Diagnostic strategy with a solid pancreatic mass

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Summary

The correct diagnosis of a patient presenting with a solid pancreatic mass requires a careful diagnostic work-up, since many differential diagnoses are possible that completely alter the following treatments. In our chapter, we have discussed the clinical approach to the problem in a sort of diagnostic flow-chart. Firstly, we analysed the different potential presentations of a solid pancreatic mass, which can be both asymptomatic or symptomatic, and the differential diagnosis based on the symptoms of presentation. Then we focused on the various imaging techniques commonly used in the diagnostic work-up, stressing on the different presentations according to the type of disease, and the operative procedures that can supplement this part. Lastly, we discussed the best diagnostic work up that should be followed to fully understand the characteristics of each disease, which is of paramount importance to choose the adequate treatment plan, with special attention to pancreatic adenocarcinoma and its many treatment strategies such as chemotherapy, surgery, or medical therapy. In patients presenting with a solid pancreatic mass it is crucial to reach a definitive diagnosis using a well determined diagnostic work-up to better characterize the lesion, since the best treatment varies widely according not only to the type of disease but also to its features.

The pancreatic nodule

The word “pancreas” derives from the Greek pan-kreas, which means “all-flesh” and describes a parenchymatous, homogenous organ, in which the presence of a solid nodule is almost always associated with a pathological condition. The incidental finding of a solid pancreatic mass is quite rare, while the occasional finding of a pancreatic cystic nodule is rather common. The prevalence of incidentally discovered pancreatic cysts detected by computerized tomography or magnetic resonance imaging (MRI) is 2.4-2.6% [1,2], increasing up to 9.3% when using high-resolution...
MRI [3]. This rate can be as high as 20%–40% considering only elderly people (7–8th decade). The most represented incidentalomas are intraductal papillary mucinous neoplasia (IPMNs) and serous cystadenomas although very small cystic lesions are difficult to characterize. For a cystic mass or in 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 scan. The prevalence of a solid pancreatic mass occasionally found at CT-scan is quite low, ranging from 0.6% [4] – 0.49% [5] to 6% in other series [6].

An appropriate diagnostic strategy is essential for the correct diagnosis of a pancreatic solid nodule to guarantee the proper treatment of the patient, avoiding over- and under-treatment. Therefore, the physician plays a pivotal role of coordination of 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 aetiology: neoplastic or inflammatory/autoimmune.

Neoplastic pancreatic nodules present a great histological variability and the likelihood of a diagnosis depends mostly on the presence of symptoms rather than an incidental diagnosis. A diagnosis of malignancy is more probable in symptomatic rather than in asymptomatic cases. A pancreatic mass finding associated to symptoms such as jaundice, weight loss, back pain suggests a diagnosis of malignancy, with an incidence of PDAC in up to 70–80% of cases [7]. Conversely, in case of incidental diagnosis of a solid pancreatic nodule, the most common diagnoses are pancreatic NEN (pan-NEN) (23–42%), followed by pancreatic ductal adenocarcinoma (PDAC) (31–34%), solid pseudopapillary tumour (3–15%), and focal chronic pancreatitis (0-11%) [8].

**Differential diagnosis**

**Inflammatory diseases**

**Chronic pancreatitis**

Chronic pancreatitis (CP) is an inflammatory disease characterised by the irreversible damage of exocrine pancreatic parenchyma and fibrosis. The incidence of CP around the world varies from 1 to 15/100,000 per years, depending on the countries [9]. The etiological risk factors associated with chronic pancreatitis are alcohol consumption, smoking habit, hereditary factors and ductal obstruction/anatomical anomalies. All these elements must be investigated during the patient history collection to achieve a differential diagnosis. CP is a well-known risk factor for developing pancreatic cancer. About 5% of patients with CP will develop pancreatic cancer over a 20 years period [10], which is mainly located in the pancreatic head. Equally, patients with CP tend to develop tumour-like inflammatory masses in the pancreatic head, called pseudotumor, which can be easily misdiagnosed as a cancer. This form of CP is also called groove pancreatitis or preduodenal pancreatitis or, in the past, cystic dystrophy of the duodenal wall. The differential diagnosis between CP and cancer is crucial to avoid unnecessary major pancreatic resection or, contrariwise, under-treatment of a potentially curable lesion.

**Autoimmune pancreatitis**

Autoimmune pancreatitis (AIP) is a very rare disease with an incidence of 0.8 per 100,000 in Japan [11]. AIP is a distinct type of chronic pancreatitis (2-11% of all cases) and it is characterized by abundant infiltration inflammatory cells and associated fibrosis that leads to organ dysfunction. It is divided into two general forms with distinctly different clinical features: lymphoplasmacytic sclerosing pancreatitis (type 1) and idiopathic duct-centric pancreatitis (type 2).

AIP type 1, the most frequent form, is characterized by periductal infiltration with IgG4-positive plasma cells, which leads to interlobular and periductal fibrosis, that can cause narrowing of the pancreatic duct and acinar atrophy; focal involvement of the pancreas and hypoattenuation, reported in 28-41% of cases, can mimic PDAC [12].

AIP was traditionally associated to other autoimmune disorders, such as primary sclerosing cholangitis (PSC), Sjögren’s syndrome or retroperitoneal fibrosis. Recent studies demonstrated that these associations are, indeed, other manifestation of AIP itself, which simulates other diseases. However, the crucial point is to recognize AIP from PDAC, since the former responds to steroid therapy and it avoids unnecessary surgery and pancreatic resection.

**Neoplastic diseases**

**Pancreatic ductal adenocarcinoma**

Pancreatic ductal adenocarcinoma (PDAC) is the most common solid tumour of the pancreas, representing about 80% of the cases of a pancreatic nodule associate to symptoms. Pancreatic ductal adenocarcinoma (PDAC) in asymptomatic patients is very rare, varying in different series from 6% up to 30%. A large case-control study comparing the incidence of early pancreatic cancer symptoms suggested that pancreatic cancer is associated with 12 alarms symptoms: weight loss, abdominal pain, nausea and vomiting, bloating, dyspepsia, new-onset diabetes, changes in bowel habit, pruritus, lethargy, back pain, shoulder pain, and jaundice.

Five symptoms have been shown to occur more than 6 months before diagnosis: back pain, shoulder pain, dysphagia, changes in bowel habit, and lethargy [13].

Differential diagnosis with a solitary nodule of the pancreas can be posed with different forms of pancreatitis, primary pancreatic neuroendocrine neoplasms, solid pseudopapillary tumours, metastasis, peripancreatic lesions as well as rare pancreatic tumours [14].

Diagnostic strategy in case of PDAC is not only focused on achieving the correct diagnosis but also in assessing the
presence of metastasis and morphological resectability, to choose the best therapeutic option.

**Pancreatic neuroendocrine neoplasm**
Pancreatic neuroendocrine neoplasms (panNEN) account for 5% of all pancreatic tumours. Most tumours secrete endocrine hormones (such as insulin, glucagon, vasoactive intestinal peptide, gastrin, or somatostatin) but only a few patients are symptomatic. Occasionally, they can present on CT and MR imaging heterogeneous and with atypical enhancement that can mimic PDAC; in these cases, serum marker or biopsy is needed for differential diagnosis [15]. Among panNEN, Neuroendocrine Carcinoma (NEC) are rare and aggressive tumours characterized by poorly differentiation with features suggesting endocrine distinction, a high-proliferative rate and frequently abundant necrosis with prominent angioinvasion.
In particular, while a panNET usually occurs as a hypervascularized lesion, NEC with high proliferative index (Ki67 > 50%) may present as a hypovascularized mass frequently associated with necrosis, thus resembling PDAC [16,17].

