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# Ampulla of Vater and Head of Pancreas Carcinoma

## 1. GROSS DESCRIPTION

### Specimen

— pancreatic and ampullary cancers classically present with painless obstructive jaundice and investigation includes liver function tests, serum CA19-9, and OGD/ERCP with cytology and biopsy. Ultrasound can confirm duct obstruction and staging for local and distant disease also includes magnetic resonance cholangiopancreatography, CT scan chest, abdomen and pelvis and PET scan. Staging laparoscopy may also be done prior to consideration of radical surgery. Pancreatic endocrine tumours more often present as a consequence of a functional hormonal syndrome and localization of the primary lesion and metastases is by octreotide and CT scans. Treatment entails complete local excision of the primary tumour with a combination of surgery and medical treatment for metastatic disease.
— endoscopic brushings or biopsy/transduodenal or percutaneous fine-needle aspirate (FNA) or needle core biopsy.
— Whipple's procedure (partial gastrectomy, duodenectomy and partial pancreatectomy). A pylorus-preserving pancreaticoduodectomy may be used for small peri-ampullary tumours, thus maintaining the storage and release functions of the distal stomach and proximal 3 cm of duodenum.
— total pancreatectomy (partial gastrectomy, duodenectomy, total pancreatectomy and splenectomy).
— weight (g) and size/length (cm), number of fragments.

Carcinomas of the ampulla and head of pancreas are considered together because of their anatomical juxtaposition, overlap and common potentially operative resection (Whipple's procedure). A majority of ampullary cancers are operable but only a minority of pancreatic carcinomas.

### Tumour

#### *Site*

— non-ampullary duodenal mucosa/duodenal papilla/ampullary mucous membrane/muscularis/pancreatic head (60–70% of pancreatic carcinomas)/terminal common bile duct/multifocal.

***Size***
— length × width × depth (cm) or maximum dimension (cm).

Ampullary cancers >2.5 cm diameter have a decreased 5-year survival. Pancreatic exocrine cancers >3 cm are often inoperable. Pancreatic endocrine tumours >2–3 cm show greater local and vascular invasion and metastatic potential.

***Appearance***
— polypoid/nodular/diffuse/ulcerated: ampullary tumours.
— scirrhous/mucoid/cystic: pancreatic exocrine tumours.
— circumscribed/pale: pancreatic endocrine tumours.

***Edge***
— circumscribed/irregular.

## 2. HISTOLOGICAL TYPE

### Ampulla
— adenocarcinoma. 80% of cases are usually of well to moderately differentiated intestinal pattern arising from adenomatous dysplasia in the peri-/intra-ampullary mucosa. Endoscopic biopsy underestimates the nature and extent of disease yielding a positive diagnosis of malignancy in only about 40% of cases. It samples the surface dysplasia but not the underlying carcinoma, which is better demonstrated as a mass lesion on imaging (ELUS, CT).
— papillary adenocarcinoma. Exophytic, well differentiated of better prognosis and can be multifocal in the extrahepatic biliary tree.
— mucinous adenocarcinoma—mucin in >50% of the tumour.
— signet ring cell adenocarcinoma.
— metastatic carcinoma, e.g. direct spread: stomach, pancreas, terminal common bile duct. Some 10–15% of ampullary adenocarcinomas arise from the terminal portion of either of the main ducts and, therefore, have a biliary phenotype making distinction from invasion by pancreatic adenocarcinoma difficult.

### Pancreas

***(a) Exocrine***
— ductal adenocarcinoma (80–90% of cases):
tubulo-acinar pattern of malignant ductal epithelium in a desmoplastic stroma with perineural invasion and dysplasia of the adjacent duct epithelium (20–30%). Pancreatic intraepithelial neoplasia (PanIN) is a microscopic papillary or flat, non-invasive epithelial neoplasm (dysplasia) comprising cubocolumnar epithelial cells with variable degrees of cytoarchitectural atypia. It usually arises in pancreatic ducts <5 mm diameter, is multifocal and seen adjacent to existing carcinoma, being regarded as a precursor to it. High-grade PanIN is

equivalent to severe dysplasia or carcinoma in situ. Note that PanIN can be mimicked by florid reactive atypia or cancerization of ducts by invasive ductal carcinoma.
multifocality 15–40%.
male preponderance.

