PANCREATIC TUMOURS

BENIGN

Solid: adenoma
Cystic: serous cystadenoma/IPMN/mucinous cystic neoplasm: cystadenoma +cystic variant of solid tumour
Islet-cell tumour (insulinoma/gastrinoma/glucagonoma/somatostatinoma)

Pre-cursor lesions: (i)**PaIN** (<5mm mucinous-papillary lesion → adenoma/carcinoma sequence) (ii)**IPMN** (iii)**MCN:C**
non-mucinous lesions have no malignant potential

MALIGNANT (EXOCRINE 95%, ENDOCRINE 5%)

Solid: adenocarcinoma (95%): ductal (80% of all PC)
Cystic: serous cystadenocarcinoma/IPMN/cystadenocarcinoma + cystic variant of solid tumour
Malignant islet-cell tumour
Poorly-differentiated types: adenocarcinoma/undifferentiated carcinoma
Secondaries (mets from stomach/bile duct)

ISLET –CELL TUMOURS

Insulinoma/Gastrinoma: see endocrine notes
Glucagonoma: a-cell; 25% benign; confined to pancreas; DM/wt loss/necrolytic migratory erythema/diarrhoea; tx= insulin
Somatostatinoma: D-cell; DM/gallstones/steatorrhoea

PANCREATIC CARCINOMA

Epidemiology:

A: middle-aged G: ESI R: black I: 9600 *5th commonest cancer; 4th most fatal cancer in men and women*

Pathology

(i)**90% sporadic** (ii)**10% germline/familial** (BRCA2,p16,ATM,STK11 in Peutoz-Jegher's,PRSS1/2,SPINK1,PALB2,DNA MMR in Lynch)
Risk factors "SAD DOC": smoking/alcohol/diabetes/ diet/obesity/chronic pancreatitis(5%) *other=HP/HIV/HepB*
Familial risk: Lynch, FAP, Peutz-Jeghers, BRCA2 etc

Arise from exocrine (95%) and endocrine pancreas (5%)
Pre-cursors: (i)Pan-IN(82%) (ii)IPMN (iii) MCN: cystadenoma
Molecular changes: (i)TS genes inactivated: P16/CDKN2A/TP53 (ii)k-ras single point mutation
Micro: ductal adenocarcinoma(80% of all)/acinar carcinoma/mucinous cystadenocarcinoma/undifferentiated
Macro:
Site: 60%H/25%B/15%tail

Spread: local=CBD/duodenum/HPV/IVC
notes=adjacent nodes and porta hepatis nodes
blood=liver/lung
transcoelomic= ascites and peritoneal seeding

CLINICAL FEATURES **80% present with unresectable disease; pain on presentation heralds likely unresectability**

Symptoms:

Pain: **epigastric** radiates into **back**; continuous; **gnawing**

Jaundice: **"painless progressive jaundice"** → pale stools/dark urine/icterus

Exocrine: malabsorption/steatorrhoea/weight loss/nutritional deficiencies

Endocrine: diabetes

Constitutionals: N&V/anorexia/**weight loss**/lethargy

Exam findings:

General: Malignancy signs (cachexia/anaemia/Virchow's node) + Jaundice (Courvoiser's Law observed in 25%)

Abdo: Mass + Sister Mary Joseph nodule (umbilical met via falciform ligament)

Other: Thrombophlebitis migrans: crops of tender nodules in superficial vessels (Trousseau's sign)

INVESTIGATIONS: DIAGNOSTIC

Start with US Abdo in any case: biliary assessment

A. Obstructive jaundice:

1. CT Pancreas Protocol before draining CBD 2. EUS+FNA cyto/histo/CEA 3. Brush cytology if (i)doing ERCP(ii) diag still unclear

B. Non-jaundiced with pancreatic abnormalities on imaging:

1. CT Pancreas Protocol 2. EUS+FNA if (i)diagnosis unclear (ii)tissue diagnosis: histo/cyto/fluid CEA

C. Pancreatic Cysts:

1. CT Pancreas Protocol or MRCP 2. EUS+FNA if (i)uncertain if malignant (ii)determine if surgery needed

D. Inherited Risk of PC

Familial PC= 2+ FDRs with pancreatic cancer (10%)