**Pseudopapillary tumour**
Solid pseudopapillary tumour is a rare pancreatic tumour (1-2% of all exocrine tumours) and it is typically seen in young women. Most cases are benign or low-grade malignant neoplasms. These tumours are usually large and encapsulated and contain of a mixture of cystic, solid and haemorrhagic components. The predominantly solid and smaller lesions can mimic PDAC, however, the young patients’ age or any identification of intratumoral bleeding or a capsule should help in distinguishing these forms [18]. Solid pseudopapillary tumours can present as solid and cystic lesions and they can be categorized in both groups depending on the type (solid versus cystic variant). Their solid variant can have similar radiological features as panNEN.

**Acinar cell carcinoma**
Acinar Cell Carcinoma (ACC) is a rare primary tumour of the exocrine pancreas (1% of all exocrine pancreatic cancer), although most of the pancreatic parenchyma is composed of acinar cells. ACC is defined as a carcinoma exhibiting pancreatic enzyme secretion by neoplastic cells, and its clinical presentation is usually related either to the local effects of the tumour or to metastases [19]. ACC should be considered when a solid hypovascular pancreatic mass is found; differential diagnosis with PDAC can be made because the hypodensity area is usually limited to the centre of the tumour, where a cystic mass is usually found; moreover, ACC typically presents significant necrosis [20-22].

**Periampullary tumour**
Periampullary neoplasms pose a challenge in evaluation of pancreatic tumours and include ampullary adenocarcinomas and adenomas, duodenal adenocarcinomas and GISTs and distal cholangiocarcinoma.

**Metastasis**
Metastatic lesions to the pancreas are uncommon (2% of pancreatic masses) and may manifest with different characteristics based on the primary tumour site. The most frequent primary tumour which metastasize to the pancreas is the renal cell carcinoma (60%), non-small-cell lung cancer, breast cancer, sarcoma, melanoma, colon cancer and, less commonly, thyroid and liver (hepatocellular carcinoma) [23,24]. Metastases are usually found in the context of a primary disease (known as metachronous disease), but isolated metastases can also be found [25,26].
A wide variety of hematologic malignancies can involve the pancreas, particularly non-Hodgkin lymphoma, ranging between 5-30% of cases either by direct extension from the surrounding contiguous lymph nodes or by haematogenous spread of the disease.
Primary pancreatic lymphoma accounts for less than 0.5% of all pancreatic malignancies and 1% of extranodal lymphomas. Most cases of hematologic malignancies are correctly identified by radiologic and clinical findings, avoiding unnecessary surgery [27].

**Clinical presentation**
A solid pancreatic mass could be completely asymptomatic. The size and the anatomic location of the mass are crucial in determining the presence of clinical symptoms: typically, a mass located in the head of the pancreas results in the obstruction of the biliary duct, leading to jaundice or pancreatic duct obstruction, with consequently impairment in exocrine function; a mass in the body and tail of the pancreas is more often asymptomatic [28,29].
If the pancreatic mass is a panNEN, in particular a functional one, the symptoms are related to the hormone released (more often insulinomas and gastrinomas), making them usually recognizable [30].
Uncommon presentation of pancreatic nodules includes acute pancreatitis (caused by obstruction of the pancreatic duct), new onset or a worsening diabetes in otherwise healthy adult and incidental finding on abdominal imaging for unrelated issue (though this modality is extremely rare) [31,32].

**Jaundice**
It 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 justifies the associated pale stools and dark urine [33].
Approximately 82% of patients with lesion of the head of the pancreas have the so-called “painless jaundice” as marked feature, and rising bilirubin levels can cause pruritus.
If the nodule is in the head of the pancreas, it occurs in 80 to 90% of patients, while it is observed in just 6% of patients when the lesion arises in the body and tail.

**Weight Loss**

The association of pancreatic nodule and weight loss is typical of pancreatic adenocarcinoma, and it may occur in the absence of jaundice or extensive carcinomatosis [34]. Weight loss may be present also in the case of focal chronic pancreatitis, due to a reduction of pancreatic enzymes necessary for food absorption.

**Pain**

Present in most patients at different time points, pain is often the symptom that prompts the patient to medical attention. Typically, it arises as pain in the upper abdomen that radiates to the back or a vague discomfort similar to an indigestion, but not responding to the common drugs [13,35]. Abdominal pain is present even if the mass is small (< 2 cm) and regardless of its location, although it was reported by more patients with a mass in the body and tail of the pancreas (90%) compared with those with cancer in the head of the pancreas (70%) [36]. The origin of pain may be multifactorial: pancreatic capsule stretching and/or ductal stenosis or obstruction may contribute to its onset, [37] as well as liver capsule pain from metastatic liver disease; if the mass is a cancer, perineural invasion is the principal cause of pain [38]. Interestingly, once pain is detected in pancreatic adenocarcinoma, it serves as a predictor of poor outcome, while in all other pancreatic malignancies, where neural invasion of cancer cells is not a key pathomorphological phenomenon, no association of pain and survival was recorded [39,40].

**Diabetes**

Diabetes of new onset in patients with a pancreatic nodule should prompt the attention towards a cancer diagnosis, since almost 80% of pancreatic cancer patients have glucose intolerance or frank diabetes. Most cases of diabetes associated with pancreatic cancer are diagnosed either concomitantly with the cancer or during the two years before the cancer is found; 71% of the glucose intolerance found in pancreatic cancer patients is unknown before the cancer is diagnosed [41]. 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 three months after surgery. Nonetheless, diabetes or impaired glucose tolerance often occurs in PanNENs patients due to tumour mass effect or because hormones secreted by the tumour interfere with glucose metabolism [42].

**Nausea and vomiting**

Clinical data indicate that early satiety, nausea and vomiting often occur in case of a very bulky mass and they are usually related to compression on the second portion of the duodenum, creating a partial or complete obstruction [34,43]. Another cause for nausea is related to delayed gastric emptying that often accompanies pancreatic nodules [44,45].

**Laboratory**

In the diagnostic work-up of a pancreatic nodule, laboratory tests are useful to guide the diagnosis and for a general overview of the patient. Laboratory tests can diagnose a sub-clinical jaundice or signs of inflammation, guiding the subsequent work-up. If a CP is suspected, faecal elastases-1 could be dosed to assess the grade of exocrine function impairment.

Measurement of serum IgG4 levels is useful when in doubt of an AIP type 1 IgG4 serum levels are usually elevated and are related to the IgG4+ plasma cells infiltrate. However, IgG4 are not specific because their value could be increased in other diseases, such as dermatitis, asthma, soma parasitic disorders, pemphigus vulgaris and pemphigus foliaceus. IgG4 are also elevated in 3% to 10% of patients with PSC, pancreatic cancer, acute or chronic pancreatitis. Thus, high serum level of IgG4 are not specific for a diagnosis of AIP [46].

**Tumour markers**

A wide variety of tumour markers derived from serum, pancreatic tissue, saliva and/or stool and of different nature (tumour-associated antigens, hormones, enzymes and immunoglobulins) have been evaluated during the diagnostic work-up of a pancreatic nodule. Tumour markers have no utility for screening but could be an important tool during differential diagnosis, staging and prognosis of a pancreatic neoplasia.

