PDAC, its variants and differential diagnoses

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Pancreatic ductal adenocarcinoma (PDAC)

- Accounts for 85-90% of all pancreatic neoplasms
- Incidence is nearly equivalent to the mortality rate because of the poor prognosis
- Mean age ~65yrs, M:F 1.2:1.0
- Rare <40yrs (consider Hereditary Chronic Pancreatitis)
- Aetiology: smoking, alcohol, red or processed meat, chronic pancreatitis, diabetes type 2 & obesity
- Familial forms account for ~5% of pancreatic cancers: hereditary predisposition syndromes, chronic inflammation, familial pancreatic cancer (FPC)
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Inheritance</th>
<th>Location</th>
<th>Genes</th>
<th>Pancreas cancer risk (fold)</th>
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<td>Autosomal recessive</td>
<td>11q22.3</td>
<td>ATM</td>
<td>Unknown</td>
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<td>Familial atypical multiple mole melanoma (FAMMM)</td>
<td>Autosomal dominant</td>
<td>9p21</td>
<td>CDKN2A (p16)</td>
<td>13-22</td>
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<td>Familial adenomatous polyposis (FAP)</td>
<td>Autosomal dominant</td>
<td>5q21</td>
<td>APC</td>
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<td>Hereditary breast and ovarian cancer syndrome (HBOC)</td>
<td>Autosomal dominant</td>
<td>13q12-13 and 17q21-24</td>
<td>BRCA1, BRCA2, PALB2, TP53</td>
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<td>Lynch syndrome (HNPCC)</td>
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<td>2p22-21 and 3p21-3</td>
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<td>STK11/LKB1</td>
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<td>Cystic fibrosis</td>
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Clinical features

- Weight loss, fatigue, epigastric pain often radiating towards the back, nausea, painless jaundice, sudden onset of type 2 diabetes mellitus
- Painless jaundice is main presenting sign of PDAC in the head of the pancreas
- No specific sign for tumours in body & tail, which consequently present at advanced stage
- Majority (60-70%) of PDACs develop in the head of the pancreas and more often resectable (than tumours in body & tail); over-represented in surgical series

Macroscopy

- Poorly circumscribed firm grey-white mass with ill-defined, highly infiltrative margin
- Can be difficult to identify and measure extent of tumour macroscopically (microscopic assessment required to establish size and extent/tumour stage)
- Haemorrhage uncommon: exception is undifferentiated carcinoma with osteoclast-like giant cells (variant of PDAC)
- Dilated MPD and/or common bile duct ('double-duct sign' on imaging)

Microscopy

- Vast majority of PDACs are of the so-called pancreatobiliary type: small to medium-sized simple or branched glands
- Tumour cells cuboidal to low columnar in shape, but irregular bizarre cells seen in poorly differentiated PDACs
- Cytoplasm may be pale eosinophilic, slightly basophilic or clear
- Varying degrees of nuclear pleomorphism

Microscopy

- Desmoplastic stroma is composed of fibroblasts, collagen fibres and a scattering of inflammatory cells (lymphocytes and histiocytes)
- Tumour stroma can vary from cellular with densely packed tumour glands to collagen rich and less cellular (particularly at the periphery of the tumour)

Microscopy – intestinal type

- 5-10% of PDACs show an intestinal-type morphology (i.e. resemble intestinal cancer)
- Tumour glands are large, well defined, and may show cribriform growth pattern
- Lumina can contain 'dirty necrosis' and are lined by tall columnar epithelium with cigar-shaped, often pseudo-palisaded nuclei
- May have more favourable outcome, but awaits definitive confirmation. Not in 2018 WHO classification

Intratumour heterogeneity

- PDAC is characterized by a marked degree of intratumour heterogeneity
- Variety of growth patterns and cytological appearances in different parts of the same tumour
- Most tumours show a range of histological grades; the highest grade should be reported, irrespective of its amount
Histological grading

<table>
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<th>Grade</th>
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<tbody>
<tr>
<td>1</td>
<td>Well differentiated</td>
<td>4</td>
<td>Undifferentiated</td>
</tr>
<tr>
<td>2</td>
<td>Modestly undifferentiated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Poorly differentiated</td>
<td>5</td>
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PDAC immunohistochemistry

- Cytokeratins (CKs) 7, 8, 18 & 19
- CK20 in PDAC of intestinal type and colloid carcinoma
- CK4 in 50% of tumours
- MUC1 & MUC6
- MUC6 in 20-25%
- MUC2 in PDAC of intestinal type and colloid carcinoma
- CEA, CA19-9 & Maspin
- CA125 in 50%
- Meso1 in 50-70%
- SMAD4 (DPC4) nuclear staining lost in 55%