Hereditary breast and ovarian ca/hereditary PCC/Lynch/P-J/AT/FAMMMS/Li-Fraumeni

Surveillance: (i)hereditary pancreatic cancer + PRSS1 (ii)FDR + BRCA1/BRCA2/PALB2/CDKN2A (p16) mutations (iii)P-J syndrome

Consider surveillance: (i)3+ FDR with pancreatic cancer across 2+ generations (ii)Lynch + FDR with PC

Method: CT Pancreas Protocol/MRCP/EUS(not offered in hereditary pancreatitis)

Other:

ERCP: (i)CBD/PD stenosis/dilatation (ii)histopath/cytology (iii)stent

Biochem: CA19.9 only elevated in 50% (S+S 80% in symptomatics but low in asymptomatics)/LFTs/Hb
(false +ive in cholestasis false –ive if absent Lewis enzyme)

INVESTIGATIONS: STAGING

CT TAP (done with CT Pancreas Protocol)

MRI: (i)for suspected liver mets (PET-CT if MRI contraindicated) (ii)relationship to ducts/vessels

EUS: (i)further T/N staging by (iii)FNA *better than CT for small lesions*

Laparoscopy + LapUS: if (i)suspect small-volume peritoneal disease (ii)liver mets in potentially resectable disease

T	N	M
Tis= Carcinoma *in situ*	0	0
T1= <2cm limited to pancreas	1 Regional lymph nodes	1 Distant metastases
T2= >2cm limited to pancreas		
T3= beyond pancreas; no CA/SMA		
T4= involves CA/SMA (unresectable)		

Nodes: superior and inferior (to head and body); anterior (anterior PD,pyloric,prox mes); posterior (post PD, CBD, prox mes); splenic (hilum, tail), coeliac

MANAGEMENT

GENERAL

Pain: EUS/image-guided **neurolytic coeliac plexus block** (uncontrolled pain/opioid adverse effects/escalating analgesic doses)
Nutrition: (i)enteric-coated **pancreatin** pre+post surgery (ii)**early enteral nutrition** after pancreatoduodenectomy
Biliary decompression: (i)resectable – **surgery if fit** instead of drainage; if **not yet fit/cholangitis** -> **plastic stent**
(ii)unresectable – **SEMS**; **bypass** only if unresectablity discovered at operation
Duodenal obstruction: (i)resectable – straight to surgery?
(ii)unresectable – gastrojejeunostomy

RESECTION

3 categories: (i)**resectable** (ii)**borderline resectable** (iii)**locally advanced (unresectable)**
Resectability criteria: arterial encasement irresectable as poor outcomes; venous encasement doesn't affect outcome
Only R0 potential = surgical candidates

RESECTABLE (DISEASE (8%)

STANDARD= Surgery w/ lymph node dissection$^{15+\ lymph\ nodes\ advised}$ *+ adjuvant chemo*
(i)HEAD= Whipple's or PPPD + dissect right hemicircumference of SMA to right of coeliac trunk
(ii)BODY/TAIL= distal pancreatectomy (body, tail, spleen) + dissect left hemicircumference of SMA to left of coeliac trunk
Adjuvant therapy: **gemcitabine+capecitabine 6 cycles**
18% 5 yr survival if curative intent

BORDERLINE RESECTABLE

High probability of R1 resection → not candidates for upfront surgery *(biliary decompression appropriate)*
ESMO: NA-chemorad (**gemcitabine or FOLFIRINOX**) →restage and MDT →surgery

UNRESECTABLE DISEASE (NEED TISSUE DIAGNOSIS FIRST)

A. Locally advanced:
(i)Combination chemotherapy/gemcitabine monotherapy if can't tolerate combination (6mths)
(ii)Chemoradiotherapy: Capecitabine as radiosensitiser
B. Metastatic disease (PALLIATIVE):
First-line: **FOLFIRINOX** for ECOG 0-1; **gemcitabine combination** therapy if not well enough for FOLFIRINOX; **gem alone**
Second-line: (i)oxaliplatin if ox-naïve ie after gemcitabine (ii)gemcitabine if progression after FOLFIRINOX
30% 5yr survival if palliative resection + adjuvant therapy