In pancreatic cancer, the most used and validated serum marker given 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 mucous type. It is synthesized by pancreatic and biliary ductal cells and by gastric, colon, endometrial and salivary epithelia. CA 19.9 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 cut-off value of 37 kU/L, CA19-9 has a mean sensitivity of 80% and specificity of 90% for pancreatic cancer. However, CA19-9 levels are correlated with tumour size and small tumours may be missed; moreover, 5-10% of the population lack the glycosyltransferase Lewis blood group antigen required for the expression of CA 19-9 [47-49].

According to American Society of Clinical Oncology (ASCO) guidelines, CA 19.9 should not be used as screening marker in asymptomatic individuals because of its low positive predictive value, but they recommend its use in guiding the therapeutic strategy [50,51]. The clinical importance of CA 19.9 is not limited only to the diagnosis: establishing serum CA 19.9 levels can provide information about prognosis, patient stratification (survival groups) and resectability of the disease. On multivariate analysis preoperative CA 19.9 levels and lymph node radio
emerged as independent predictors of survival in patients with resected PDAC [52]. Other studies demonstrated that lower value of preoperative CA 19.9 correlates with tumour resectability [53] and better prognosis [54]. Moreover, it is useful for monitoring patients after surgery and during chemotherapy. In case of a functioning panNEN, hormone secretion is crucial in determining symptoms and guiding the diagnosis. In non-functioning NEN, the symptoms could be absent or aspecific. Many serum markers have been proposed to sustain and guide to a diagnosis. The most important are chromogranin A (CGA), neuron-specific enolase (NSE), and pancreastatin testing and they should be performed to evaluate the presence of a NEN, even if hormonal hypersecretion syndrome is not evident [55]. In the same way CA 19.9 is not used as a screening tool in PDAC, these marker should not be investigated for screening intent, but only in case of obvious clinical or imaging suspect of a NEN.

**Imaging techniques**

**Ultrasonography (US)**

US is frequently the first-line diagnostic tool for patients presenting with jaundice or abdominal pain, as it is a non-invasive and cost-effective modality [56]. The diffusion of US and its non-invasiveness make it the first line investigation for abdominal pathology and this results in the high rate of incidental pancreatic nodules found by this technique performed for other reasons. However, diagnostic ability of ultrasonography greatly depends on the operator’s experience and the patient’s condition in terms of obesity and bowel gas content. Despite US may be useful in detecting a pancreatic nodule or its indirect signs (such as biliary duct dilatation, main pancreatic duct dilatation), its value in determining the exact diagnosis is poor. The typical signs compatible with PDAC on ultrasound are: a hypoechoic mass, dilatation of the pancreatic duct and dilatation of the bile duct. In case of aggressive tumours with very rapid growth, necrosis and colliquation are recognized as markedly hypoechoic central areas. The presence of a large, well-defined mass with heterogeneous appearances, due to solid and cystic composition, suggests the presence of a pseudopapillary tumour [57]. Conversely if the pancreas appears atrophic, calcified or fibrotic, chronic pancreatitis should be suspected. In case of pancreatic body or tail nodule, the detection rate is lower due to the lack of indirect signs and the presence of abdominal meteorism. The sensitivity and specificity of ultrasound for pancreatic cancer range from 75% to 89% and from 90% to 99%, respectively [58]. Doppler US might be useful for evaluating the nodule vascualrization and peripancreatic vessels (portal vein, superior mesenteric artery and vein, splenic artery and vein, aorta and inferior vena cava). While PDAC usually presents scarce or absent vascualrization, the presence of a high-vascularised nodule is suggestive for panNEN. Signs of vascular infiltration are the absence of the echogenic interface between the mass and the vessel wall, or a narrow lumen, with changes in blood flow velocity [59,60]. The administration of contrast medium enables better evaluation of the margins and size of the lesion and its relationship with peripancreatic arterial and venous vessels for local staging; however, it is not as diffused as EUS [61]. Overall, transabdominal US is an acceptable first-imaging method, but it requires further investigations for a confident diagnosis.

**Multi-detector row computer tomography**

Given its excellent spatial and temporal resolution and wide anatomic coverage, Multi-detector row computer tomography (MDCT) is gold-standard technique in investigating a pancreatic solid mass. The optimal CT examination protocol consists of four phases (unenhanced, pancreatic/late arterial phase, portal/venous phase, and late phase) and it allows the differentiation between different types of solid nodules (*figures 1–4*).

**CT scan appearance of pancreatic adenocarcinoma**

CT-scan is the most used imaging examination for detection and staging of pancreatic cancer. This technique allows both local and distant disease staging at the same time [62]. On imaging, it is typically detected as a hypovascular mass with poorly defined contours, without necrosis and haemorrhage, with a tendency for focal infiltration and vascular encasement. CT best detects this hypovascularisation in the pancreatic phase, that should be completed by exploration of the whole abdominal cavity in the portal phase.

In the early phase of dynamic CT, pancreatic carcinoma is characterized by abundant fibrous stroma and...
sheathing of the celiac trunk and/or mesenteric artery and intralesional calcification [63]. MDCT is considered the gold standard also for the evaluation of vascular involvement (in particular length and the circumferential extension of vascular infiltration), but not so accurate in the detection of focal vessel infiltration, [64] which is the most important factor for predicting the tumour resectability. The reported positive predictive value, sensitivity, and specificity for predicting the resectability of pancreatic cancer are 89%, 100%, and 72%, respectively [38]. In terms of treatment monitoring following chemotherapy or surgery, MDCT is the primary imaging modality, and it is used in conjunction with PET/CT [65]. Nonetheless, some lesions are still difficult to find, in particular small tumour (< 2 cm), absence of biliary dilatation, vascular involvement and mass effect, and little attenuation difference compared to normal pancreatic parenchyma [66]. Moreover, it is not very sensitive for detecting nodal involvement and may be quite inaccurate in detecting small hepatic and peritoneal metastases. Up to a third of patients with no obvious metastases on a high-quality CT may be found to have small liver or peritoneal metastases at surgery. Hepatic metastases are seen as bad-defined, low-density lesions on the venous phase of contrast-enhanced CT or MRI [67,68]. Even when seen, lesions < 10 mm may not be characterized with certainty on CT. These should not be considered metastases, as many of such small lesions, even in a patient with PDAC, are benign ones. In this respect, MRI is superior to differentiating a small cyst or haemangioma from metastases [69].

**CT scan appearance of neuroendocrine pancreatic neoplasms**

PanNET usually present as hyper vascularized lesions on CT, while NEC with higher proliferative index (ki67 > 50%) may present as a hypo vascularized mass frequently associated with the presence of necrosis, resembling PDAC appearance [16].

**CT scan appearance on pancreatitis**

At CT scan, chronic pancreatitis presents with specific signs such as dilatation of the main pancreatic duct and side branches, diffuse parenchymal atrophy and parenchymal calcifications. However, focal chronic pancreatitis can lead to localized atrophy or enlargement of part of the gland simulating PDAC. The duct-penetrating sign (a smoothly stenotic or normal main pancreatic duct penetrating a pancreatic mass on magnetic resonance cholangiopancreatography) can be used to differentiate it from PDAC since it has been reported more often in chronic pancreatitis [70].

Both forms of groove pancreatitis can mimic PDAC and differentiation must be based on histologic confirmation (peripancreatic vascular invasion or metastatic disease is usually absent in groove pancreatitis).

