Pathology of exocrine neoplasms of the pancreas

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Abstract
Epithelial neoplasms of the exocrine pancreas in adults can be divided into solid neoplasms (ductal adenocarcinoma, acinar cell carcinoma) which have a poor prognosis, or cystic neoplasms (serous, mucinous, intraductal papillary and solid pseudopapillary types), which are less common but have a much better prognosis; mesenchymal tumours and primary lymphoma are exceedingly rare. Secondary involvement of the pancreas can occur; the commonest metastatic tumours are renal cell carcinoma and malignant melanoma. Pancreatoblastoma is the commonest malignant pancreatic neoplasm in childhood, but is extremely rare.

Keywords exocrine pancreas; neoplasm; adenocarcinoma; serous cystic; mucinous; intraductal; solid pseudopapillary

Neoplasms of the exocrine pancreas may be epithelial, mesenchymal or secondary. Confusion over terminology may arise because different names have been given to the same entity; the WHO classification of neoplasms of the exocrine pancreas is used in this contribution. Epithelial neoplasms of the exocrine pancreas in adults can be divided into solid neoplasms (ductal adenocarcinoma, its variants, and acinar cell carcinoma), which have a poor prognosis, or cystic neoplasms (serous, mucinous, intraductal papillary and solid pseudopapillary types), which are less common but have a much better prognosis. Mesenchymal tumours and primary lymphoma are exceedingly rare and are not discussed. Metastases may be found in the pancreas, usually renal cell carcinoma and malignant melanoma. Pancreatoblastoma is the commonest malignant pancreatic neoplasm in childhood but is extremely rare.

Serous cystic neoplasms

Serous microcystic adenoma
Serous microcystic adenoma (also known as ‘glycogen-rich cystadenoma’ and ‘serous cystadenoma’) is a benign neoplasm, accounting for 1–2% of exocrine pancreatic neoplasms, and occurring predominantly in females (mean age 65 years). It occurs as a solitary lesion anywhere in the pancreas, ranging from 1–25 cm in diameter, but typically 5–10 cm. Rare cases of multiple tumours have been reported.

Presentation is with non-specific symptoms (e.g. abdominal pain, nausea, vomiting, weight loss). A palpable mass may be present, but often they are found incidentally on imaging. CT may show a honeycomb pattern and thin septa within the mass, together with a ‘sunburst’ of calcification.

Macroscopically, there is a round, well-circumscribed mass with an irregular bossed external aspect. On sectioning, there is a characteristic sponge-like or honeycomb appearance (Figure 1a) with multiple tightly-packed tiny cysts of varying sizes (typically <5 mm) containing clear watery serous fluid with fibrous septa. Larger neoplasms may show a central or eccentric fibrous stellate scar with calcification.

Microscopically, the cysts are thin-walled and lined by glycogen-rich cuboidal or flattened epithelial cells with clear cytoplasm, well-defined cytoplasmic borders and central small uniform nuclei (Figure 1b). There may be papillary projections of epithelium into the cysts, but mitoses or nuclear pleomorphism are absent. A fibrous pseudocapsule may separate the neoplasm from the adjacent pancreatic parenchyma.

Prognosis: complete resection is curative but serous microcystic adenoma can be managed conservatively.

Variants
Serous oligocystic adenoma – a few cases of this macrocystic variant have been reported, as has a solid variant. The oligocystic variant has few relatively large cysts or a single macroscopic cyst up to 8 cm in size and lacks a stellate scar.

Serous cystadenocarcinoma has been described in case reports, mostly focusing on its deceptively bland histology. The diagnosis was typically made on the basis of metastatic spread.

Mucinous cystic neoplasms
Mucinous cystic neoplasms account for 2–5% of exocrine pancreatic neoplasms, occur almost exclusively in females (mean age 50 years) and are found predominantly within the tail of the pancreas.

Presentation is with abdominal pain and/or an abdominal mass.

