# Pancreatic pathology: where are we in 2019?

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## Abstract

Pancreatic ductal adenocarcinoma (PDAC) takes centre stage in the field of pancreatic pathology. It is the most common pancreatic neoplasm and carries a dismal prognosis with rising mortality rates. Tissue diagnosis focuses on the identification of PDAC and its distinction from non-neoplastic disorders such as chronic pancreatitis and rarer, less aggressive pancreatic neoplasms. Pathology also plays a key role in the assessment of well characterized macroscopic precursor lesions of PDAC: mucinous cystic neoplasms and intraductal papillary mucinous neoplasms. Endoscopic ultrasound-guided fine needle biopsies are becoming an increasingly used tool in the diagnosis of pancreatic lesions with paraffin-embedded material facilitating ancillary tests. Pathological examination of tissue samples from the pancreas allows typing and grading of neoplasms and in resections will also provide information on stage, resection margin status and response to any neoadjuvant treatment given. It plays a vital role in the multidisciplinary care of patients with pancreatic diseases and will form the basis for genomic analysis of tumours to facilitate personalized treatment approaches. This article summarizes types of tissue samples, followed by descriptions of the most important non-neoplastic and neoplastic, solid and cystic lesions, including recent developments.

**Keywords** Cancer; neoplasia; pancreas; pancreatitis; pathology

## Introduction

The pancreas is composed of acinar, ductal and endocrine cells with associated soft tissue resulting in a multitude of pathologies. Pancreatic ductal adenocarcinoma (PDAC), accounting for 85–90% of neoplasms of the pancreas, is of particular importance. PDAC is often regarded to be synonymous with pancreatic cancer. However, as approximately 85% of patients with pancreatic cancer present at an advanced stage where curative surgery is no longer possible, it is likely that most cases of 'pancreatic cancer' are in fact carcinoma in the head of pancreas which may also include a certain proportion of advanced carcinomas of intrapancreatic bile duct or the ampulla of Vater, which can resemble pancreatic ductal adenocarcinoma histologically. Pancreatic cancer is the 11th most common cancer in the UK with almost 10,000 new cases diagnosed every year with the incidence projected to rise by a further 6% by 2035. Almost half of patients present as an emergency, most to accident and emergency departments. Pancreatic cancer has a very poor prognosis with a mortality almost equalling incidence, a 5-year survival of 3% (6% globally), and virtually unchanged mortality rates for more than four decades.[1]

The clinical presentation of pancreatic pathologies can be non-specific and abnormalities might only be detected on imaging. Radiologically detected localized abnormalities in the pancreas essentially fall either into a solid or a cystic category. PDAC is almost always a solid lesion and needs to be distinguished from chronic pancreatitis and other solid tumours. Pancreatic cysts are common and are found in up to 13% of people aged between 70 and 80 years; 85% of pancreatic cystic lesions are pseudocysts complicating pancreatitis. They need to be differentiated from cystic neoplasms, some of which are precursors to pancreatic cancer. Histopathological examination plays a vital role in the diagnosis of non-neoplastic, preneoplastic, and neoplastic conditions of the pancreas.

## Pathological tissue specimens from the pancreas

### Diagnostic samples

The retroperitoneal location of the pancreas, its close proximity to vital organs, and the risk of pancreatitis pose a particular challenge for diagnostic tissue acquisition.

**Endoscopic ultrasound (EUS) tissue acquisition** has become the standard of care in the diagnosis of solid pancreatic lesions. EUS fine needle aspiration (FNA) cytology has been well established for more than 20 years with a sensitivity of 85–90% and specificity of 100% for PDAC.[2] Material can be examined as direct spreads, liquid-based cytology preparations, and/or cell block. Diagnostic yield will depend on endoscopist's experience, needle size/type and rapid on-site evaluation (ROSE), the latter being costly and often not practical. FNA diagnosis relies on cytological features such as cell type, nuclear and cytoplasmic appearances, cellularity and microarchitecture, and tissue evaluation will be influenced by the expertise of the cytopathologist. Low diagnostic yield due to discontinuous growth and dense desmoplastic stroma in PDAC and well-differentiated variants of PDAC may represent particular challenges when relying purely on cellular changes without any intact tissue architecture. EUS fine needle biopsies (FNBs) using novel needle designs are being increasingly used to obtain tissue core fragments which can be processed as routine histology specimens and allow evaluation of intact tissue architecture. FNBs have shown at least equal or superior accuracy to FNA with less inadequate samples, fewer required tissue passes and no need for ROSE. FNBs allow evaluation of formalin-fixed paraffin-embedded (FFPE) tissue including reliable use of ancillary tests aiding the diagnosis of lesions such as lymphomas, mesenchymal neoplasms, rare carcinomas, and autoimmune pancreatitis (see Figures 1, 4 and 5). In the era of precision medicine, they provide archival material for future ancillary genomic analyses and may be utilized to

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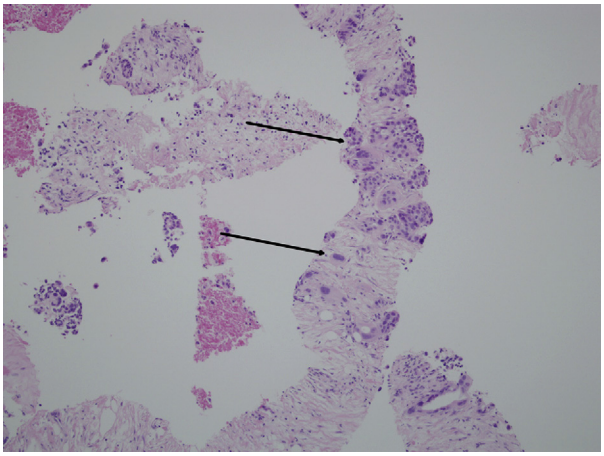

**Figure 1** EUS-guided fine needle biopsy (FNB) showing intact tissue core infiltrated by PDAC showing irregular glands and single large atypical cells in a desmoplastic stroma (arrows).

produce PDAC organoids.[2,3] EUS also plays an important role in the diagnostic work-up of pancreatic cysts with EUS FNA, FNB of cyst wall nodules, and through-the-needle intracystic biopsy complementing imaging and biochemical fluid analysis.