Diffuse enlargement of the pancreas and effacement of the lobular contour of the pancreas (“sausage-like” appearance), is a
typical finding in AIP. Sometimes the imaging of AIP is isoattenuating or hypoattenuating in respect to the surrounding segment of the non-enlarged pancreatic parenchyma, resulting indistinguishable from pancreatic cancer. However, in very late sequences, contrast uptake by the nodule is usually observed in case of AIP [71,72]. Moreover, as fibro-inflammatory changes involve the peripancreatic adipose tissue, a capsule-like rim surrounding the pancreas, is specifically detected in some AIP patients. Additionally, usually neither vascular encasement nor calcifications are detected [71,73,74].

**CT scan appearance of other pancreatic masses**

Pseudopapillary tumours are usually seen as a well-encapsulated lesion with varying solid and cystic components owing to haemorrhagic degeneration. Enhanced solid areas are typically noted peripherally, whereas cystic spaces are usually more centrally located. Calcifications and enhancing solid areas may be present at the periphery of the mass [75].

Peripapillary tumours show poor contrast uptake in arterial and pancreatic phase with slight delayed enhancement on CT scan. Most are well-defined lobulated but infiltrative masses. Carcinoma of the ampulla of Vater is a high-grade epithelial malignancy that often manifests as a discrete nodular mass that obstructs the main pancreatic duct (and the "double duct sign") with lobular or infiltrating margins. At non-contrast-enhanced CT, the tumour typically appears as a hypoattenuating mass and it usually demonstrates enhancement on arterial and portal venous phase images [76-78].

Duodenal adenocarcinoma usually manifests at an advanced stage, and at imaging the tumour is typically hypovascular at CT scan and manifests as either a polypoid or intraluminal mass, with eccentric duodenal wall thickening [79].

The imaging appearance of Gastrointestinal Stromal Tumours (GISTs) can vary from small homogeneous masses to large necrotic masses: smaller tumours typically are sharply demarcated, smooth-walled, homogeneous soft-tissue masses with at least moderate contrast, while larger tumours tend to undergo central necrosis and cavitation and demonstrate heterogeneous enhancement at imaging [80].

Distal cholangiocarcinoma is commonly related to a biliary duct dilatation that terminates abruptly at the level of the mass. This finding is associated with both subtypes of extrahepatic cholangiocarcinoma, the infiltrating and the polypoid ones. At cross-sectional imaging, an infiltrating cholangiocarcinoma manifests itself as a high-attenuating mass and it is typically characterized by ductal wall thickening and sudden luminal obliteration.

A polypoid lesion may appear as a low-attenuating mass within the dilated bile duct and it is identical to masses in the hilar area or intrahepatic ducts [81,82].

In 50–75% of cases, pancreatic metastasis are found as solitary hypodense masses with peripheral contrast on CT, but they usually present well-defined margin compared to primary PDAC, while there is no statistically significant difference concerning tumour size, echogenicity and location [83]. Dilatation of the main pancreatic duct is not a common finding, but when it
occurs, differential diagnosis from primary pancreatic cancer is extremely difficult [84].
Pancreatic metastases from renal carcinoma cells appear hypo-
dense or isodense on enhanced CT, multiple, with a round shape and well defined margins; the fundamental clues for the differential diagnosis with PDAC consist in the pattern of enhancement after contrast medium (hypervascularization), the multifocality and the absence of infiltration of peripancreatic vessels [85].

**Endoscopic ultrasonography and fine needle aspiration**

Endoscopic Ultrasonography (EUS) is the second level gold standard technique for pancreatic nodule definition. EUS is considered one of the best methods for the detection of pancreatic nodule, especially for small ones (2 cm or less) and for histopathologic sampling allowing definitive diagnosis. The sensitivity and specificity of EUS combined with histopathologic sampling are 86.8% and 95.8%, respectively, for diagnosing a solid pancreatic mass [86] (figures 5-7).

Typical EUS appearance of PDAC is a heterogeneous and hypoechoic mass with irregular margins. However, morphological features lead to a diagnosis in only 50% of the cases since these features could be present also in focal pancreatitis, in neuroendocrine tumours and metastasis. EUS accuracy can be improved by elastography. Elastography is a technology that measures tissue stiffness, allowing a more precise differential diagnosis in case of a solid pancreatic nodule. PDAC usually has a different elastographic pattern compared to panNEN or focal pancreatitis, thus resulting in a gain in terms of specificity.

Pancreatic neuroendocrine tumours on EUS usually appear as a hypoechoic well-delimited, high-vascularised nodule. Because of their intense vascularization, EUS employing Doppler mode is particularly useful in identifying panNENs. The accuracy and specificity of EUS in detecting panNENs is very high, reaching 93% and 95% respectively.

EUS diagnosis of focal pancreatitis is very difficult, due to differential diagnosis with malignant tumour. Despite the introduction of EUS criteria regarding parenchyma and main duct characteristics, the sensitivity of the technique is rather low for diagnosis of focal chronic pancreatitis.

In addition to characterizing the nodule and giving a potential diagnosis, EUS can be very useful in determining other information: EUS can detect and sample hepatic metastases (in the left lobe), ascites or distant lymph nodes, which cannot be seen using other imaging studies. Therefore, scrupulous search for these lesions is strongly recommended during EUS. EUS-guided fine-needle aspiration (FNA) or occasionally fine-needle biopsy of suspicious pancreatic masses should be performed to obtain a precise diagnosis of these lesions, especially when therapeutic plan may be influenced by the pathological result.

**Cytology**

Fine needle aspiration (FNA) is usually performed during EUS and is almost always fundamental to achieve a definitive diagnosis of a solid pancreatic nodule. Accurate diagnosis of a malignant nodule and its differentiation from a benign disease are critical for a timely treatment. Approximately 10% of the pancreaticoduodenectomies performed for presumed malignancy reveal benign disease on pathological evaluation [87]. The reported sensitivity and accuracy of cytology after EUS-guided FNA for the diagnostic evaluation of pancreatic masses exceeds 90% [88-90], with a sensitivity for malignancy ranging from 64% to 96%. Cytology allows the evaluation of cellular findings suggestive of malignancy, such as anisonucleosis, nuclear membrane irregularity and nuclear enlargement, that needs to be distinguished from reactive processes due to inflammation that leads to cellular changes that can be difficult to distinguish from well-differentiated neoplasia [91-93]. In case of doubt, immunohistochemistry analysis can be a fundamental support to achieve a diagnosis. Immunohistochemistry is essential also in case of panNEN diagnosis to determine mitotic index, proportional to Ki67 expression and thus tumour grading which is a crucial data in evaluating a possible surgical strategy rather than a follow-up.

**Figure 5**

Endoscopic ultrasound imaging of a PDAC, localised in the pancreatic body, with infiltration of the portal vein (PV) and superior mesenteric vein (SMV)
**Figure 6**
Endoscopic ultrasound and elastosonography of PDAC (T) of the pancreatic head

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<th>Primary tumour</th>
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<td>T&lt;sub&gt;0&lt;/sub&gt;</td>
<td>No evidence of primary tumour</td>
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<td>Carcinoma in situ (including PanIN-III classification)</td>
<td>Stage IA</td>
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<td>M&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Distant metastasis</td>
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**Figure 7**
The 8<sup>th</sup> edition of TNM classification for pancreatic cancer published by the Union for International Cancer Control (UICC)
Magnetic resonance imaging

Magnetic resonance imaging (MRI) is a second-line technique in investigating pancreatic nodule. MRI offers better soft tissue contrast compared with CT but a lower spatial resolution. In addition, MRI can be implemented with magnetic resonance cholangiopancreatography (MRCP), allowing an accurate investigation of the pancreatic ductal system: this method can detect ductal narrowing that may indicate the presence of a small mass and exclude the presence of stones, which are an alternative cause of biliary or pancreatic ductal dilatation. PDAC is usually well recognized on T1-weighted and DW images, owing to differences between the histological components of the tumour and the surrounding parenchyma. There is, however, no significant diagnostic advantage of MRI over contrast-enhanced CT for the identification of PDAC [94]. Nevertheless, thanks to its greater soft-tissue contrast, MRI demonstrated superior in some cases to MDCT: small lesions, hyperpophied pancreatic head, isoa attenuation pancreatic cancer and focal fatty infiltration of the parenchyma and it can be helpful in differential diagnosis between PDAC and cystic lesions [95,96]. Pancreatic perfusion is decreased in patients with chronic pancreatitis due to chronic inflammation and fibrosis, resulting in reduced and delayed enhancement of the pancreatic signal, allowing a better differential diagnosis of CP with PDAC [97].