Palliative:
Biliary: stent/palliative bypass
Gastroduodenal: gastrojejeunostomy

Outcomes
23 deaths/day in UK||mean survival from diagnosis: 4-6mths||5% 5yr survival *not improving*
ESMO: no evidence supporting follow-up after initial therapy for curative intent

IPMN

Mucin-producing epithelial neoplasm of pancreas arising from main duct/branch duct
Epid: 50+/2 per mill
Micro: **papillary architecture** (absence of ovarian stroma differentiates from MCN:C) (difficult to differentiate from PanIN)
Macro: **mucin**/evidence of **pancreatitis** episodes/**papillary** epithelial projections
Site: 70% head, 20% body-tail, 10% spread
Nat Hx: *slow growth with 7x PC risk overall* (i)MD 92% progress to PC (ii)BD less malignant potential

Diagnosis

Clinical features: pain/obstructive jaundice/pancreatitis/malabsorption/diabetes/constitutionals
Investigations (i)Cross-sectional = **CT Pancreas**/MRCP(MD= dilated duct; BD= grape-like cystic lesions)
(ii)Endoscopic= **EUS-FNA**/ERCP
(iii)Bloods: **CA 19-9/CEA**
MD>10mm/growth>2mm per year/tumour>40mm/mural nodules/cytology suggest malignancy

Management

(i)Main Duct: resect all
(ii)Branch Duct: symptoms/tumour 30mm+/mural nodules/PD>6mm/cytology (Sendai criteria)
Partial pancreatectomy with frozen sections to ensure margins

Outcomes/follow-up

Annual CT/MRI (no routine TM use recommended by IAP)
Recurrence: predicted by head/invasive/high CA 19-9 seen up to 62mths
Main survival determinant is invasiveness

OTHER

SEROUS CYSTIC ADENOMA

60+ Female
Pathology: microcystic (multiple cysts <2cm) and macrocystic (similar to mucinous neoplasms); associated with VHL
Micro: Cuboidal epith/lack of mitotic activity
Macro:
Site: Throughout pancreas
Clinical features: 1/3 symptomatic
Natural History: Malignancy exceedingly rare
Treatment: conservative

MUCINOUS CYSTIC NEOPLASM

Epid: 40+ female
Micro: mucin-producing cells WITH ovarian stroma (differentiate from IPMN)
Macro:
Site: Tail
Nat Hx: malignancy risk; recur in >40% if invasive carcinoma
Clinical features:
Treatment: resect all (distal pancreatectomy usually)

PANCREATIC CYSTS

Hx: obst jaundice sx + cholangitis + pancreatic cancer RFs + constitutionals PMHx: T2DM, chronic panc, acute anc
FHx: pancreatic cancer genetic syndromes Medx: smoking, EtOH SHx:
Diff dx: pancreatic cyst/pseudocyst/serous cystadenoma/mucinous cystic neoplasm/IPMN/cystic variant
Ix: (i)Bloods (CA 19-9, CEA) (ii)CT Pancreas (iii)MRCP for ductal communication (v)EUS-FNA cytology/CEA/amylase
Cytology: Cancer= Cells MCN= CEA raised+mucin cells; Pseudocyst=amylase +inflamm cells SCA= glycogen-producing cells

PAINLESS PROGRESSIVE JAUNDICE

History: obst jaundice symptoms + cholangitis features + pancreatic cancer risk factors + cosntitutionals of cance
PMHx: T2DM, chronic panc Medx: EtOH, smoking SHx: FHx: pancreatic cancer genetic syndromes (PJ/Lynch/BRCA etc)

Examine: full abdo exam + peripheral signs of pancreatic cancer

Ix: Bloods (LFTs, CEA, CA 19-9, clotting), US → MRCP/ERCP if cholangitis or need to exclude stones + CT Pancreas
Complete the staging with CT Thorax + EUA-FNA for tissue diagnosis

MDT: resectability

Mx: as for pancreatic cancer