**Common bile duct (CBD) brush cytology** obtained during ERCP can aid in the diagnosis of pancreatic tumours, which have eroded the CBD. While specificity may be 90–100%, the sensitivity can be as low as 30%. The UroVysion FISH assay has been shown to substantially improve the performance of brush cytology for the diagnosis of malignant biliary strictures from 35% to 52% and is now widely used in the United States and some EU countries as an ancillary diagnostic tool for evaluating biliary strictures.

**CT-guided, laparoscopic or open core biopsies** of the pancreas are taken if other diagnostic modalities have not been able to establish a diagnosis but carry an increased risk of peritoneal seeding.

**Intraoperative frozen sections** of the pancreas are used to assess indeterminate primary lesions, tumour margins, presence of metastases, and/or any unsuspected pathology. Frozen sections are available within minutes, but the section quality is inferior to FFPE, and distinction of reactive glands from adenocarcinoma may be very difficult. Good-sized, well-preserved specimens, pathologist's consistent application of diagnostic criteria, and good communication between surgeon and pathologist will optimize results. Frozen sections of pancreatic neck margins have significant limitations and further resection after positive neck margin frozen section for PDAC is not associated with improved overall survival.[4] Frozen section assessment of pancreatic duct involvement by intraductal papillary mucinous neoplasms (IPMN) is recommended but may be hampered by epithelial denudation or suboptimal epithelial preservation. Skip lesions may also occur. The use of frozen section core biopsies for definite intraoperative diagnosis should be best avoided as they may contain too little material.

### Resection specimens

**Pancreatoduodenectomy**, either pylorus preserving or classical, is the most common resection specimen. The most frequent indication is periampullary carcinoma which includes PDAC of the head of pancreas, ampullary carcinomas, distal common bile duct carcinomas and occasional duodenal carcinomas. The role of pathology is to establish or confirm the diagnosis, inform prognosis, assess response to neoadjuvant treatment, facilitate selection of patients for adjuvant treatment including participation in clinical trials and allow correlation with radiological and surgical assessment. Pathology reports are also prerequisites for accurate data collection for cancer registries and epidemiological studies, and allow audit and comparison of surgical practices. The cancer dataset for carcinoma of the pancreas, ampulla and distal common bile duct, published by the Royal College of Pathologists, provides guidelines for the consistent and accurate pathological examination of pancreato-duodenectomy specimens.[5] The most important prognostic factors to assess are tumour type, tumour size, differentiation, lymph node status and resection margins. Regarded as one of the most complex resection specimens in pathological practice, dissection of a pancreato-duodenectomy specimen requires confident identification and examination of key anatomic structures including any resected major vessels. Transection margins (duodenum/stomach, pancreatic neck, bile duct, and any named vessel) need to be sampled, and dissection margins (superior mesenteric vein, superior mesenteric artery and posterior retroperitoneal margin) differentially inked. Axial slicing is advocated, ideally with detailed photographic documentation, to allow visualization of the tumour in relation to key anatomic structures and comparison with cross sectional imaging. Macroscopic assessment and sampling is crucial for accurate microscopic evaluation and with regards to determining the origin of the tumour from pancreas, bile duct or ampulla by evaluating the location of the tumour epicentre. Problems ascertaining tumour origin may be encountered when the tumour is very extensive or poorly defined. Histological examination may provide additional clues, such as periampullary or bile duct dysplasia, but advanced PDACs, distal common bile duct and pancreatobiliary-type ampullary carcinomas can look identical microscopically. In instances of uncertain tumour origin, a multidisciplinary approach is advocated. Due to its characteristically discontinuous growth, PDAC is usually more extensive microscopically than macroscopically, requiring extensive sampling of the dissection margins for accurate assessment of resection margin status. Assessment of complete response post-neoadjuvant chemotherapy may require assessment of the entire specimen. Total and subtotal pancreatectomies, distal pancreatectomies and local excisions, as well as pancreaticoduodenectomy for lesions other than periampullary carcinoma, are less common but follow similar systematic dissection protocols.

## Non-neoplastic solid lesions

### Chronic pancreatitis

Chronic pancreatitis (CP) is a group of fibro-inflammatory processes of the pancreas which need to be distinguished from PDAC. CP occurs at a younger age of 30–40 and it is seen more commonly in men. Alcoholic chronic pancreatitis (ACP), accounting for approximately 80% of CP, is a chronic calcifying pancreatitis characterized by fibrosis, dilated ducts, calculi, fat necrosis and pseudocysts histologically. Ductular/tubular

transformation of atrophic acini may present a challenge in the differentiation from PDAC. The overall preserved lobular pattern and lack of significant cytological atypia in atrophic tissue in the context of characteristic clinical history and imaging will allow safe distinction. Hereditary and tropical pancreatitis display similar histological features to ACP and an aetiological distinction could not be made based on histology. Obstructive chronic pancreatitis can be distinguished by lack of calculi. ACP and in particular hereditary pancreatitis carry an increased risk of pancreatic carcinoma, and obstructive chronic pancreatitis may be the result of an obstructing tumour. Therefore features of CP may co-exist with PDAC, and if clinically there is a high index of suspicion of PDAC, it has to be considered that a pathological diagnosis of CP in a biopsy could represent a sampling error.

In addition, there are pathologically distinct types of chronic pancreatitis, which clinically and on imaging can mimic PDAC by causing tumefactive/mass lesions.