— ductal adenocarcinoma variants:
mucinous non-cystic colloid carcinoma (1–3%): mucin in >50% of the tumour.
adenosquamous: at least 30% squamous component.
microglandular/signet ring cell—poor prognosis. Exclude a gastric carcinoma secondary deposit.
oncocytic.
clear cell.

— undifferentiated carcinoma (2–7%: syn pleomorphic/giant cell/sarcomatoid carcinoma):
spindle cells/pleomorphic cells/mitoses/lymphovascular invasion. Variant with osteoclast-like giant cells may have a slightly better prognosis.

— intraductal papillary or mucinous neoplasms/tumours (IPMNT):
IPMNT is a clinically detectable grossly visible, non-invasive, mucin-producing papillary epithelial neoplasm. It arises from the main pancreatic duct or branch ducts with varying duct dilation (>1 cm) and cytoarchitectural atypia. It is benign/borderline or malignant according to the degree of dysplasia ± invasion (20–30% are associated with colloid or ductal adenocarcinoma). 80% are in the head of pancreas and multifocal within the duct system. It shows indolent behaviour marked by MUC 2 phenotype in distinction from the MUC 1 aggressive ductal phenotype of usual pancreatic cancer.

— serous macro/microcystic tumours:
elderly in the head or tail (50–75%) and mostly benign (microcystic/oligocystic serous adenoma) but occasionally malignant. It comprises glycogen-rich, clear cuboidal epithelium lining fluid-filled microcysts with a central scar. Diagnosis can be aided by analysis of aspirated cyst fluid which, in distinction from mucinous cystic tumours and pseudocysts, has low viscosity and zero levels of leucocyte esterase. Surgical excision is curative.

— mucinous cystic tumours:
benign/borderline/malignant spectrum of appearance and behaviour tending to malignancy. Prognosis relates to the degree of invasion (which can be focal within a lesion) into pancreatic and extrapancreatic tissues. The carcinoma is usually ductal in character, occasionally adenosquamous or pleomorphic/giant cell. In general, indolent growth with spread to abdominal cavity occurring in middle-aged women but 90–95% 5-year survival if completely excised. Uni-/multilocular, body/tail of pancreas and potentially resectable. Characteristic ovarian type stroma in the wall (helpful to distinguish from pancreatic pseudocyst when the epithelial lining is lost) and no connection to the duct system.

— solid-cystic-papillary tumour (syn. solid-pseudopapillary tumour):

adolescent girls/young women of low malignant potential but usually benign. It comprises pseudopapillae covered by several layers of uniform, endocrine-like epithelial cells and a vascularized, hyalinized stroma with necrosis and mucinous cystic change. Alpha-1-antitrypsin/vimentin/CD10 positive, ± neuroendocrine markers (chromogranin/CD56/synaptophysin), and cytokeratin negative.

— acinar cell carcinoma:
1–2% of cases in the head of pancreas and uniform cells with cytoplasmic granules resembling normal pancreas. Enzyme antibody positive, e.g. lipase, amylase, trypsin. Nodal and liver metastases can be present in 50% of cases at diagnosis and aggressive.

— mixed differentiation carcinoma:
acinar/endocrine or ductal/endocrine are rare and behave as for ductal carcinoma. The endocrine component must be at least 30 % of the tumour.

— small cell carcinoma:
presents at late stage, poor prognosis.

— pancreaticoblastoma:
malignant in children and favourable prognosis if resected before metastases (nodal/hepatic 35% of cases). Also chemoresponsive. Consists of epithelial (acini, squamous nests) and mesenchymal (spindle cell) components.

***(b) Endocrine (islet cell tumours)***

— arise from pluripotential ductal cells showing neuroendocrine differentiation.

— forming a minority of pancreatic neoplasms (1–5%) usually occurring in adults. Small (<1–2 cm), circumscribed and solid/trabecular/gyriform/glandular cell patterns with hyaline (±amyloid) stroma. The majority are benign insulinomas (80–90%). Prognosis depends on the functional subtype, adequacy of surgical excision and the extent of disease.