Histological patterns

- Have no known biological, genetic or prognostic relevance
- Foamy gland pattern: mucin-rich cytoplasm with apical condensation
- Clear cell pattern: clear cytoplasm
- Large duct pattern: dilated tumour glands
- Cystic papillary pattern: dilated tumour glands with intraluminal papillary projections

Tumour propagation

- PDAC has highly infiltrative growth pattern & propensity for propagation along preformed channels
- Perineural invasion (>90% of tumours) – tissue facing superior mesenteric artery and around extrapancreatic common bile duct
- Lymphatic invasion – duodenal wall & ampulla rich in lymphatics
- Vascular invasion (small vessel in 70% of tumours)
- Intraductal growth (70% of tumours) – ‘duct cancerization’

Staging

- UICC TNM 7th edition for PDAC & its variants
- T1 & T2 are resectable tumours
- T3 border line resectability
- T4 regarded as unresectable (in most cancer centres)


Prognosis

- 5yr SR for PDAC is <5% (mean survival 3-5months)
- ‘Curative’ resection only possible in 10-20% patients -> 5yr SR of 10-20%
- Adjuvant therapy doubles the 5yr SR to 40%
- Best hope for reducing the cancer-specific mortality of PDAC lies in early diagnosis and treatment, ideally at a pre-cancerous stage (PanN, IPMN, MCN)
- Strong evidence that IPMNs & MCNs are present for years before they progress to invasive cancer (large window of opportunity to detect potentially curable neoplastic lesions)
Genetic progression - PDAC

- Average total of 21.2 yrs from tumour initiation until patient's death from metastatic disease

Yachnis S et al. Nature 2010; 467: 1154-7
Iscovich-Doroshua CA. Gut 2012; 61: 1085-84

PanIN detection

- Lobulo-centric atrophy (LCA)
- Centre of lobule undergoes atrophy of acinar parenchyma, acinar to ductal metaplasia, and fibrosis
- PanIN causative or part of process
- LCA detectable on EUS: screening tool, but occurs all grades of PanIN

Histological variants of PDAC

- Tumours that exhibit other significant features of differentiation in addition to the morphology of conventional PDAC
- Also differ clinically, including patient outcome
- Rare (3-4% of all malignant exocrine tumours)
- Colloid carcinoma less uncommon, because can develop in association with intraductal papillary mucinous neoplasm (IPMN)

Adenosquamous carcinoma

- At least 30% of the tumour should show squamous differentiation
- Pure squamous cell carcinoma extremely rare; sample thoroughly to exclude ductal differentiation & exclude metastasis (eg. lung)
- IHC for CK5/6 & p63
- Resected tumours have poorer prognosis than pure PDAC

Colloid carcinoma

- At least 80% of tumour show large extracellular mucin pools partially lined by neoplastic epithelium and containing free-floating tumour cells
- Usually large and well circumscribed
- Occur almost exclusively in association with IPMN
- CDX2, MUC2, CK20, CEA, CA19-9
- SMAD4 retained
- More favourable prognosis than conventional PDAC
Signet ring cell carcinoma

- At least 50% of the tumour should show signet ring cell differentiation
- Very rare variant
- Not associated with IPMN
- Prognosis seems to be extremely poor
- Differential diagnosis: metastasis from stomach

Medullary carcinoma

- Poorly differentiated tumour
- Soft tumour
- Pushing border
- Syncytial growth pattern, intratumoral T-lymphocytes
- Can be MSI and lose mismatch repair proteins
- Sporadic and Lynch syndrome
- Differential diagnosis: acinar cell carcinoma
- More favourable prognosis

Hepatoid carcinoma

- Extremely rare variant with significant component of hepatocellular differentiation
- Large polygonal cells with abundant eosinophilic cytoplasm, central nucleus with single nucleolus
- Trabecular pattern
- Bile production
- HepPar+, canalicular pCEA & CD10
- AFP in some tumours
- Differential diagnosis: liver metastasis, acinar cell carcinoma (can be AFP+)

Undifferentiated carcinoma

- Significant tumour component lacks definitive direction of differentiation
- Necrosis & haemorrhage
- Anaplastic pleomorphic mononuclear tumour cells & bizarre often multinucleate giant tumour cells
- Cell cannibalism (tumour cells, erythrocytes, inflammatory cells)
- Sarcomatoid, spindle-shaped pleomorphic cells
- Bone, cartilage or skeletal muscle
- Extremely poor prognosis

Undifferentiated carcinoma with osteoclast-like giant cells

- Pleomorphic tumour cells and non-neoplastic multinucleate histiocytic giant cells (often found in areas of necrosis or haemorrhage)
- Tumour cells are vimentin+ and some are epithelial markers+ (MNF116, AE1/AE3, CKs, EMA, CEA), KIT+ high proliferation rate
- Osteoclast-like giant cells are CD45+, CD68+, low proliferation rate, negative for epithelial markers
- Osteoid/bone formation & chondroid differentiation

