PDAC, its variants and differential diagnoses

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Sarajevo, November 2015

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)**

Pancreatic cancer risk in inherited syndromes & disorders

	Inheritance	Location	Genes	Pancreas cancer risk (-fold)
Ataxia-telangiectasia	Autosomal recessive	11q22.3	*ATM*	Unknown
Familial atypical multiple mole melanoma (FAMMM)	Autosomal dominant	9p21	*CDKN2A (p16)*	13–22
Familial adenomatous polyposis (FAP)	Autosomal dominant	5q21	*APC*	4–5
Hereditary breast and ovarian cancer syndrome (HBOC)	Autosomal dominant	13q12-13 and 17q21-24	*BRCA1* *BRCA2* *PALB2*	2.3 3–10 Unknown
Li-Fraumeni syndrome	Autosomal dominant	17p13.1	*TP53*	Unknown
Lynch syndrome (HNPCC)	Autosomal dominant	2p22-21 and 3p21.3	Mismatch repair genes	4.5–8.6
Peutz-Jeghers syndrome	Autosomal dominant	19p13.3	*STK11/LKB1*	132
Cystic fibrosis	Autosomal recessive	7q31.2	*CFTR*	2.6–5.3
Hereditary chronic pancreatitis	Autosomal dominant	7q35	*PRSS1*	26.3–53
Familial pancreatic cancer (FPC)	Autosomal dominant (in 58–80 %)	Unknown	Unknown	2–32

Campbell F, Verbeke CS. Pathology of the pancreas – a practical approach. Springer-Verlag, London, 2013

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

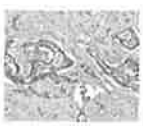
- Vast majority of PDACs are of the so-called pancreatobiliary type; small to medium-sized simple or branched glands
- Tumour cells cuboidal to low columnar in shape, but irregular bizarre cells seen in poorly differentiated PDACs
- Cytoplasm may be pale eosinophilic, slightly basophilic or clear
- Varying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

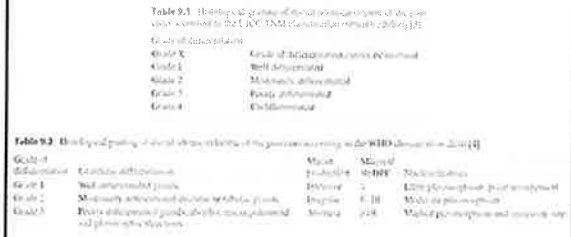
- 5-10% of PDACs show an intestinal-type morphology (ie. resemble intestinal cancer)
- Tumour glands are larger, well defined, and may show cribriform growth pattern
- Lumina can contain 'dirty necrosis' and are lined by tall columnar epithelium with cigar-shaped, often pseudo-palisaded nuclei
- May have more favourable outcome, but awaits definitive confirmation. Not in 2010 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



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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

PDAC immunohistochemistry

- Cytokeratins (CKs) 7, 8, 18 & 19
- CK20 in PDAC of intestinal type and colloid carcinoma
- CK4 in 50% of tumours
- MUC1 & MUC5AC
- MUC6 in 20-25%
- MUC2 in PDAC of intestinal type and colloid carcinoma
- CEA, CA19-9 & Maspin
- CA125 in 50%
- Mesothelin in 50-70%
- SMAD4 (DPC4) nuclear staining lost in 55%

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

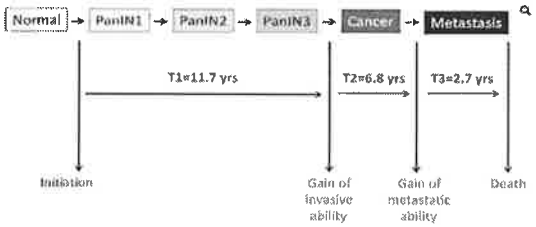
- UICC TNM 7th edition for PDAC & its variants
- T1 & T2 are resectable tumours
- T3 borderline resectability
- T4 regarded as unresectable (in most cancer centres)

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 (PanIN, 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)

Lennon AM et al. Cancer Res 2014; 74: 3381-9

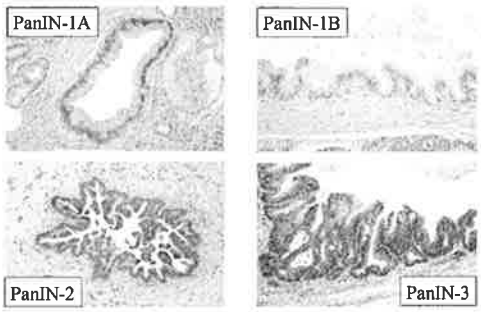
Genetic progression - PDAC



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

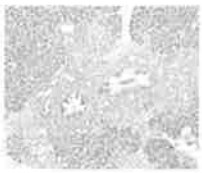
Yachida S et al. Nature 2010; 467: 1114-7
Iacobuzio-Donahue CA. Gut 2012; 61: 1085-94

PanIN



PanIN detection

- **Lobulocentric 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 CKs5/6 & p63**
- **Resected tumours have poorer prognosis than pure PDAC**

Colloid carcinoma

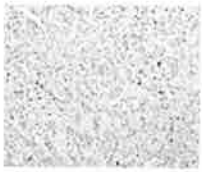
- **At least 80% of tumour show large extracellular mucin pools partially lined by neoplastic epithelium and containing free-floating tumour cells**
- **Usually large and well circumscribed**
- **Occur almost exclusively in association with IPMN**
- **CDX2, MUC2, CK20, CEA, CA19-9**
- **SMAD4 retained**
- **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), Ki67 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 MPD, branch ducts and the distal common bile duct
- Prognosis is poor

Mixed carcinoma (WHO 2010)

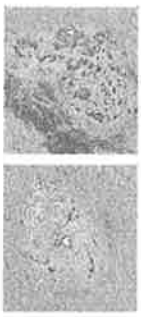
- Very rare
- Each component should comprise at least 30% of the overall tumour mass, and there should be intimate admixture of the various components
- (Differ from 'collision tumours', in which the components are topographically separated within the tumour mass)
- Mixed ductal adenocarcinoma - neuroendocrine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

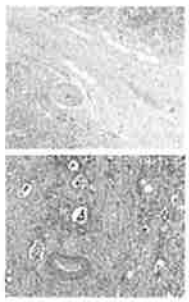
Differential diagnosis - CP

- 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

  Hyland C et al. Am J Surg Pathol 1981; 5: 179-91
- 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

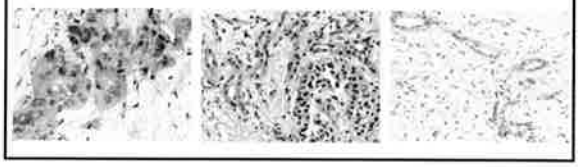
Major and minor criteria

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

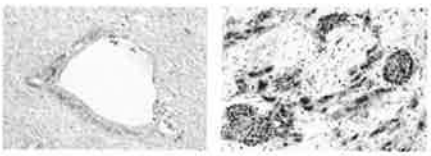
Nuclear size variation equal to, or greater than 4:1

- **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**



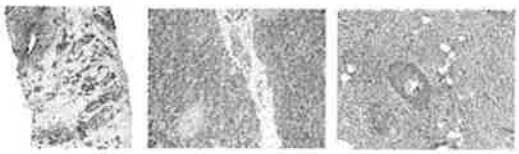
Incomplete glandular lumina

- **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**

Minor criteria

- **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**