1. Functional hormonal syndrome (60–85%)
   gastrinoma: pancreatic head, duodenum, gastric antrum, Zollinger-Ellison syndrome (multiple gastroduodenal ulcers, carcinoid tumourlets or microadenomas).
   insulinoma: body and tail—psychiatric/neurological symptoms/hypoglycaemia.
   vipoma: body and tail—watery diarrhoea, hypocalcaemia and achlorhydria.
   glucagonoma: body and tail—diabetes mellitus/skin rash/stomatitis.
2. Non-functional
   somatostatinoma: also in the duodenum with a glandular pattern and psammoma bodies and must be distinguished from well-differentiated adenocarcinoma.
   Ppoma.
   neurotensinoma.

calcitoninoma.
small cell carcinoma: ± ectopic ACTH secretion, hypercalcaemia.

Cellular density, atypia, necrosis, mitoses (>2–10/10 hpfs) and a Ki-67 index >5% give some guide as to malignant potential but they are not reliable. Better indicators are:

— tumour type: insulinoma, 85–90% benign; gastrinoma, 60–85% malignant.
— size (>2–3 cm), site (e.g. duodenal) and invasion of vessels.
— unequivocal evidence of malignancy is gross invasion of adjacent organs, metastases to regional nodes, liver and other distant sites. Tumour growth is indolent and even patients with metastases can survive several years. Some respond to chemotherapy, e.g. streptozotocin. Occasional cases are of poorly differentiated high-grade small cell type.

Association with multiple endocrine neoplasia (MEN) syndrome. The pancreas is involved in 80–100% of type 1 MEN syndrome, gastrinoma being the commonest (50%) lesion. Associated abnormalities are hyperplasia or tumours of parathyroid, pituitary and adrenal glands.

***(c) Mixed exocrine/endocrine carcinoma***

— <1%; bivalent amphicrine cells or adjacent foci of mixed differentiation (the endocrine component being at least one-third of the tumour).

***(d) Metastatic carcinoma***

— direct spread: stomach, colorectum, biliary tract, abdominal mesothelioma/lymphoma.
— distant spread: pleomorphic carcinoma of the pancreas has to be distinguished from metastatic malignant melanoma, sarcoma, choriocarcinoma and large cell lung carcinoma. Small cell lung carcinoma and renal carcinoma.

It can be difficult to distinguish adenocarcinoma of the pancreas and adenocarcinoma of the terminal common bile duct from adenocarcinoma of the ampulla of Vater, as they can share similar histological features of biliary phenotype. Careful examination of the exact anatomical location is required and circumstantial evidence for a point of origin, e.g. an adenomatous lesion in the ampullary mucosa or dysplasia in the pancreatic/bile duct epithelium. Ampullary cancers tend to an intestinal phenotype and immunoprofile (CK7 negative/CK20 positive) and pancreatic cancers a ductal appearance and different immunoexpression (CK7 positive/CK20 positive). Sometimes the only conclusion can be adenocarcinoma of the pancreatico-ampullary-biliary region.

**3. DIFFERENTIATION**

Well/moderate/poor/undifferentiated, or, Grade 1 /2/3/4.

Pancreatic ductal and ampullary adenocarcinoma can be graded according to the percentage tumour gland formation (well/G1 >95%: moderate/G2 50–95%: poor/G3 <50%).

By convention and definition signet ring cell adenocarcinoma and undifferentiated carcinoma (no glandular differentiation) are grade 3 and grade 4, respectively. Well-differentiated pancreatic adenocarcinoma can be difficult to distinguish from non-neoplastic ducts. Malignant glands are of variable size, shape and angularity with atypical nuclear/nucleolar features. Cell cytoplasm is tall and pale to clear in character. Perineural invasion is diagnostically helpful.

Intraduct papillary lesions are:

| | |
|---|---|
| Low-grade | mild nuclear atypia<br>no mitoses |
| Intermediate | moderate nuclear atypia<br><5 mitoses/10 hpfs |
| High-grade | severe cellular atypia<br>mitoses >5/10 hpfs |

Endocrine tumours are not graded because of poor correlation of cytological features and growth pattern with biological behaviour.