**Autoimmune pancreatitis (AIP)** often presents with obstructive jaundice and a pancreatic mass (tumefactive lesion) clinically, and distinction from PDAC is of utmost importance. AIP is characterized by a dramatic response to steroids and its accurate diagnosis will avoid unnecessary surgery. In contrast to other types of CP, it is characterized by duct narrowing/obstruction caused by periductal fibrosis and lymphoplasmacytic inflammation. Two types with unique histopathology and different demographic profiles, clinical characteristics and natural history are recognized. Type 1 is described as lymphoplasmacytic sclerosing pancreatitis and represents the pancreatic manifestation of immunoglobulin G4-related disease (IgG4-RD). IgG4 RD is a T-cell—driven inflammatory process with clones of plasmablasts, and elevated IgG4 probably indicates an increased anti-inflammatory response. It affects older males and often presents with high serum IgG4 levels, extrapancreatic manifestations and disease relapses. Defining histopathological features are dense lymphoplasmacytic infiltrate, storiform fibrosis, and obliterative phlebitis. Increased eosinophils are also a common finding. Granulomas, neutrophilic infiltration, and necrosis, generally exclude this diagnosis. Elevated tissue IgG4 plasma cell count and ratio of IgG4 to IgG positive plasma cells >40% are additionally required for histological diagnosis, but in isolation are a non-specific finding. Type 2 AIP is less commonly recognized, and best termed idiopathic duct-centric chronic pancreatitis (IDCP) or AIP with granulocytic epithelial lesion (GEL). Patients are younger, disease is confined to the pancreas and there is a 25% association with inflammatory bowel disease. Neutrophilic infiltration of the duct epithelium (granulocytic epithelial lesion = GEL) is the defining histological feature. Histopathology plays an important role in the diagnosis of AIP/IgG4-RD, but there has to be awareness that the diagnosis rests on characteristic morphological features seen only in intact tissue. Diagnosis cannot be made on cytology, and will be very limited in small biopsies, as changes can be focal. Furthermore, the morphological features are not specific, and immunohistochemistry for IgG4 cannot be used as a diagnostic tool in isolation. Ultimately, the correct diagnosis of this rare condition relies on a multidisciplinary approach.[6,7]

**Paraduodenal pancreatitis** is now the most widely accepted term for an inflammatory lesion, which is also known as cystic dystrophy of the duodenal wall developed in heterotopic pancreas, paraduodenal wall cyst, and groove pancreatitis. It develops mainly in men in their 5th decade, who might present with symptoms suggestive of pancreatic cancer. Key pathogenetic factors are heavy alcohol use and anatomic or functional obstruction of the papilla minor, i.e. due to gallstones. Macroscopically, a pseudotumourous nodular appearance of the duodenal mucosa is characteristic. The duodenal wall is markedly thickened by cysts with surrounding scarring. Microscopically, the cysts correspond to dilated ducts, which may contain protein plugs and stones. In addition to fibrosis, there is also usually evidence of 'ectopic' pancreatic tissue, proliferation of myoid cells, neural proliferations and, importantly, marked Brunner's gland hyperplasia, accounting for the nodular duodenal mucosa. Symptomatic cases often require surgery, but conservative management with stenting may be an option, and accurate preoperative diagnosis is important.[7]

**Follicular pancreatitis** is a rare and recently described disease of unknown aetiology, which has been described in older adults with a slight male predominance. Histologically, it shows extensive lymphoid follicle formation, particularly around pancreatic ducts, and distinction from lymphoma is paramount.[7]

Pancreatic involvement by systemic diseases, such as granulomatosis with polyangiitis (Wegener granulomatosis) or rheumatoid arthritis, can also cause a pancreatic mass.

### Miscellaneous non-neoplastic solid lesions

Intrapancreatic splenic heterotopia can mimic endocrine tumours on imaging; ectopic liver may give rise to hepatocellular carcinoma. Hamartomas of the pancreas are well-circumscribed solid and cystic lesions, consisting of non-neoplastic acini and ducts, without elastic fibres, peripheral nerves or islets of Langerhans. Lipomatous hamartomas contain abundant mature adipose tissue.

## Neoplastic solid lesions

### Pancreatic ductal adenocarcinoma

PDAC accounts for 85—90% of all pancreatic neoplasms. It most commonly occurs between the ages of 60—80 and may present with unexplained weight loss, back pain and obstructive jaundice. Approximately two-thirds are found in the head of pancreas. Risk factors for PDAC can be divided into non-hereditary and hereditary. The former may be modifiable such as smoking, obesity, alcohol abuse, chronic pancreatitis, solid organ transplantation and infection, or non-modifiable such as diabetes, older age, male gender, as well as specific premalignant lesions (mucinous cystic neoplasms [MCNs] and IPMNs). Hereditary conditions account for a minority of pancreatic cancer and incorporate familial pancreatic cancer, breast and ovarian cancer gene mutations (BRCA-1 and 2), Lynch syndrome (HNPPC), familial atypical multiple mole melanoma (FAMMM), Peutz-Jeghers syndrome and hereditary pancreatitis. Raised serum CA19-9 and dilatation of pancreatic duct and CBD on imaging (double duct sign) are highly suggestive of pancreatic cancer, but tissue diagnosis remains the gold standard (Figure 1).