PanNENs are easily detected in T1-weighted sequences, using fat suppression technique, and high b-value diffusion weighted image (DWI). The typical hypervascularization of PanNENs is usually detected with contrast-enhanced US or contrast-enhanced CT-scan, but it might be missed on contrast-enhanced MRI. The rate of non-hyperenhancing PanNENs may reach 65% of cases, [98] but DWI is useful in overcoming this limit. DWI can distinguish normal pancreatic parenchyma from a NEN and may provide an indication in discerning a low-grade panNEN (G1 or G2) from an high-grade one (G3) [99].

Positron emission tomography

Positron emission tomography (PET), usually associated with a CT scan, is an established molecular imaging modality that uses radiotracers for studying metabolic cellular activity. The most commonly used radiotracer is 18-fluorodeoxyglucose (FDG), a glucose analogue, whose uptake is particularly enhanced during metabolic activity. The main limitation of FDG-PET is the difficult differentiation of inflammatory processes from neoplasms and therefore is not very useful in the differential diagnosis of a pancreatic nodule. Moreover, its inherently low spatial resolution and false-positive results, caused by normal physiologic FDG uptake, are well-known disadvantages [100]. Nevertheless, FDG-PET in PDAC is useful for treatment monitoring during chemo-radiotherapy: it has a great sensibility in detecting both cancer recurrence after resection and the presence of metastases in the entire body [101].

Conversely, PET is very useful in the diagnostic strategy in case of a diagnosis of a panNEN. NEN are characterised by overexpression of somatostatin receptors. The radioactive tracker 68-gallium (68Ga) is able to target, through linking to different peptides, these receptors and is then detected by a PET-scan. The 68Ga-DOTA-PET has shown excellent results in NEN imaging, much more better than conventional somatostatin receptors scintigraphy [102]. The combination of the two techniques, FDG-PET and 68Ga-DOTA-PET, is fundamental in the diagnostic strategy in case of a panNEN to obtain crucial information such as presence of metastases, grade of differentiation, metabolic activity.

Operative procedures during diagnostic work-up

Laparoscopic staging

Laparoscopic staging is particularly suitable in case of a diagnosis of pancreatic cancer. Careful selection of patients for surgery is important to avoid unnecessary procedures and their associated morbidities, and although advances in radiologic imaging techniques have led to great improvement in the evaluation of PDAC patients, laparoscopy can detect metastases not visualised on CT scanning, enabling better cancer staging. The routine use of staging laparoscopy is not universally supported, with critics suggesting that radiologic imaging is nowadays sufficient for accurate cancer assessment and that laparoscopy is not always reliable in detecting factors such as true tumour size and lymph node metastases, which preclude resection, meaning that the resection rate at laparotomy remains low even after laparoscopy [103]. Moreover, there are suggestions that the number of laparotomies resulting in curative resection is not significantly improved by the addition of preoperative laparoscopy [104]. On the other hand, several studies have demonstrated that laparoscopy prevents a significant number of laparotomies, in particular for tumours in the body or tail of the pancreas [105]. The addition of intraoperative ultrasound increases sensitivity by its ability to detect small liver metastases not visualized by CT scanning [106,107].

In conclusion, even considering its limitations, laparoscopy proves to be a useful tool in the selection of patients for further surgery, and it prevents a significant number of laparotomies, especially in selected groups of patients [108,109].

Jaundice palliation

Endoscopic palliation

Therapeutic endoscopy intervention has a fundamental role in the treatment of patients with pancreatic ductal adenocarcinoma: in addition to resolving jaundice and associated pruritus, normalize serum bilirubin prior to systemic chemotherapy (a bilirubin < 2.5 mg/dL is required, as inadequate biliary excretion...
of metabolites may result in chemotoxicity), biliary drainage improves anorexia, indigestion, and quality of life [110].
More than 50% of patients present with jaundice; the preferred intervention for palliation is endoscopic cholangiopancreatography (CPRE), which has favourable (80–90%) short term (< 90 day) success rate in the setting of distal bile duct obstruction when performed by experienced providers.
Complications occur in 10% of cases, including cholangitis, perforation, bleeding and post-CPRE pancreatitis [111,112]; moreover, plastic stents inevitably occlude because of bacterial biofilm formation, uncovered metallic stent can occlude because of tumour ingrowth or proximal or distal tumour overgrowth and biliary sludge, while the covered ones are at higher risk of migration.
However, given the immediate complications but also the surgical-related complications that are increased after CPRE [113], patients should be selected carefully with reference to their therapeutic options.
In particular, in those receiving neoadjuvant therapy, metallic self-expandable stent (SEMS) should be preferred over plastic ones given that plastic stent exchanges are often necessary as these stents inevitably occlude because of bacterial biofilm formation [114,115]; in patients with advanced disease, plastic stent should be used if the expected survival is less than 4 months.
For patients with resectable disease, preoperative biliary decompression is only indicated when surgery will be delayed, or complications of jaundice exist (for example, cholangitis or intractable pruritus).

Percutaneous palliation
Percutaneous transhepatic biliary drainage (PTBD) provides biliary decompression for patients with malignant biliary obstruction who are not candidates for CPRE because of anatomy-altering surgical procedures or have failed attempted endoscopic stent placement [116].
The most common indications are to reduce the serum bilirubin to allow delivery of chemotherapy and treat cholangitis and intractable pruritus, but in contrast to ERCP quality of life after the procedure do not increase; contraindications include bleeding diatheses, severe ascites, intrahepatic ductal obstructions due to diffuse hepatic parenchymal metastases, and chronic liver disease [117,118].
PTBD is performed using fluoroscopic guidance and initial percutaneous transhepatic cholangiography to evaluate biliary anatomy and the location of the obstruction. Ultrasound may be used to guide initial bile duct puncture, especially if ducts are dilated by downstream obstruction.
The treatment is chosen by relying on the possible obstruction of the hepatic duct (right or left) by the tumour and on the volume of functioning liver left.

PTBD can be accomplished using one of three types of devices: an external biliary drainage catheter, an internal–external biliary drainage catheter, or an internal SEMS.
Overall, PTBD is a safe procedure with success and complications rate similar to CPRE [119], but when feasible the endoscopic treatment is the preferred choice, because no exterior catheter is placed with possible catheter-related pain, leakage, and/or accidental dislodgement.