#### 4. EXTENT OF LOCAL TUMOUR SPREAD

Border: pushing/infiltrative.

Lymphocytic reaction: prominent/sparse.

The TNM classification applies to carcinomas of the ampulla of Vater and exocrine pancreas.

***Ampulla***

| | |
|---|---|
| pTis | carcinoma in situ |
| pT1 | tumour limited to the ampulla or sphincter of Oddi |
| pT2 | tumour invades duodenal wall |
| pT3 | tumour invades pancreas |
| pT4 | tumour invades peripancreatic soft tissues or other adjacent organs or structures. |

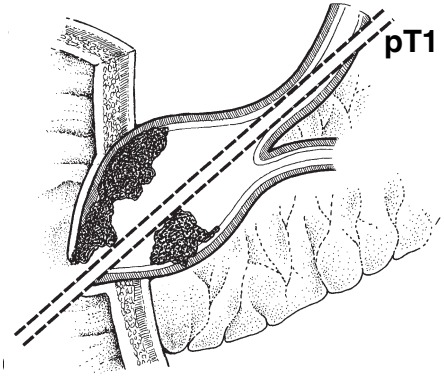


**FIGURE 3.1.** Ampulla of Vater carcinoma.

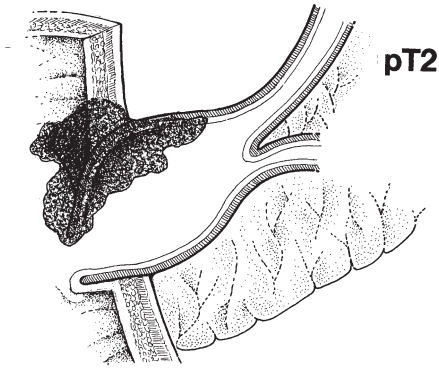


**FIGURE 3.2.** Ampulla of Vater carcinoma.

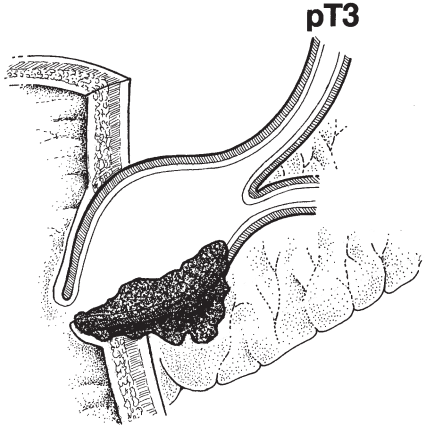


**FIGURE 3.3.** Ampulla of Vater carcinoma.

***Pancreas***

| | |
|---|---|
| pTis | carcinoma in situ |
| pT1 | tumour limited to the pancreas, ≤2 cm maximum dimension |
| pT2 | tumour limited to the pancreas, >2 cm dimension |
| pT3 | tumour extends beyond pancreas*, but without involvement of coeliac axis or superior mesenteric artery |
| pT4 | tumour involves coeliac axis or superior mesenteric artery. |

*Beyond pancreas includes the retroperitoneal fat and space, mesenteric fat, mesocolon, greater and lesser omenta and peritoneum. Direct invasion to bile ducts and duodenum includes involvement of the ampulla of Vater. Peripancreatic soft tissue involvement is an adverse prognostic indicator.

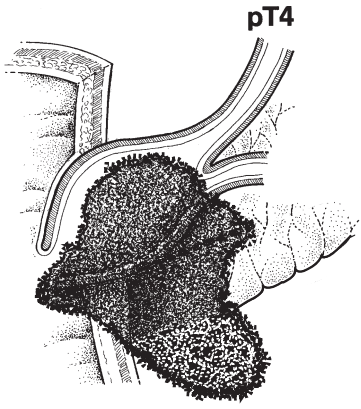


**FIGURE 3.4.** Ampulla of Vater carcinoma.

### 5. LYMPHOVASCULAR INVASION

Present/absent.
Intra-/extratumoral.