Macroscopically, they are usually solitary and form a well-defined, smooth round mass, ranging from 1 cm to 30 cm in diameter (mean size 5–10 cm). Opening reveals a multilocular mucin-filled cyst (Figure 1c) with a thick fibrous pseudocapsule that may show foci of calcification; cysts may contain haemorrhagic material. The inner lining of the cysts may be smooth, trabeculated or papillary; solid nodules may be present. The papillary and solid areas must be sampled because these are likely to show high-grade dysplasia or malignancy.

Microscopically, the cysts are lined by columnar mucin-producing epithelium with associated pathognomonic ovarian-type stroma.
Serous microcystic adenoma with a honeycomb cut-surface (arrow) and b a lining of clear, glycogen-rich, cuboidal cells (arrows). This c oligocystic lesion may be a mucinous cystic neoplasm, pseudocyst or serous oligocystic adenoma. Borderline mucinous cystic neoplasm showing d tall columnar mucin-producing epithelium with moderate dysplasia (black arrow) and typical ovarian stroma (blue arrow).

**Figure 1**

(Figure 1d). The epithelium may show intestinal differentiation with scattered neuroendocrine cells.

**Classification:** mucinous cystic neoplasms are classified in the WHO classification as:
- benign (mucinous cystadenoma)
- borderline/low-grade malignant (mucinous cystic neoplasm with moderate dysplasia)
- malignant (mucinous cystadenocarcinoma, non-invasive or invasive).

Some authors think that all mucinous cystic neoplasms should be considered to have low-grade malignant potential.

Mucinous cystadenoma shows little epithelial atypia and no mitotic activity. In mucinous cystic neoplasms of borderline malignant potential, the epithelium may show papillary projections, pseudostratified nuclei and mitoses. Non-invasive mucinous cystadenocarcinoma is characterized by severe dysplasia i.e. a papillary epithelium with irregular branching and budding, nuclear stratification and pleomorphism, and numerous mitoses.

Invasive mucinous cystadenocarcinoma is characterized by invasion into the stroma. Severe dysplasia or invasive carcinoma may be focal and therefore extensive sampling is required.

**Prognosis:** the prognosis for non-invasive mucinous cystic neoplasms is excellent if excision is complete; there is a risk of recurrence if excision is incomplete. The prognosis for invasive mucinous cystadenocarcinoma depends upon the extent of invasion.

**Pancreatic pseudocysts:** the epithelium in mucinous cystic neoplasms may be flattened or denuded, necessitating extensive sampling to confirm the diagnosis and avoid the potential misdiagnosis of a pseudocyst. Pancreatic pseudocysts may be intra-pancreatic or, more frequently, extra-pancreatic but attached to the pancreas. Pseudocysts are solitary, unilocular, round to oval...
and fluctuant, contain colourless or brown thick fluid, and have a wall comprising fibrin, granulation tissue and collagen. They lack an epithelial lining and do not have ovarian-type stroma. The other main differential diagnosis for mucinous cystic neoplasms is intraductal papillary mucinous neoplasm (Table 1).

**Intraductal papillary mucinous neoplasms (IDPMNs)**

IDPMN (also known as ‘intraductal mucin hypersecretory neoplasm’, ‘mucinous ductal ectasia’ and ‘diffuse papillomatosis’) is characterized by cystic dilation of the main pancreatic duct or its major branches (branch-duct type), together with associated intraductal proliferation of mucin-producing cells.

IDPMNs account for 1–5% of exocrine pancreatic tumours, are more common in males (mean age of 60 years) and occur predominantly in the head of the pancreas. There is an association between IDPMNs and other neoplasms. Many patients are diagnosed with chronic pancreatitis (see page 81) before the diagnosis of IDPMN is made.

**Macroscopically,** IDPMN may be localized or diffuse within the main pancreatic duct or within the branch ducts. The cystically dilated ducts are distended with mucus that may extrude from the ampulla of Vater, a diagnostic endoscopic feature. The lining of the ducts is usually papillary but may be smooth. One must identify:

- communication with the duct system
- mucin extrusion from the ampulla
- the distribution of the lesion to distinguish IDPMN from the mucinous cystic neoplasms (Table 1).