Diagnostic assessment for therapeutic purposes

Pancreatitis
Treatment of CP includes change in patient’s lifestyle habits, such as stopping alcohol consumption and tobacco use, and pain management. For patients with severe chronic pain not responding to painkilling medication derivative surgery should be considered.
AIP is a distinct form of chronic pancreatitis which can easily be misdiagnosed because its typical presentation is obstructive jaundice associated with a pancreatic mass. These features are analogous to PDAC clinical presentation and sometimes lead to unnecessary surgical resection. For this reason, the diagnostic assessment is particularly important in planning the appropriate treatment. The treatment goal of AIP is to achieve remission of the acute phase. Remission is usually referred to symptoms because normalization of serum IgG4 and resolution of radiologic alterations may take more time. Although the lack of retrospective randomized trial on steroid use in AIP, it is universally recognised that this disease is exclusively responsive to steroid therapy, [120] and this is among the 5 cardinal features for the diagnosis of AIP (mnemonic acronym HI-SORT): Histology, Imaging, Serology, other Organ involvement and Response to corticosteroid Therapy [121].

Solid-pseudopapillary tumour
Solid pseudopapillary neoplasm is a relatively indolent tumour with a moderately low malignant potential. However, distant metastasis and local invasiveness have been described and consequently surgical resection is the gold standard treatment and the prognosis after surgery is favourable.

Metastasis
Isolated pancreatic metastases are rare and there is a very limited experience in surgical resection and the role of surgery in the management of these patients remains unclear. However, the pancreas is an elective site for metastases from renal cell carcinoma (RCC). In the past, pancreatic metastases were considered an end-stage condition while the recent reduction in operative risk following pancreatic resections and the initial experiences seem to rehabilitate the role of surgery in the management of pancreatic metastases from RCC. Surgery could be hypothesised only in case of isolated pancreatic metastases, while surgical resection in case of metastases in

other organs does not result in an improved prognosis. Standardised pancreatic resection, depending on the location of the nodule, are recommended for single metastasis. In case of multiple metastases, the treatment is debated: whereas some authors recommend total pancreatectomy, others critically reject surgery [122].

Pancreatic neuroendocrine tumours

The approach to panNET depends on the tumour characteristics and dimensions. If the tumour is resectable and there are no distant metastases, there are two treatment strategies: when the tumour is > 2 cm requires surgical resection, if the tumour is < 2 cm, surveillance is possible if it is a low grade neoplasia, with a Ki 67 < 2% and if at FDG-PET and ⁶⁸Ga-DOTA-PET the tumour shows respectively low and high uptake activity, confirming that it expresses somatostatin receptors and hence it is a well differentiated tumour (imaging tests are necessary to ensure the diagnosis because Ki 67 may represent only a small part of the tumour not representative of its complete biology and aggressiveness) [123]. If the tumour is resectable with metastases limited to the liver, surgical resection should be considered. If the tumour is locally advanced at diagnosis or it presents with widespread extra-hepatic metastases or liver metastases that require major hepatectomies, chemotherapy, targeted therapies and peptide receptor radionuclide therapy (PRRT) should be offered in a tailored approach that considers morphology, Ki 67 and performance status [124,125]. Patients with well differentiated NECs resectable at diagnosis should undergo surgery with curative intent, while in patients with locally advanced disease there are different therapies: PRRT, somatostatin analogues long-acting release, temozolomide-based or streptozocin-based chemotherapy, and target therapies; the treatment should be tailored considering tumour morphology, Ki67 index, performance status and aim of the treatment (douchnizing/staging) [126]. As for NENs, if the tumour is resectable with metastases limited to the liver, surgical resection is feasible [127], while in the presence of locally advanced or widespread metastasis medical therapies should be considered.

Poorly differentiated NECs are a group of very aggressive malignancies, characterized by a high Ki 67 index. Patients with resectable non-metastatic NECs should undergo surgical resection, and the administration of adjuvant treatment was associated with improved survival [128]. Patients with locally advanced or metastatic tumours should undergo chemotherapy, and the most appropriate chemotherapy regimen is based on ki67 index: if ki67 < 55%, platinum-based chemotherapy should be offered, while when ki67 > 55% other agents should be considered (for example temozolomide) [125]. Surgical metastasectomy is not recommended as well in the management of NEC.

Adenocarcinoma

Diagnostic strategy in pancreatic adenocarcinoma is fundamental not only to achieve a correct diagnosis but also to choose the appropriate treatment. In addition to the histological data, the key elements to establish the correct treatment are the morphological presentation, the biological aggressiveness indicated by the marker and patient general condition. Surgical resection represents a fundamental phase of a multimodal treatment for curative purposes of pancreatic cancer and, historically, patients with potentially resectable tumours are candidates for surgical resection as a primary therapeutic modality. However, most patients who undergo pancreatectomy relapse and approximately 20% of patients who experience surgical resection die from the disease within one year of the intervention. Furthermore, in 75% of the relapse cases, patients develop distant metastasis, which are usually hepatic. This high rate of relapse is correlated with the presence of metastases already present at time of diagnosis, that are unfortunately undetectable with modern imaging techniques, regardless of whether the initial disease is still resectable. It is for this reason that awareness concerning the approach to pancreatic cancer has been growing for years. It has also been ascertained that, even when resectable, this cancer must be treated systemically with a multidisciplinary approach, for example with adjuvant chemotherapy after resective surgery to reduce the risk of relapse. The execution of postoperative adjuvant therapy is often problematic in pancreatic cancer patients because of the high level of complication associated with the surgical intervention. Complications often result in a long and challenging disease course for the patient. That is the main reason for the rather low level of compliance to adjuvant protocols, with percentages ranging from 51 to 62%.

Therefore, a new strategy based on the use of neoadjuvant protocols was introduced, similarly to what has been implemented in other types of cancer. The most recent studies show that patients’ survival improves by broadening the indications for use of neoadjuvant therapy. The indications should now consider also those patients with a morphologically locally advanced disease or even "borderline resectable" disease with characteristics of aggressiveness. In these cases, a neoadjuvant approach could lead to better survival and a higher percentage of radical resections after surgery. Given these considerations, indications for upfront surgery should not be based solely on classical morphological resectability criteria but must ponder the indicators of biologic disease aggressiveness.

Staging

Staging of pancreatic carcinoma is based on the International Union Against Cancer (UICC) staging protocol/TNM (tumour-node-metastasis) classification, an internationally accepted standard protocol and it is considered to be a major factor of
appropriate treatment stratification and prognosis predictor [129].

The eighth TNM edition introduced a new strictly size-based T staging system and a refined N stage based on the number of positive lymph node for PDAC: this classification allows a better identification of minimally invasive tumours and therefore an improved discrimination of the prognostic impact of the T status [130–132].

**Criteria for resectability**

Surgical resection represents a fundamental phase of multimodal treatment for curative purposes of pancreatic cancer and, historically, patients with potentially resectable tumours are candidates for surgical resection as a primary therapeutic modality. However, most patients who undergo pancreatectomy relapse and approximately 20% of patients who experience surgical resection die from the disease within one year of the intervention.

Furthermore, in 75% of relapse cases patients develop distant metastasis, which are usually hepatic. This high rate of relapse is correlated with the presence of metastases which are already present at the time of diagnosis but are not detectable with modern imaging techniques, regardless of whether the initial disease is still resectable.

For this reason, awareness and progress concerning the approach to pancreatic cancer have been growing for years. It has also been ascertained that, even when resectable, this cancer should be treated systemically with a multidisciplinary approach, along with adjuvant chemotherapy after surgery. Indeed, adjuvant chemotherapy reduces the risk of relapse, as demonstrated by several studies [133,134].