Perineural space involvement is common in pancreatic carcinoma and lymphovascular invasion is present in up to 50% of cases with spread to local regional nodes at the time of diagnosis. Invasion of portal vein has adverse independent prognostic significance. Sites of distant metastases are liver, peritoneum, lung, adrenal, bone, skin and CNS. Regional node involvement is also present in 35–50% of ampullary carcinomas.

### 6. LYMPH NODES

Site/number/size/number involved/limit node/extracapsular spread.
Regional nodes: peripancreatic, pancreaticoduodenal, common bile duct, pyloric and proximal mesenteric. A regional lymphadenectomy will ordinarily include a minimum of 10 lymph nodes.

pN0 no regional lymph node metastasis
pN1 metastasis in regional lymph node(s).

### 7. EXCISION MARGINS

Distances (mm) to the following margins; proximal (gastric/duodenal), distal (duodenal), common bile duct, distal pancreatic, posterior pancreatic surface (deep radial).

The commonest site for local recurrence of invasive carcinoma after a Whipple's procedure is the posterior pancreatic soft tissue margin. This should be inked accordingly and the distance of tumour to it measured. Similarly for the non-peritonealized margin of the uncinate process. Local recurrence from intraductal tumour is more likely at a ductal resection margin.

## 8. OTHER PATHOLOGY

Cholestatic jaundice—carcinoma head of pancreas and ampulla.

***Ampulla***

— duodenal adenoma(s), familial adenomatous polyposis coli (ampullary carcinoma is one of the commonest causes of death in FAPC).

***Pancreas***

— 3–10% of pancreatic carcinoma are familial—hereditary, BRCA2, HNPCC.
— disseminated intravascular coagulation, thrombophlebitis migrans (25% of cases, particularly with mucin-secreting tumours).
— gastrointestinal neuroendocrine syndromes, e.g. Zollinger-Ellison syndrome (diarrhoea, gastric hyperacidity with gastric/duodenal/jejunal ulcers), Werner-Morrison syndrome, WDHA syndrome (watery diarrhoea, hypokalaemia, alkalosis).
— chronic pancreatitis shows acinar atrophy, distortion and regenerative changes with stromal fibrosis and residual islet tissue and can mimic pancreatic carcinoma. Similar changes are also seen upstream and adjacent to pancreatic carcinoma due to duct obstruction indicating that interpretation and sampling can be problematic. Ductules in chronic pancreatitis tend to retain their lobular architecture, lack significant malignant cytological change and show no invasion of nerve sheaths or peripancreatic fat. Jaundice of short duration in a patient older than 60 years is suspicious of malignancy. Other indicators are elevated serum CA19-9 (usually in cancers >3 cm diame-

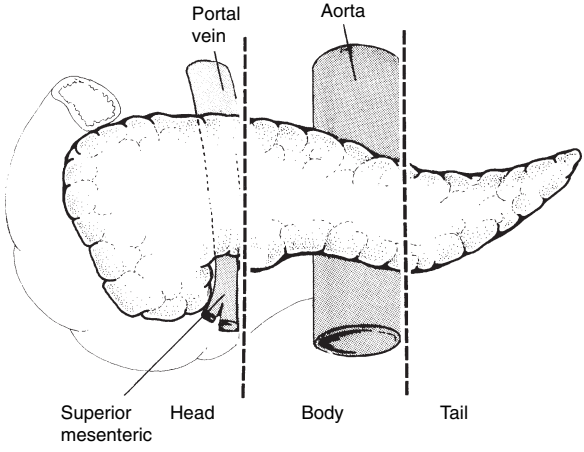


**FIGURE 3.5.** Pancreas.

ter), duct stricture at ERCP or a mass lesion on CT/ELUS. Imaging is important in establishing contraindications to surgery (distant nodal/major vessel involvement) or other potentially operable diagnoses, e.g. serous or mucinous cystic tumours. A tissue diagnosis may be obtained by positive duct cytology brushings or transduodenal/percutaneous FNA or needle core biopsy. This is important to exclude other treatable malignancies, e.g. lymphoma in peripancreatic nodes. In a proportion of cases a firm diagnosis will not be obtained and must be assumed on the basis of clinical probability. Thus pancreaticoduodenectomy has a 5% false negative rate on the basis of benign disease.