Undifferentiated carcinoma with osteoclast-like giant cells

- Large soft tumour, well-defined pushing border
- Solid tumour, haemorrhage, cystic cavities are common
- In rare cases, bone formation extensive and visible as spiky white areas
- Tumour has propensity to grow along MDP, branch ducts and the distal common bile duct
- Prognosis is poor
Mixed carcinoma (WHO 2010)

• Very rare
• Each component should comprise at least 30% of the overall tumour mass, and there should be intimate admixture of the various components
• (Differ from 'collision tumours', in which the components are topographically separated within the tumour mass)
• Mixed ductal adenocarcinoma - neuroendocrine carcinoma (MANEC)
• Mixed ductal - acinar cell carcinoma
• Mixed acinar cell - neuroendocrine carcinoma
• Mixed ductal - acinar cell - neuroendocrine carcinoma

Differential diagnosis - CP

• Biopsies, frozen section (confirming complete resection or confirming diagnosis of PDAC), or resections for known chronic pancreatitis
• Features of both in same specimen
• In chronic pancreatitis (CP), atrophy and fibrosis result in large areas of fibrous stroma with a small number of scattered ductular structures, some of which may show architectural and cytological atypia
• In well-differentiated PDAC, invasive tumour glands may show only mild atypia and are spread out in desmoplastic stroma

Differential diagnosis - CP

• Two key features for distinguishing CP from PDAC are the lobular architecture and the proximity of ducts to muscular vessels
• Lobular architecture is preserved in CP (readily seen at low power and on large sections of tissue) whereas in PDAC the tumour glands are haphazardly arranged
• In CP, the intralobular stroma is looser and paler than the dense collagen that surrounds the lobules, and lacks the cellularity of desmoplastic stroma

Differential diagnosis - CP

• In the normal pancreas, ducts do not run alongside muscular blood vessels
• In advanced CP, with marked acinar atrophy, residual ducts may come to lie close to muscular vessels
• Atypical duct adjacent to a muscular blood vessel should be considered suspicious for PDAC

Differential diagnosis - CP

• Necrosis and intravascular invasion occur in PDAC but not in CP
• 'Naked glands' within fat occurs with PDAC. In fatty atrophy, the ducts of CP are still surrounded by a small amount of connective tissue

Differential diagnosis - CP

• Distinguishing CP from PDAC on basis of ductular architecture and cytological atypia can be difficult
• Hyland et al 1981 established 3 major criteria and 5 minor criteria for distinguishing neoplastic from non-neoplastic ducts on frozen section
• These criteria are equally applicable to paraffin-embedded tissue
• The major criteria are seen in all PDACs
• The minor criteria occur with variable frequency in PDAC

Page 5
Major and minor criteria

Major criteria
- Nuclear size variation equal to, or greater than, 4:1
- Incomplete glandular lumina
- Disorganized duct distribution

Minor criteria
- Huge, irregular epithelial nucleoli
- Necrotic glandular debris
- Glandular mitoses
- Glands unaccompanied by stroma in smooth muscle fascicles
- Perineural invasion

Nuclear size variation equal to, or greater than 4:1
- In PDAC, within the same neoplastic gland, the largest nucleus is at least 4 times the size of the smallest
- In CP the maximum nuclear size variation within a duct is 3:1

Incomplete glandular lumina
- In PDAC, malignant glands have defects in the epithelial lining so that the lumina opens on to the stroma; cords of cells; small groups of cells without lumina; cribriform glands.
- None of these features are seen in CP

Disorganized duct distribution
- In PDAC, malignant glands are haphazardly arranged, can be found between lobules, in lobules admixed with benign ducts, adjacent to muscular blood vessels, and infiltrating into peripancreatic fat.
- None of these features are found in CP

Minor criteria
- Huge irregular epithelial nucleoli: in PDAC, neoplastic cells can have large (eosinophilic) nucleoli with irregular contour. In contrast, in CP, nucleoli are small, round and regular
- Necrotic glandular debris is found in lumina of neoplastic glands in PDAC, but is not found in the small ducts of CP
- Glandular mitoses, including atypical forms can be found in neoplastic glands of PDAC, but are rarely found in ducts of CP
- Glands unaccompanied by stroma in smooth muscle fascicles: in PDAC, neoplastic glands infiltrate the duodenal muscularis propria but the glands do not have accompanying connective tissue. In CP, ducts do not infiltrate smooth muscle.
- Perineural invasion in PDAC