Macroscopically, PDAC is a firm sclerotic mass, which is often poorly defined, requiring extensive tissue examination to accurately stage the tumour (Figure 2). Microscopically, PDAC is an adenocarcinoma composed of duct-like structures, lined mostly by a single layer of epithelium, with luminal or intracellular mucin, and associated with a prominent desmoplastic stromal reaction. Extension into peripancreatic tissues, duodenal wall, ampulla and CBD is often seen, and is accompanied by perineural and vascular invasion. The most important prognostic factors are resection margin and lymph node status, including lymph node ratio. Complete resection (R0) in the UK is defined as clearance greater than 1 mm at transection and dissection margins, and 0 mm at the anterior surface of the pancreas, but the definition of an R1 resection is not uniform globally. Detailed pathological examination of resection specimens using above definitions for positive margins will reveal R1 rates in excess of 80%, mirroring the local recurrence rate following surgery. The percentage of R1 resections is considered the most important quality parameter of pathological assessment. Grading and staging are also prognostically relevant. A defined three-tier grading system is applied and the highest grade is assigned. Most PDAC will be poorly differentiated. PDAC is staged according to the 8th edition of the American Joint Committee on Cancer (AJCC)/International Union Against Cancer (UICC) TNM staging system,[8] which has changed from previous editions by making a distinction between pT2 (2−4 cm) and pT3 (>4 cm) based on size rather than anatomic extent of infiltration, requiring accurate microscopic measurements. It has additionally introduced three subcategories for pT1 for detailed staging of early carcinomas, and two tiers for the assessment of lymph node positivity (pN1 metastases in 1−3 lymph nodes, pN2 metastases in four or more lymph nodes). Lymph node ratio, nodal micrometastasis and high-grade tumour budding have been identified as prognostically relevant pathological findings but are not reported routinely. Specific histological variants of PDAC also have a bearing on prognosis. Colloid carcinoma, characterized by more than 80% mucin pools and almost exclusively associated with an intestinal type intraductal papillary neoplasm, and medullary carcinoma, which is akin to microsatellite unstable colorectal carcinoma, have a better prognosis compared to conventional PDAC. Adenosquamous carcinoma, requiring at least a 30% squamous component, undifferentiated/anaplastic carcinoma, undifferentiated carcinoma with osteoclast-like giant cells and hepatoid carcinoma have a very poor prognosis. Hepatoid carcinomas are very rare and the possibility of metastatic hepatocellular carcinoma has to be ruled out. Signet ring carcinoma is also very rare and the possibility of metastatic disease from stomach/breast needs to be excluded. Cystic papillary, foamy gland, clear cell and large duct pattern PDAC are not known to be prognostically distinct, but need to be distinguished from IPMNs, pancreatic intraepithelial neoplasia (PanINs) or normal ducts.[9,10]

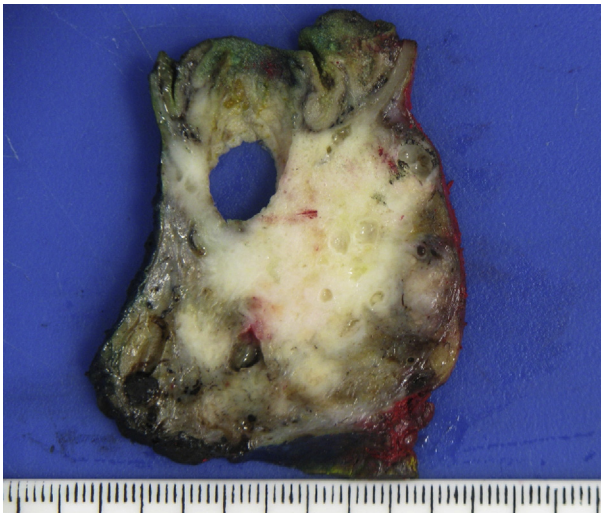

**Figure 2** Macroscopically, PDAC is a firm, sclerotic mass with ill-defined margins.

The most important differential diagnosis of PDAC is chronic pancreatitis. The non-lobular distribution of glands, their irregularity with incomplete lumina, and significant nuclear variation are key features of PDAC. Desmoplastic stroma, perineural invasion, and association of ducts with arteries are also helpful features. There are no reliable immunohistochemical markers for the distinction of benign from malignant glands, and PDAC does not have a specific immunohistochemical profile to allow distinction from bile duct, gallbladder or upper gastrointestinal tract adenocarcinomas. Other solid epithelial neoplasms of the pancreas tend to be much more cellular with minimal or hyalinized stroma and distinct histological features.

PDAC follows an aggressive clinical course with mortality rates still rising. Surgery is currently the only curative treatment, and only 20% of cases are still resectable at the time of presentation. Cases resected with curative intent have a 5-year survival of approximately 27% with an up to 85% recurrence rate likely related to microscopically incomplete resection.[10] Neoadjuvant chemotherapy using treatment regimes, such as FOLFIRINOX (oxaliplatin, irinotecan, fluorouracil and leucovorin), has become a therapeutic option for locally advanced PDAC with the prospect of downstaging borderline resectable tumours, and has shown increased survival in resected patients.[10,11]

Pathological reporting of pancreatectomies post-neoadjuvant therapy can be challenging with inflammation, fibrosis and atrophy rendering interpretation difficult. Tumour regression may be patchy in distribution and affect confirmation of tumour origin (Figure 3). For pathological evaluation of tumour regression following neoadjuvant therapy RCPath recommends the CAP grading (Table 1).[5] Treatment of PDAC is evolving, and recent genomic analysis have stratified PDAC into four groups: squamous, pancreatic progenitor, immunogenic and aberrantly differentiated endocrine exocrine, with prognostic and potential personalized treatment implications.[12]

### Pancreatic neuroendocrine tumours

Pancreatic neuroendocrine neoplasms (PanNENs) are rare tumours with an incidence of approximately 0.5 per 100,000 and accounting for 1−2% of all pancreatic neoplasms. They are likely to arise from duct related endocrine cells, and commonly occur between the age of 40 and 60 years with an equal gender distribution. They can be functional or non-functional, and represent a spectrum of tumours ranging from clinically indolent to highly aggressive malignant neoplasms. Functioning tumours account for approximately half of all PanNENs, and may be associated with hormone secretion appropriate to the pancreas

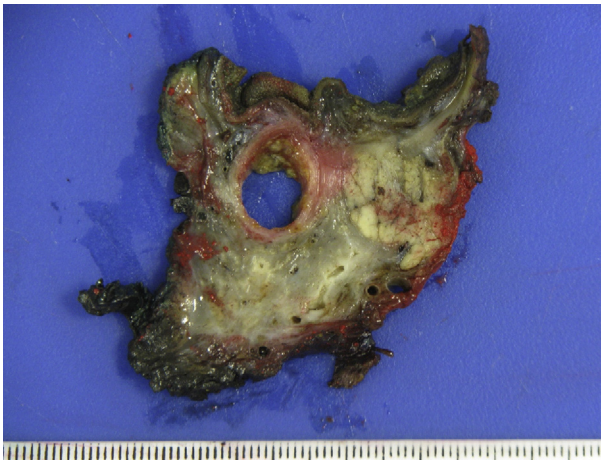

**Figure 3** Axial section through pancreatoduodenectomy following neoadjuvant chemotherapy with no macroscopically visible tumour.