**Microscopically,** the cystic spaces or dilated ducts are lined by tall, columnar mucin-containing epithelial cells that usually form papillary projections. The papillae may show intestinal, pancreaticobiliary or gastric (‘null’)-type morphology.

**Classification:** IDPMNs are classified according to the grade of epithelial dysplasia into adenoma, borderline malignant potential, carcinoma in situ/non-invasive (Figure 2a and b) or invasive (papillary mucinous carcinoma). IDPMNs must be sampled comprehensively because of the variability within a single tumour. The papillary and firm areas must be sampled because these are where the highest degree of dysplasia or invasion is most likely to occur. The background pancreas shows the features of chronic pancreatitis resulting from the obstruction of the duct system.

About one-third of IDPMNs have associated invasive adenocarcinoma that may be a colloid/mucinous carcinoma (and behave in an indolent fashion) or may be a ductal adenocarcinoma (which is more aggressive).

**Prognosis:** the prognosis for IDPM adenomas and borderline tumours is excellent (five-year survival of 100%). Survival rates for non-invasive carcinomas are high. Survival for patients with invasive carcinoma may be higher than for patients with ductal adenocarcinoma. Incomplete excision can lead to recurrence, and is a particular risk in multifocal disease.

<table>
<thead>
<tr>
<th>Sex/age</th>
<th>Females/50 years</th>
<th>Males/60 years</th>
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<tbody>
<tr>
<td>Location</td>
<td>Tail</td>
<td>Head</td>
</tr>
<tr>
<td>Communicate with ductal system</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Mucin extrusion from ampulla of Vater</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Ovarian stroma</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

**Table 1**

![Intraductal papillary neoplasm showing typical papillary architecture (arrows) and severe dysplasia (carcinoma in situ; arrow).](image)

**Figure 2**
Solid pseudopapillary neoplasms

Solid pseudopapillary neoplasm (also known as ‘solid and cystic tumour’, ‘papillary cystic tumour’ and ‘Frantz’s tumour’) is a clinically benign or low-grade malignant neoplasm that has cystic degeneration within a solid neoplasm, rather than true epithelial-lined cysts. Solid pseudopapillary neoplasm accounts for 1–5% of exocrine pancreatic tumours, predominantly affects adolescent and young females (mean age 25 years) and may be found anywhere within the pancreas (but usually in the tail).

**Presentation:** symptoms are non-specific and include abdominal pain, nausea, vomiting, or a palpable mass (which may be an incidental finding). Solid pseudopapillary neoplasms are hypovascular or avascular on imaging.

**Macroscopically,** solid pseudopapillary neoplasm is usually a solitary, sharply-demarcated, round mass (mean diameter of 10 cm) with a fibrous pseudocapsule (Figure 3a). The cut surface shows brown solid areas and cystic spaces. There may be extensive central necrosis with a rim of preserved tumour beneath the fibrous pseudocapsule. Calcification may be present.

**Microscopically,** there are solid monomorphic areas of uniform polygonal cells resembling endocrine tumours, and pseudopapillary areas with intervening cystic spaces containing red blood cells, necrotic debris and foamy macrophages (Figure 3b–d). The neoplastic cells have eosinophilic or clear cytoplasm and may contain periodic acid Schiff-positive hyaline globules. Glycogen and mucin are absent; mitoses are rare. The nuclei are round/oval with fine chromatin and are often grooved. The connective tissue between the neoplastic cells may be hyalinized, sclerotic and/or calcified.

**Malignancy** may be defined by perineural invasion, vascular invasion and/or invasion into the surrounding tissue (such neoplasms are termed ‘solid-pseudopapillary carcinoma’) but these are not reliable criteria.