***Immunophenotype***

— neuroendocrine: chromogranin, synaptophysin, CD56.
— hormonal: specific peptides—insulin, glucagon, gastrin, pancreatic polypeptide, VIP, ACTH, somatostatin.
— exocrine carcinoma: cytokeratins (including CK7, CK8, CK18, CK19, ±CK20), CEA, CA19-9, CA-125, MUC I—expressed in >80% of ductal

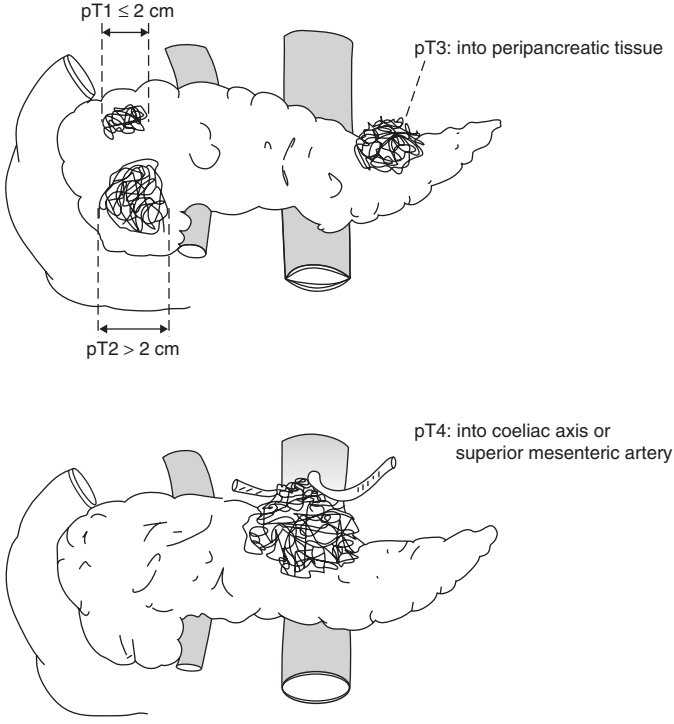


**FIGURE 3.6.** Pancreatic carcinoma.

lesions, ±CDX-2.

**Prognosis**

Prognosis in pancreatic ductal carcinoma is poor with most patients dead within several months. It relates to tumour site (body and tail are worse than head, as the latter may present early with obstructive jaundice), size (>4.5 cm is adverse), histological grade and stage. Overall 5-year survival is 2%, even disease confined to the pancreas only reaching 15%. There is limited suitability for resection (5–10% of cases), namely, node-negative tumours of the pancreatic head <3 cm diameter with no major (superior mesenteric or portal) vessel invasion. The majority present with advanced disease into lymph node and retroperitoneal tissues. Treatment is palliative with relief of ductal biliary obstruction by open or laparoscopic bypass or endoscopic stent insertion. Mucinous cystic tumours are less frequent but potentially resectable. Pancreatic endocrine tumours may present with their associated metabolic or gastrointestinal syndrome and have an indolent time course being of low- to intermediate-grade malignancy. Ampullary carcinoma is more favourable than pancreatic or bile duct carcinoma with a 5-year survival of 25–50%. This can improve to 80–85% if the tumour is at an early stage and confined to the sphincter of Oddi (pT1). Transduodenal wide local excision may be adequate for carefully selected ampullary tumours, e.g. adenoma, but only after careful staging and exclusion of an underlying mass lesion requiring radical surgery.

## 9. OTHER MALIGNANCY

***Leukaemia***

***Lymphoma***

— usually spread from para-aortic/peripancreatic nodal lymphoma.
— extramedullary plasmacytoma.

***Sarcoma***

— rare
— leiomyosarcoma, liposarcoma, fibrosarcoma, osteosarcoma.
— exclude secondary from gut (spindle cell carcinoma/GIST/sarcoma) or retroperitoneum.