**CAP tumour regression grading system for PDAC[5]**

| Grade | Proportion of residual viable tumour |
|---|---|
| 0 | No viable cancer cells (complete histological response) |
| 1 | Single cells or rare small groups of cancer cells (near complete response) |
| 2 | Residual cancer with evident tumour regression, but more than single cells or rare small groups of cancer cells (partial response) |
| 3 | Extensive residual cancer with no evident tumour regression (poor or no response) |

**Table 1**

(insulin, glucagon and somatostatin) or extrapancreatic hormones such as gastrin, vasoactive intestinal peptide, growth hormone releasing factor or ACTH. Insulin-producing tumours are most common with characteristic hypoglycaemia, followed by gastrin producing tumours, which may become clinically apparent through Zollinger Ellison syndrome. Most PanNENs are sporadic and single, but some occur in the context of specific genetic syndromes, usually at a younger age and with multiple tumours. The most important syndrome is multiple endocrine neoplasia type 1 (MEN-1). PanNENs in Von Hippel-Lindau (VHL) syndrome often display clear cell change. PanNENs can also be seen in neurofibromatosis, tuberous sclerosis and Mahvash disease.[13]

According to the 2017 WHO classification, PanNENs are typed as well-differentiated neuroendocrine tumours grade 1, 2 or 3 (PanNET G1, PanNET G2 or PanNET G3) and poorly differentiated neuroendocrine carcinomas (PanNEC G3), which may be small or large cell. The term neuroendocrine carcinoma is now solely reserved for poorly differentiated tumours. Mixed neuroendocrine-non-neuroendocrine neoplasms (MiNENs) refer to tumours with at least 30% of either component. The non-neuroendocrine component may be squamous, acinar or adenocarcinoma. The UK Royal College of Pathologist's dataset for the reporting of neuroendocrine tumours of the gastroenteropancreatic tract is currently undergoing revision with soon to be effective updated reporting guidelines (Box 1).[14] PanNENs are staged according to the European Neuroendocrine Tumour Society (ENETS) TNM 2006 staging. WHO 2004 classification and, in particular, the term 'well-differentiated neuroendocrine carcinoma (low-grade malignant)' are no longer used. Grade boundaries for PanNENs, depending on Ki67 proliferation index and mitotic count, have been modified from previous classifications highlighting the importance of assessing absolute values for

**Pathological reporting of pancreatic neuroendocrine tumours in the UK[14]**

**Type** (WHO classification 2017)[13]
Well-differentiated neuroendocrine tumour, PanNET G1
Well-differentiated neuroendocrine tumour, PanNET G2
Well-differentiated neuroendocrine tumour, PanNET G3
Poorly differentiated neuroendocrine carcinoma, NEC G3, small cell
Poorly differentiated neuroendocrine carcinoma, NEC G3, large cell
Mixed neuroendocrine-non-neuroendocrine carcinoma, MinNEN
**Grade**
G1 (<2 mitoses/2 $mm^2$, Ki-67 index <3%)
G2 (2–20 mitoses/2 $mm^2$, Ki-67 index 3–20%)
G3 (>20 mitoses/2 $mm^2$, Ki-67 index >20%)
Actual Ki-67 index and number of mitoses
**Peptide hormones**
Insulin, glucagon, somatostatin, pancreatic polypeptide, gastrin
**Lymphovascular invasion**
**Perineural invasion**
**Tumour deposits in peripancreatic adipose tissues**
**Necrosis**
**Background islet cell microadenomatosis (seen in MEN-1) or chronic pancreatitis**
**Stage (ENETS)**
pTX Primary tumour cannot be assessed
pT0 No evidence of primary tumour
pT1 Tumour limited to the pancreas and size <20 mm
pT2 Tumour limited to the pancreas and size 20–40 mm
pT3 Tumour limited to the pancreas and size >40 mm
pT4 Tumour invading the wall of adjacent large vessels (coeliac axis or superior mesenteric artery), stomach, spleen, colon, adrenal gland
**Number of positive lymph nodes, total number of lymph nodes**
pNX regional lymph node status cannot be assessed
pN0 no regional lymph node metastasis
pN1 regional lymph node metastasis
pM0 no distant metastases
pM1 distant metastases
**Resection margins**
R0 complete resection at all surgical margins
R1 microscopic disease at surgical margin
R2 macroscopic disease at surgical margin

**Box 1**

mitotic count and Ki67% in the continuous development of prognostic stratification of these rare tumours.

PanNETs are all potentially malignant. Approximately 60% of them arise in the tail of the pancreas. They are usually solid, soft, tan coloured, and circumscribed tumours. Histologically, they show an 'organoid' architecture, which may be very varied but is commonly nested or trabecular. The cells display fairly uniform nuclei with 'salt and pepper' chromatin. Stromal contents vary and amyloid can be observed, particularly in insulin-secreting tumours. PanNETs are slowly progressive neoplasms. Surgery with curative intent is the treatment of choice for solitary tumours. Resection, chemoembolization, somatostatin analogues and chemotherapy are the treatment options for advanced and higher grade disease. It is now recognized that G3 PanNENs (Ki67 $>$ 20%) encompass a spectrum of morphologically well-differentiated PanNETs with elevated Ki67 index (usually less than 40%) and poorly differentiated neuroendocrine carcinomas (PanNEC G3) with greater than 20 mitoses/2 $mm^2$ and Ki67 usually greater than 55%. This dichotomy is corroborated by molecular changes with PanNET G3 commonly showing inactivation in MEN-1, DAXX or ATRX, similar to PanNETs G1 and G2. In contrast, PanNECs are associated with mutations in p53, RB1 and p16. PanNECs are rare ($<$1% of pancreatic carcinomas), have a very poor prognosis with platin-based chemotherapy, the treatment of choice. Macroscopically, they are ill-defined. Microscopically, they consist of sheets or tightly packed nests of cells with extensive necrosis and frequent mitoses, resembling their small and large cell counterparts in the lung.