Regarding the approach to PDAC, an element that has been gaining more and more importance is the observation that the definitive histological examination of patients who initially underwent surgical resection often present with unfavourable pathological prognostic factors, such as: G3 tumour grade, the presence of metastatic lymph nodes, microscopically infiltrated surgical resection margins [134].

These pathological features indicate an aggressive disease, even if it is surgically resectable (hence considered in the “initial phase”), and it is independent from the morphological characteristics of the lesions.

All these factors negatively influence the prognosis and eventually lead to a further dilemma. The completion of postoperative adjuvant therapy is frequently problematic in pancreatic cancer and it is often caused by the high level of complication associated with surgery that result in a long and challenging disease course for the patient. This is the main reason that explains why compliance to adjuvant protocols remains rather low, with percentages ranging from 51 to 62%.

Considering all these problems, a new strategy based on the use of neoadjuvant protocols was introduced, similarly to what has been implemented in other types of cancer. The most recent studies show that patients’ survival improves by broadening the indications for the use of neoadjuvant therapy, which should now also consider those patients with a morphologically locally advanced disease or even “borderline resectable” disease with characteristics of aggressiveness. In all these cases a neoadjuvant approach could lead to better survival and a higher percentage of radical resections after surgery. On these grounds, the indications for “up front” surgery are considered not only with the classical morphological resectability criteria, but also with indicators of disease aggressiveness. These surgical resectability predictors may not result in a beneficial therapy for an oncologic patient.

**The necessity of introducing resectability criteria**

The primary purpose of surgery should be the radical removal of the tumour from both the microscopic and macroscopic view. An R0 resection, in fact, is one of the most important prognostic factors in pancreatic cancer.

Hence, it is necessary to elaborate selection criteria that could divide patients in those who would and would not benefit from surgical intervention due to the presence of a non-resectable disease, especially for those with distant metastases or vascular infiltration. This anatomical concept is also associated with the aggressiveness of the disease as well as early relapse after surgery. The primary objective of surgery remains the oncological radicality and all the proposed criteria aim to identify not only the patient in whom this is not possible, but also the patient in which there is a high risk of non-radical surgical resection. The general characteristics of the patient should be considered, including age, performance status, potential comorbidities, and all the elements that may concern the choice of a possible surgical intervention, with reference to the high level of mortality and morbidity that accompanies any surgical resection.

The following criteria are uniformly accepted as distinctive of a state of non-resectability, as indicative of systemic and not radically removable disease [135]:

- presence of distant metastasis;
- presence of lymph node metastasis in non-local-regional lymph node stations, which are lymph node stations that were not taken away during expected standard lymphadenectomy with the pancreatic resection in question (for example mediastinal or supraclavicular lymph nodes, mesentery lymph nodes, inter-aortal-caval or peri-aortal lymph nodes);
- direct infiltration of contiguous visceral extra-pancreatic structures, except via the biliary tree and the duodenum.

In these cases, also in the presence of technically susceptible situations of surgical removal, as in the case of single hepatic metastasis or metastatic adenopathy to the inter-aortal-caval lymph nodes, there are no benefits in terms of survival [136].
"Borderline" resectable pancreatic cancer and locally advanced disease

In addition to the criteria of non-resectability, already described and deriving from the expression of an already systemic disease, it exists an entire other series of criteria that refer to the local extension of a tumour. These other criteria are aimed at identifying patients with a higher risk of non-radical resection and are at high risk of early recurrence after surgery from a technical point of view. The criteria of resectability for pancreatic cancer, therefore, can be divided into three groups [137]:

• morphological resectability criteria, which derive principally from the involvement of the arterial axis and peri-pancreatic veins;
• criteria for biological resectability, which reflect the aggressiveness of the disease with a risk of diffusion that goes beyond what can be found in the instrumental staging exams;
• in addition to the criteria of resectability, there are some operability criteria linked to the patient’s characteristics and to the risk of a possible surgical intervention, both in terms of morality and postoperative complications.

Morphological criteria for pancreatic cancer resectability

Morphological resectability criteria are based on the local extent of the disease, which is defined by imaging and mainly consists of the possible involvement and extent of peri-pancreatic vessels infiltration.

Based on the morphological resectability criteria, three different situations can be identified:

• resectable disease, in which there is no evidence of infiltration of the porto-spleno-mesenteric venous axis and of the arterial vessels (coeliac spleno-mesenteric artery, hepatic artery);
• "Borderline resectable" disease;
• locally advanced disease.

Borderline resectable disease

The definition of "borderline resectable" pancreatic cancer (BRPC) emphasizes the presence of a "technically" resectable pancreatic cancer, but which is nearby or directly involves the peri-pancreatic venous or arterial vessels. Many definitions of BRPC have been proposed from the morphological point of view. The most important point of debate is related to the involvement of the portal vein and the superior mesenteric vein [138-140]. Some heterogeneities also depend on the experience of the individual surgeons involved in the care of these patients. This is made evident when the evaluation of specialized centres leads to the change of the therapeutic approach in 20-30% of cases [141,142].

The BRPC definition from the morphological point of view, which was used in the Intergroup Trial A021101, is based on objective radiological criteria. This definition was adopted to increase the uniformity of judgment among the various centres [138] and by the NCCN guidelines of 2016 [13]. The 2016 NCCN guidelines which considered pancreatic cancer as "borderline resectable" are as follows:

• solid tumour contacts with the portal vein or the superior mesenteric vein (SMV-PV) > 180° or a contact of < 180° with contour irregularities of the vein or thrombosis of the vein but with suitable vessels proximal and distal to the site of involvement allowing a safe and complete resection and vein reconstruction;
• solid tumour contact < 180° with the upper mesenteric artery. In this case, the presence of anatomical anomalies (e.g.: a right accessory hepatic artery originating from the mesenteric artery) which may affect a possible resection and arterial reconstruction should also be taken into consideration;
• solid tumour contacts with the common hepatic artery, in the absence of involvement of the coeliac trunk or bifurcation. Also, in this case, a radical resection and a subsequent reconstruction must be possible in a safe and complete way. The removal of a BRPC, according to morphological criteria, often requires a vascular resection associated with a total pancreatectomy, making it necessary to perform vascular reconstruction.

A recent meta-analysis study showed that, compared to patients undergoing standard pancreatic resection, those undergoing vascular resection of the portal vein or superior mesentery had an increased risk of perioperative mortality (risk difference, RD: 0.01), an increased risk of R1 or R2 resection (RD: 0.09), as well as a lower 5-year overall survival rate [143]. Similar results were reported in the case of surgery associated with resection of the upper mesenteric artery, the common hepatic artery or coeliac trunk.

In another meta-analysis study, arterial resections are linked with a significantly higher risk of perioperative mortality (OR: 5.04) and are associated with poorer three-year survival (OR: 0.39) compared to patients who did not perform arterial resection [144].

A similar argument regarding the involvement of the splenic artery is gaining recognition. The infiltration of this artery was recently revealed to be a negative prognostic factor. This data was not included in the formal definition of the morphological BRPC since pancreatic cancer involving only the splenic artery is usually technically removable. However, three studies indicated that the 5-year overall survival rate was practically non-existent for patients with infiltration of the splenic artery at a definitive histological examination, compared to a 5-year survival rate ranging from 8 to 31.5% in cases where the artery was free [145-147]. We can, therefore, hypothesize that a vascular infiltration documented during staging represents an indicator of a more advanced and biologically more aggressive disease, identifying a higher risk of non-radical resection (R1 and R2) and a lower survival rate even in the case of R0 resection [148].
Locally advanced disease
The locally-advanced disease is defined by all those cases in which the vascular involvement is greater than the "borderline" resectable disease. It is summarized as follows:
- infiltration > 180° or occlusion of the portal-spleno-mesenteric venous axis, the presence of portal thrombosis;
- infiltration of the coeliac trunk, superior mesenteric artery, hepatic artery, inferior vena cava or aorta.