**Differential diagnosis:** immunohistochemistry can help to distinguish solid pseudopapillary neoplasms from endocrine tumours and acinar cell carcinoma. α1-antitrypsin and α1-antichymotrypsin strongly stain single tumour cells or small clusters of cells. This staining is characteristic of solid pseudopapillary neoplasm and contrasts with acinar cell carcinoma, most cases of which show diffuse immunopositivity. Immunostaining with neurone-specific enolase and vimentin is diffuse. Most

![Figure 3](image_url)

a Solid pseudopapillary neoplasm with b cystic spaces (arrows), c solid endocrine-like areas and d papillary areas.
tumours are negative for islet cell hormones, stain only focally and faintly for cytokeratins, and have β-catenin mutations.

**Prognosis** is very good; complete resection is usually curative.

**Ductal adenocarcinoma**

Ductal adenocarcinoma accounts for 85–90% of pancreatic neoplasms, and is usually diagnosed in the age range 60–80 years.

**Risk factors:** there is a strong association with cigarette smoking and an increased risk in genetic syndromes such as:

- hereditary pancreatitis
- familial atypical multiple mole melanoma syndrome
- Peutz-Jeghers syndrome
- hereditary non-polyposis colon cancer.

**Staging:** the Japanese Pancreas Society and the UICC TNM classification systems can be used to stage ductal adenocarcinoma.

**Prognosis** for ductal adenocarcinoma is extremely poor (mean survival of three months for untreated disease). Survival after radical resection is poor (median of 18 months and a five-year survival of <5%). Only 10–15% of cases of ductal adenocarcinoma are potentially operable at the time of presentation.

**Pancreatic intraepithelial neoplasia**

Pancreatic intraepithelial neoplasia describes the microscopic precursors to infiltrating ductal adenocarcinoma that may be seen in resection specimens. It is divided into four types:

- 1A: mucinous cell hypertrophy/hyperplasia
- 1B: ductal papillary hyperplasia
- 2: moderate dysplasia
- 3: severe dysplasia, carcinoma *in situ*.

There is histological and genetic progression from type 1 through type 2 and type 3 to invasive ductal adenocarcinoma.

Most ductal adenocarcinomas in surgical series are found in the head of the pancreas because they present (with obstructive jaundice; see page 74) at an earlier stage than those in the body or tail. Ductal adenocarcinomas of the body or tail may be large and widely invasive at the time of diagnosis, involving the spleen, stomach, adrenal gland and colon.

**Macroscopically**, ductal adenocarcinomas are firm, ill-defined masses with a solid, yellow-white cut surface replacing the normal lobular architecture. They usually invade the common bile duct or the pancreatic duct, leading to chronic obstructive pancreatitis. Distinguishing adenocarcinoma from chronic pancreatitis macroscopically may be difficult.

**Histological variants of ductal adenocarcinoma**

**Mucinous non-cystic (colloid) carcinoma** is uncommon and consists of large pools of mucin (accounting for at least 80% of the tumour) partially lined by, or containing dissociated floating tumour cells (some of which may be signet-ring cell type, see [Figure 4a](#)).

**Histological details:**

- **Well-differentiated ductal adenocarcinoma** is characterized by large- to medium-sized glandular structures, resembling ducts, with mucin-containing columnar cells with eosinophilic or clear cytoplasm. The nuclei are round-ovoid with nucleoli, and may show loss of polarity; mitoses are scarce.
- **Moderately-differentiated ductal adenocarcinomas** show a mixture of medium-sized, duct-like and tubular structures with incomplete glands and variation in size and shape of the nucleus. There are mitoses but less production of mucin.
- **Poorly-differentiated ductal adenocarcinomas** comprise small irregular glands, small nests and individual tumour cells with marked nuclear pleomorphism, scant mucin and more mitoses.

All grades of ductal adenocarcinoma are associated with abundant myxoid desmoplastic stroma ([Figure 4a](#)). Most have perineural invasion within the tumour and extending into the peripancreatic nerve plexi. Lymphovascular invasion is extremely common.
below). Colloid carcinoma should not be confused with mucinous cystic neoplasms, which have a much better prognosis.

**Signet-ring cell carcinoma** is extremely rare and comprises predominantly (>50%) of signet-ring cells with intracellular mucin. Prognosis is very poor. Differential diagnosis includes metastatic spread from a primary tumour of the gastrointestinal system or breast.