The differential diagnosis for PanNETs includes acinar cell carcinoma, solid pseudopapillary neoplasm and pancreaticoblastoma (see below). PanNECs need to be distinguished from poorly differentiated adenocarcinomas. Immunohistochemistry for synaptophysin, chromogranin and CD56 will confirm the neuroendocrine nature. Islet-1, PDX1, Pax-8 and specific hormones may be helpful in confirming pancreatic origin of a PanNET in liver biopsies of metastases, which are present at first diagnosis in more than 50% of cases.[9]

### Acinar cell carcinoma

Acinar cell carcinoma is rare, accounting for only 1–2% of all pancreatic neoplasms. It resembles acinar cells and produces exocrine enzymes. Most occur in late adulthood with a male predominance, but approximately 5% are seen in children. In 10–15% of patients, lipase hypersecretion syndrome may lead to subcutaneous fat necrosis and polyarthralgia. The tumours are usually large, well circumscribed and soft and occur more commonly in the head. Histologically, acinar cell carcinomas are highly cellular and stroma poor. Cells are commonly arranged in acini or solid sheets and central nucleoli and granular cytoplasm are characteristic features (Figure 4). Staging is identical to PDAC and a three-tier grading system based on prominence of nucleoli has been suggested.[9] Though aggressive, acinar cell carcinoma overall has a slightly better prognosis than PDAC. The most important differential diagnosis is pancreatic NET, which tends to be more stroma rich, less mitotically active and does not stain for trypsin or chymotrypsin. BCL-10 staining may also help in identifying acinar differentiation. Mixed tumours contain $>$30% of another component such as ductal and/or neuroendocrine carcinoma.

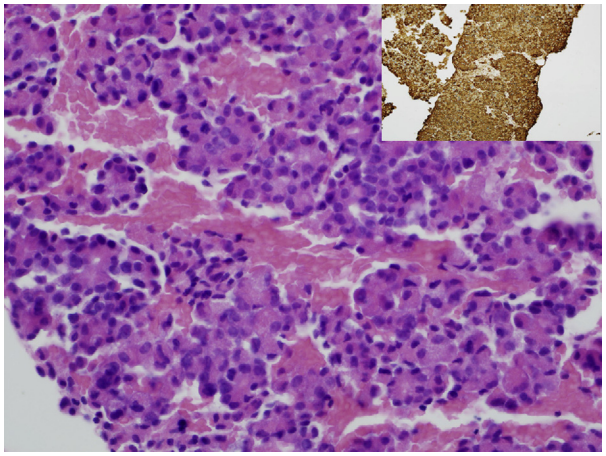

**Figure 4** EUS-guided FNB of pancreatic acinar cell carcinoma showing typical acinar arrangement of cells with positive immunohistochemistry for trypsin (inset).

### Pancreatoblastoma

Pancreatoblastoma is a very rare malignant tumour occurring mainly during the first decade of life with only rare cases described in adults. It may be associated with Beckwith-Wiedemann syndrome, and appears to be more common in Asians. Tumours tend to be large, and by definition show an acinar component and squamoid nests in organoid architectural arrangements with dividing stromal bands. A neuroendocrine component and rarely a ductal component can also be seen. Pancreatoblastoma is staged like PDAC. It is an aggressive neoplasm with 50% of patients dying of their disease. Surgery is the treatment of choice. There is distinct overlap with acinar cell carcinoma with squamoid nests being the distinguishing feature. Both tumours can be associated with elevated serum AFP.[10]

### Solid pseudopapillary neoplasm

Solid pseudopapillary neoplasms are enigmatic tumours, in which the cell origin has not been elucidated. They can occur anywhere within the pancreas and have a propensity towards haemorrhagic cystic degeneration. They account for up to 3% of all pancreatic neoplasms and up to 5% of pancreatic cystic neoplasms. Ninety per cent present in women with a mean age of 25. Most are found incidentally. They are well circumscribed with a mean size of 10 cm and a tan haemorrhagic surface. Microscopically, they are composed of poorly cohesive monomorphic cells arranged in solid sheets or pseudopapillae with intervening degenerative, haemorrhagic cystic areas (Figure 5). Intracytoplasmic eosinophilic globules are characteristic and intensely alpha-1-antitrypsin-positive. Clear cell and pigmented variants have been reported. Nuclear/cytoplasmic staining for beta-catenin is typical, and the cells also label for CD10 and progesterone receptors, among other markers. The cells do not consistently label with cytokeratin or neuroendocrine markers, which allows distinction from pancreatic NETs, which are the closest mimic morphologically. Solid pseudopapillary neoplasms are negative for trypsin and lipase, separating them from acinar cell carcinoma. Solid pseudopapillary neoplasms are low-grade malignant tumours, and complete surgical removal will be curative in 85–95% of cases. There is no reliable morphological feature to predict malignancy, but aggressive behaviour appears

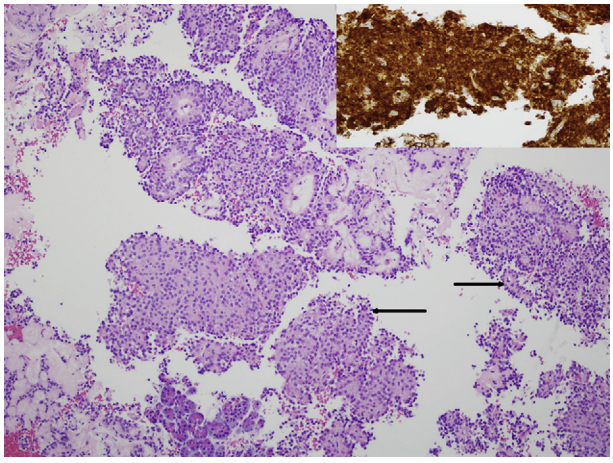

**Figure 5** EUS-guided FNB of solid pseudopapillary neoplasm showing pseudopapillary arrangements due to poor cell cohesion (arrows) and positive nuclear and cytoplasmic immunohistochemical staining for beta-catenin (inset).

to be associated with a high mitotic rate, marked nuclear atypia and tumour necrosis. The tumours are staged like PDAC.[9]