As already mentioned when talking about BRPC, the minor 180° infiltration of the upper mesenteric artery or a "short stretch" of the hepatic artery or the 180° major infiltration of the portal-spleno-mesenteric venous axis are considered, by some authors, as criteria for defining a "borderline resectable" neoplasm but only if radical intervention with vascular reconstruction can be performed. Previously published survival data for locally advanced disease, however, suggested reserving this intervention to only selected patients who have already been treated with neoadjuvant, thus with possible down-staging after treatment, and with a good performance status [144,149].

Biological criteria for pancreatic cancer resectability
The historical progression of pancreatic cancer treatment has always been confronted with a high rate of early relapse after surgery despite an initially resectable disease. As already discussed in the previous paragraphs, the probability of a hidden metastasis is extremely high. It is these unknown metastases that account for all those patients who develop recurrence within a year, with percentages that can reach up to 37% [150,151].

Among the biological markers associated with early recurrence the level of carbohydrate antigen 19.9 was recommended (CA 19.9). CA 19.9 values above 200 U/ml were correlated with a high "burden" of disease along with the presence of micro-metastatic disease [150,152-154]. Other studies, however, correlated high levels of CA 19.9 with the presence of unresectable disease and an increased risk of early relapse [32,140].

A recent study that analysed 10,806 patients with morphologically resectable pancreatic cancer, with data extrapolated from the National Cancer Data Base (NCDB), showed that those with a CA 19.9 after surgical resection of greater than 37 U/ml had significantly lower survival rates at 1 and 3 years (56% vs. 68% and 15% vs. 25%, respectively) when compared to patients whose levels normalized (< 37 U/ml) [154].

The reliability of CA 19.9 as a prognostic marker, however, is undermined by the numerous confounding factors that may occur. In fact, the efficacy CA 19.9 as a marker is significantly reduced in many patients with pancreatic cancer who present with jaundice and even very modest alterations of bilirubin values at time of diagnosis [156]. It is for this reason that the value of CA 19.9 should be considered only after treating jaundice and after normalization of serum bilirubin values [156].

Another factor that has been described as an indicator of biological aggressiveness is the symptom of back pain at presentation [157]. This typical pain of pancreatic cancer seems to be due to a peri-neural invasion of the nerve fibres that are found in this anatomical area (i.e. the coeliac ganglion).

The interaction of tumour cells with different types of cells in the tumour stroma is now acknowledged to play a decisive role in the progression and prognosis of many types of tumours. Despite the well-described interactions of tumour cells with different stromal components (i.e. inflammatory cells, fibroblasts associated with cancer, endothelial cells, etc.), the analysis of their relationship with nerve cells is still in its infancy.

Pancreatic cancer, with its abundant stroma, is one of the most studied examples of a malignant tumour with a reciprocal interaction between cancer cells plus both intra-peri-tumour and nerve fibres. In the last 15 years, however, this heterotypic interaction seemed to be a simple collateral element in the biology of this tumour. Only in recent years has peri-neural invasion established itself not only for its association with typical pain but also for its correlation with tumour progression and early recurrence after surgery [158].

The nerve fibres in pancreatic cancer are a rich source of neurotrophic factors such as: nerve growth factor (NGF), the neurotrophic factor derived from glial cells (GDNF), chemokines like Fraklaline, as well as autonomic neurotransmitters like noradrenalin. The release of these factors can increase the invasiveness of pancreatic cancer through the up-regulation of metalloproteinase (MMP), thereby contributing to peri-neural invasion. Likewise, cancer cells can feed intra-pancreatic nerves with trophic factors, thus increasing neuroplasticity with the development of new nerve pathways that eventually promote the spread of cancer. The clinical correlation of the interactions between tumour cells and nerve fibres and of the peri-neural invasion causing neuropathic pain typical of pancreatic cancer have been identified as true markers of the disease aggressiveness [159].

A further marker of aggressiveness is the presence of intra-tumour necrosis, which is observed during CT imaging as an area of central hypodensity within a tumour. A recent study analysed anatomopathological preparations from 352 pancreatic resections. Macroscopic necrosis was present in 235 cases (66.8%) and significantly correlated with tumour size, nodal metastasis, nerve plexus invasion, and early recurrence. The presence of necrosis more than 2 mm broad, has been significantly associated with both a minor overall survival and a lower disease-free survival [160].

Likewise, the metabolic activity data of the neoplasia can be a useful tool in defining the biological aggressiveness of the disease also the metabolic activity data of the neoplasia can be a useful tool in defining the biological aggressiveness of the disease and, therefore, the treatment strategies. Pergolini et al. [161] demonstrated that (18)fluoro-deoxyglucose positron
emission tomography could play a pivotal role during treatment planning. SUVmax ≥ 6.0 was an independent predictor of both disease-free and disease-specific survival. The combination of SUVmax ≥ 6.0 and a Ca 19.9 ≥ 200 U/ml was associated with a remarkably poor prognosis. 18FDG-PET might be considered in preoperative evaluation to direct patient at high risk of early recurrence to preoperative treatment.

**Operation criteria related to the patient**

Finally, some patients may be considered “borderline resectable” because of their general conditions and associated comorbidities. Any pancreatic resection is considered as a highly invasive procedure and burdened by mortality and a high rate of complications [162].

Addition of adjuvant therapy following resection is considered mandatory to improve the operating system [133]. However, post-operative complications associated with pancreatic resection may prevent the administration of adequate adjuvant therapy. Indeed, the percentage of effective adherence to the adjuvant protocol in CONKO-001 does not exceed 62% of patients [133].

Of the 1,144 patients who underwent pancreaticoectomy at Johns Hopkins University, only 54.3% managed to undergo adjuvant therapy and these data are in line with adjuvant chemotherapy rates reported in national databases (51-54%) [163].

The factors that have been recognized as indicators of poor adherence to adjuvant protocols include the risk of postoperative complications and the nutritional index [149,150].

These patients at high risk of not being able to perform adjuvant therapy could also be considered “borderline” from the perspective of operability and therefore could be candidates for neoadjuvant therapy. This would lead to a pre-emptive systemic therapy before the trauma caused by the surgical intervention and its possible associated consequences.

**Conclusion**

In conclusion, the diagnostic strategy of a solid pancreatic mass is fundamental not only to reach a diagnosis but to program the therapeutic plan in order to give the best treatment to patients. This is particularly important in the case of adenocarcinoma, where a correct staging is mandatory for the subsequent decisions such as the choice of upfront surgery, neoadjuvant chemotherapy or medical treatment, which depends on vascular infiltration, local tumour invasiveness, values of biological aggressiveness markers and patients’ comorbidities.

An accurate diagnosis is fundamental also in the case of NENs, where histological findings, Ki 67 value and tumour dimension guide the therapeutic decisions.

**Acknowledgement:** PhD Scholarships of both Dr Valentina Andreasi and Dr Giulia Gasparini were supported by Gioja Bianca Costanza Fund.

**Disclosure of interest:** the authors declare that they have no competing interest.

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Diagnostic strategy with a solid pancreatic mass


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Diagnostic strategy with a solid pancreatic mass