**Adenosquamous carcinoma** is rare; it is composed of a mixture of glandular and squamous components, with the latter comprising >30% of the tumour. Prognosis is poor with median survival of 12 months.

**Undifferentiated (anaplastic) carcinoma** is also called ‘giant cell carcinoma’, ‘pleomorphic large cell carcinoma’ or ‘sarcomatoid carcinoma’. It comprises sheets of large pleomorphic and/or spindle cells with scant stroma. Some glandular differentiation is usually present. Perineural, lymphatic and vascular invasion are present in most cases. The mean survival is six months.

**Undifferentiated carcinoma with osteoclast-like giant cells** is rare, comprising pleomorphic and spindle neoplastic mononuclear cells with scattered non-neoplastic osteoclast-like giant cells. These giant cells:
- may have >20 nuclei
- are often found around areas of haemorrhage
- may contain haemosiderin.

The atypical mononuclear cells express epithelial markers; the giant cells show histiocytic differentiation. Mean survival is 12 months.

**Hepatoid carcinoma** is a very rare variant showing hepatocellular differentiation.

**Medullary carcinoma** is a poorly differentiated carcinoma with pushing margin, sheets of tumour cells, necrosis and microsatellite instability.

**Mixed ductal-endocrine carcinoma** (also known as ‘mixed exocrine-endocrine tumour’) is rare and is characterized by ductal carcinoma cells and endocrine cells in the primary tumour and in the metastases. The endocrine cells should comprise at least one-third of the tumour by definition. Prognosis is identical to that for typical ductal adenocarcinoma.

**Acinar cell carcinoma**

Most of the pancreas comprises acinar cells, but acinar cell carcinoma is rare (1–2% of exocrine pancreatic tumours in adults). Males are more commonly affected (mean age of 60 years). Acinar cell carcinoma may occur anywhere in the pancreas but is more common in the head.

**Presentation** is with non-specific symptoms (abdominal pain, weight loss, nausea, diarrhoea). Fifteen percent of patients may have the lipase hypersecretion syndrome (particularly those with hepatic metastases), which is characterized by polyarthritis, extrapancreatic (subcutaneous) fat necrosis and peripheral blood eosinophilia. An increased concentration of α-fetoprotein in serum is seen in some patients.

**Macroscopically**, acinar cell carcinomas are usually circumscribed, soft and multinodular, with a mean size of 10 cm. The cut surface is yellow-brown and necrosis may be present. Rare cystic variants (acinar cell cystadenoma, acinar cell cystadenocarcinoma) have been described.

**Microscopically**, the tumour is lobulated with nodules of eosinophilic (zymogen-rich) tumour cells with granular cytoplasm, little nuclear pleomorphism, prominent central nuclei and mitotic activity, separated by fibrous bands (Figure 4b). The myxoid desmoplastic stroma seen in ductal adenocarcinoma is not usually present. Tumour cells are arranged in an acinar pattern with tiny lumina, as solid nests lacking lumina, a glandular pattern (with dilated acini) or a trabecular pattern. The zymogen granules within the tumour cells are diastase-periodic acid Schiff-positive, but staining may be weak. Immunohistochemistry for trypsin, chymotrypsin, lipase and elastase can show the acinar differentiation.

The **differential diagnosis** includes solid pseudopapillary neoplasms, endocrine tumours and pancreatoblastoma.

**The prognosis** is very poor; median survival is 18 months and five-year survival is <10%.

**Pancreatoblastoma**

Pancreatoblastoma is a rare malignant epithelial tumour of young children (mean age four years) that can be associated with Beckwith–Wiedemann syndrome. It can also occur in adults. It is found more commonly in the head and tail of the pancreas, and may range in size from 1 cm to 20 cm. It is usually a well-circumscribed, soft, lobulated tumour with fibrous bands.

**Microscopically**, it is composed of solid nests of polygonal cells with areas of acinar formation, together with characteristic squamoid corpuscles. An increased concentration of α-fetoprotein in serum may be seen in some patients.

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**Further Reading**