Very rare non-epithelial solid neoplasms such as mesenchymal tumours include benign lipoma and schwannoma. Inflammatory myofibroblastic tumours and solitary fibrous tumour may show a spectrum of behaviour. Leiomyosarcoma is the most common frankly malignant mesenchymal tumour of the pancreas and may present with a large, partially necrotic mass. Unusual childhood sarcomas such as Ewing's sarcoma and desmoplastic small round cell tumour can also be seen.[9]

## Non-neoplastic cystic lesions

Non-neoplastic cystic lesions can be divided in epithelial and non-epithelial lesions. Non-neoplastic non-epithelial include pancreatitis-associated pseudocysts and parasitic cysts. Pseudocysts account for 85% of cystic lesions in the pancreas and need to be distinguished from cystic neoplasms. Occurring in the context of pancreatitis they are almost always symptomatic. There is a male predominance, and age at presentation is younger compared to cystic neoplasms. They can be treated conservatively by surgical drainage. Imaging and cyst fluid analysis will allow characterization of cystic lesions. A high cyst fluid amylase will be more common in pseudocysts, whereas CEA and viscosity will be elevated in mucin producing cystic neoplasms. FNA from pseudocysts might show fibro-inflammatory debris, whereas cystic neoplasms will yield epithelial cells, which can be assessed for degree of atypia informing surgical treatment. Non-neoplastic cystic lesions with epithelial components including lymphoepithelial cyst, mucinous non-neoplastic cyst, and enterogenous cyst are very rare.

## Neoplastic cystic lesions

In addition to primarily cystic neoplasms, there are also a number of solid neoplasms that can undergo cystic change due to degeneration, in particular solid pseudopapillary neoplasm, PanNETs, but also PDAC and acinar cell carcinoma.

Primarily cystic neoplasms account for approximately 10–15% of all cystic lesions and only 5% of pancreatic neoplasms. The vast majority are benign serous tumours and two different types of mucin producing tumours: mucinous cystic neoplasms and intraductal papillary mucinous neoplasms. Non-invasive mucin-producing cystic neoplasms of the pancreas are established macroscopic precursor lesions of PDAC (Table 2). Their early detection and complete surgical removal will be curative.

### Serous neoplasms

Serous cystic neoplasms are uncommon and account for 1–2% of all pancreatic neoplasms. They present at a mean age of 60 with a slight female predominance and vague abdominal symptoms, or may be found incidentally. Importantly they occur in VHL-syndrome, where they can be multiple and associated with PanNETs. The classical serous cystadenoma (synonymous with microcystic serous cystadenoma) is found more commonly in the body and tail of the pancreas. Tumours are circumscribed with a mean size of 6 cm, a central stellate scar and a 'sunburst' pattern of calcification observed on imaging. The cut section shows a sponge-like appearance. The cells lining the microcysts display central, small, regular nuclei surrounded by clear cytoplasm. Occasional small papillae can be seen, but there is no atypia. Different histological variants are described, all with the same cell morphology. Macrocystic serous cystadenoma is more ill-defined, occurs more commonly in the head, contains larger (>1 cm) cysts and can even be unilocular, rendering clinical distinction from other cystic neoplasms challenging. Solid serous adenoma tends to be smaller (2–4 cm) and show a solid cut surface. VHL-associated serous cystic neoplasms can involve the pancreas diffusely. Microcystic serous cystadenoma with subtotal cystic degeneration may mimic a pseudocyst histologically, as there may be only focal residual epithelium present. Mixed serous neuroendocrine neoplasms may show intermingling or independence of both components and raise a strong possibility of VHL-syndrome. Serous cystadenomas are characterized by slow growth. They can be followed conservatively if clinically uncomplicated and radiologically typical. Locally advanced cases with complications can occur, but cases of true malignant serous cystadenocarcinoma with metastatic disease, as defined by the 2010 WHO classification, have not been verified.[15] Clear cell tumours such as metastatic renal cell carcinoma and pancreatic neuroendocrine tumours have to be considered in the differential diagnosis, particularly in the context of VHL-syndrome.[9]

### Mucinous cystic neoplasm (MCN)

MCNs account for approximately 10% of all pancreatic cystic neoplasms. Ninety-five per cent occur in women with a mean age of 40–60 years. Tumours are usually single, found in the body or tail of pancreas, and can present with non-specific epigastric discomfort or incidentally. Macroscopically, they are well circumscribed, unilocular or multilocular with a pseudocapsule. There is no communication with the pancreatic duct system. Their average size is 6–10 cm. Individual cyst locules are lined by gastric- or intestinal-type mucinous epithelium. Dense, oestrogen and progesterone receptor positive, ovarian type stroma is a defining feature. Two-thirds of tumours are non-invasive at the time of presentation. The degree of atypia in the lining epithelium is assessed as either low-grade or high-grade dysplasia.

**Macroscopic precursor lesions of pancreatic ductal adenocarcinoma**

| | Mucinous cystic neoplasm (MCN) | Intraductal papillary mucinous neoplasms (IPMN) | Intraductal tubulopapillary neoplasm (ITPN) |
|---|---|---|---|
| Percentage of cystic neoplasms | 8% | 20% | <1% |
| Gender (female:male) | 20:1 | 2:3 | 1:1 |
| Age | 40–60 | 60–70 | Mean 56 |
| Clinical presentation | Non-specific epigastic discomfort | Abdominal pain, recurrent pancreatitis | Abdominal discomfort |
| Location in pancreas | Body and tail | Head >> body/tail | Head > body > tail |
| Relation to ducts | None | In main and/or branch ducts | In dilated ducts |
| Imaging | Cystic mass with thick wall, displaces ducts | Dilated ducts, cysts and filling defects | Like IPMNs |
| Size | Mean 6–10cm | >1cm | Average 6cm |
| Macroscopy | Well defined unilocular or multilocular cyst with thick wall, Mucin or haemorrhagic material | Dilated ducts ± visible papillae, Abundant mucin | Intraductal solid/nodular mass *No* mucin |
| Microscopy | Mucinous columnar cells, ovarian type stroma | Flat or papillary mucinous epithelium (gastric, intestinal, pancreaticobiliary, oncocytic) | Back to back tubular glands with cribriform arrangements |
| Associated invasive carcinoma | 30% of MCNs, ductal type | 30% of IPMN, colloid type in intestinal type IPMN, otherwise ductal | 40% of ITPN, Tubular/ductular type |
| Classification | MCN with low-grade dysplasia<br>MCN with high-grade dysplasia<br>MCN with an associated invasive carcinoma | IPMN with low-grade dysplasia<br>IPMN with high-grade dysplasia<br>IPMN with an associated invasive carcinoma | ITPN (usually high-grade dysplasia)<br><br>ITPN with an associated invasive carcinoma |

