary ducts with signs of alarm (nonspecific abdominal pain or single or recurrent episodes of acute pancreatitis not attributable to other causes, cysts of diameter ≥3 cm, main pancreatic duct dilation 5–9 mm, uptake of contrast medium of mural nodules, sudden change in the caliber of the pancreatic duct with distal pancreatic atrophy) or signs of a high risk of malignancy (obstructive jaundice, mural nodules, main pancreatic duct dilation greater than 10 mm) [21, 38]. In patients undergoing EUS, the dilemma is to decide when a sample of the cyst content is needed. The answer is when there is an unclear imaging diagnosis at CT/MRI, in inoperable patients who require chemotherapy, asymptomatic branch duct-IPMNs of 3 cm in size or with signs of a high risk of malignancy. However, MRI associated with MR pancreatography should be scheduled for monitoring pancreatic cystic lesions in branch-duct IPMNs as follows: a diameter less than 10 mm every 12 months, a diameter between 10 and 20 mm

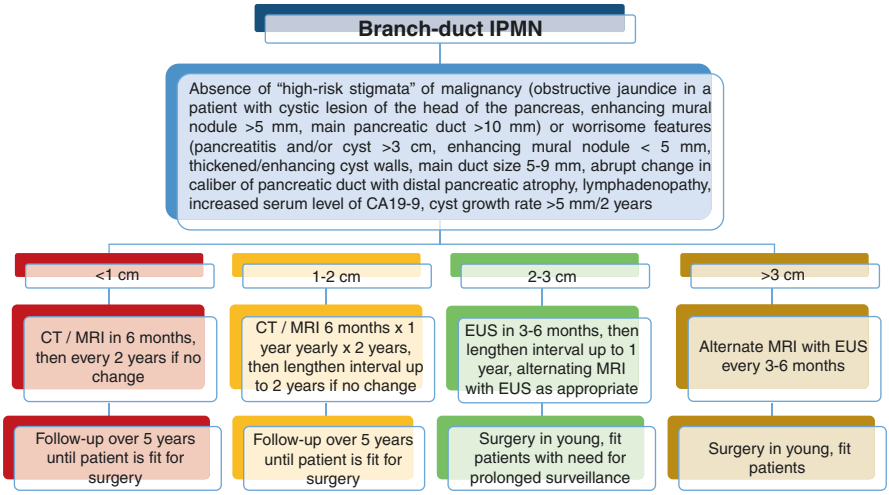

Fig. 1.2 Management of branch-duct intraductal papillary mucinous neoplasms (IPMNs). *CT* computed tomographic scan, *MRI* magnetic resonance imaging, *EUS* endoscopic ultrasonography, *CA 19-9* Carbohydrate Antigen 19-9

every 6–12 months and a diameter greater than 20 mm every 3–6 months; if the cystic lesion is stable 2 years after the initial diagnosis, the timing of the follow-up can be modified as follows: a diameter less than 10 mm every 24 months, a diameter between 10 and 20 mm every 18 months and a diameter greater than 20 mm every 12 months [71]. The question is how long should the follow-up be; whereas American guidelines recommend stopping the follow-up after 5 years if the clinical picture has not changed [72], and increasing evidence has suggested that the follow-up should be extended for more than 5 years due to the possibility of detecting malignant transformation after this period [73, 74]. The last question is the quality of life of patients followed long-term clinically and radiologically; the answer is that patients with IPMNs have a quality of life similar to the general population from both a physical and a mental point of view [19] and, thus, the long-term follow-up does not seem to affect the well-being of these subjects.

1.7 Conclusions

Clinical signs in solid tumors are important in reaching a diagnosis whereas pancreatic cysts are mainly asymptomatic, and radiological and cytological examinations are important tools in order to reach a diagnosis. In this respect, a CT scan is the optimal modality for the initial evaluation of solid pancreatic masses, including local and distant staging, and surgical planning whereas MRI/MRCP is the preferred modality for cystic pancreatic lesion assessment and can be used without contrast to follow-up incidental lesions. Endoscopic ultrasound combined with MRCP in evaluating cystic lesions is able to document the presence of carcinoma

transformation by means of an evaluation of fluid analysis and FNA of any mural nodules. Of course, in patients with cystic lesions, such as branch-duct IPMNs, who do not need immediate surgery and are fit for surgery, a medical and radiological follow-up is important to detect malignant transformation.

Conflict of Interest None to declare.

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