**Table 2**

Surgical removal of non-invasive tumours is curative. Between 12% and 20% of tumours are associated with an invasive carcinoma with virtually no risk of malignancy in lesions less than 4 cm. The invasive tumour is commonly of conventional ductal type, with a 5 year survival of approximately 60%.[9]

### Intraductal papillary mucinous neoplasm (IPMN)

IPMNs are >1 cm, grossly visible intraductal cystic epithelial neoplasms which can be associated with invasive carcinomas. They account for 1–3% of pancreatic neoplasms and approximately 20% of all cystic neoplasms of the pancreas. They occur most commonly at age 60–70 years with a slight male predominance. IPMNs can present with pancreatitis-like symptoms. IPMNs occur most commonly in the head of pancreas. About 40% of cases are multifocal. Macroscopically, they can be classified into main duct, branch duct or combined/mixed type. Grossly they may either show intracystic villous projections or a flat lining (ductectatic pattern). Main duct IPMNs are associated with a higher risk of high-grade dysplasia and invasive carcinoma. Histologically, there are four distinct types: intestinal, gastric foveolar, pancreaticobiliary and oncocytic. The cytological atypia in IPMNs is graded as low- versus high-grade dysplasia. The intestinal type is usually main duct and resembles colonic villous adenoma. Associated invasive carcinomas tend to be of colloid type with a better prognosis compared to ductal type. The pancreaticobiliary type is rare, usually affects the main duct, and displays high-grade dysplasia. Associated carcinomas will be of ductal type. The gastric foveolar type tends to be smaller, affecting branch ducts and displaying mostly low-grade dysplasia. The oncocytic type has recently been recognized as a distinct entity with a different molecular pathway, clinical presentation and biological behaviour. It shows architectural complexity and granular eosinophilic lining cells, often displaying high-grade dysplasia, and may be associated with an oncocytic carcinoma, which has a better prognosis than the ductal subtype. Multiple subtypes can co-exist in one IPMN (Figure 6), and the possibility that the pancreaticobiliary type may represent high-grade progression from a low-grade gastric type has been postulated. Gastric foveolar branch duct IPMNs show histological overlap with pancreatic intraepithelial neoplasia (PanIN), which is a microscopic (<0.5 cm) intraductal lesion with a two-tier grading of atypia that has been well characterized as a precursor to PDAC. IPMN is favoured in a radiologically detectable lesion, more prominent mucin production and longer papillae. Lesions between 0.5 cm and 1 cm can be either small IPMNs or large PanINs, with incipient IPMN restricted to those small lesions with intestinal or oncocytic papillae. Thirty per cent of resected IPMNs show an associated invasive carcinoma. Features highly predictive of malignancy include jaundice, presence of an enhancing mural nodule (≥5 mm)/a solid component, positive cytology and main pancreatic duct measuring ≥10 mm.[16] The five year survival for non-invasive IPMNs is up to 100%, whereas it is only 34–62% if an invasive carcinoma is present. Surgery is the treatment of choice and curative in patients with non-invasive IPMNs. It is crucial to rule out an invasive component to an IPMN by extensive if not complete pathological

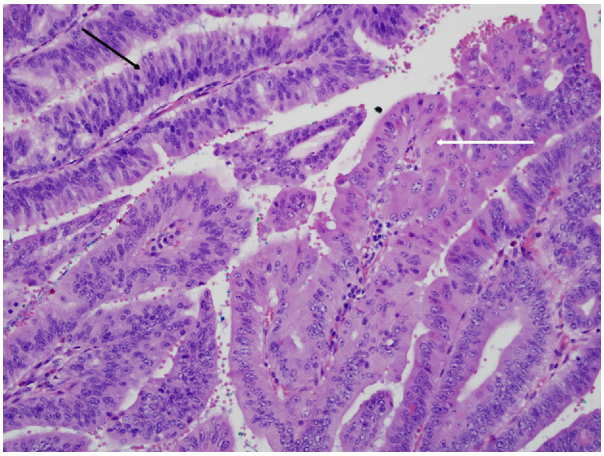

**Figure 6** Microphotograph of IPMN showing adjacent intestinal (black arrow) and oncocytic (white arrow) subtype.

examination of the lesion. Associated versus concomitant status of the invasive component is prognostically important and assessed by sampling tissue between the IPMN and the invasive lesion. An associated invasive carcinoma is measured separately from the intraductal component and given the appropriate T-stage. Duct rupture with mucin spillage can be seen in intestinal-type IPMNs mimicking invasion and distinction from truly invasive colloid carcinoma may be difficult. A pathological category of indeterminate/suspicious for invasion may have to be used in rare cases.[17]

Accounting for only a 3% fraction of intraductal neoplasms are intraductal tubulopapillary neoplasms, which are distinct from IPMNs because of lack of overt mucin production and the presence of tubules rather than papillae. They occur at a mean age of 55 with an average size of 6 cm and show high-grade cellular atypia. An associated invasive ductal type carcinoma is seen in 40% of cases.[9]

## Conclusion

Pathological examination of tissue specimens is an integral part of the multidisciplinary care of patients with pancreatic diseases. Consistent application of pathological diagnostic criteria in the clinical context and close co-operation between pathologist and surgeon/physician are pre-requisites for accurate patient diagnosis and management. ◆

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