GASTROENTEROPANCREATIC NTS (GEP-NETs)

Increasing incidence 3/100,000 (incidentalomas); second commonest GI cancer; slight female preponderance
Risk factors: diabetes/family history of cancer *not smoking or EtOH*
Associations: familial endocrine cancer syndromes (MEN1/MEN2/NF1/VHL/Carney complex)
(a)Dominant secretion of peptide/hormone (ACTH/CRF etc) or (b)Non-functioning

Immunoreactivity: (*1.Diagnosis 2.Monitoring treatment response 3.Prognostication)*
Chromogranin A: identifies proteins of neurosecretory granules; only general marker for NETs:
- elevated regardless of functionality; variable in poorly-differentiated tumours
Pancreastatin: post-translational product of CgA; not elevated by other CgA-elevating conditions
Synaptophysin: immunoreactivity to this alone and not CgA implies mixed exocrine-endocrine tumour
Neuron-specific enolase/PGP9.5 not as specific; used for some tumours (antibodies against cytosolic markers)

WHO Classification by:
1. Proliferation rates (Ki67/Mib-1 antibody staining against proliferation antigen)
Grade 1: low mitotic index; Ki67 index 3% or under|| Grade 2: Ki67 index 3-20% || Grade 3: Ki67 index >20%
2. Mitotic index (number of mitoses per $2mm^2$ or 10 high-powered fields)
***Extensive surgery is more likely to be beneficial in differentiated tumours with low proliferation*
***Chemotherapy has more benefit with higher proliferation rates*

GASTRIC NETS (8% of all NETs)

Investigations:
Biopsy: for **atrophic gastritis**/**antral oxyntic hyperplasia**/**ECL hyper+dysplasia**/assess **infiltrative depth** and **EMVI**
Immunoreactivity: stain with **endocrine tumour markers** and **proliferation markers** (chromogranin A, Ki67)
Bloods: Serum **CgA elevated** in CAG Type A with ECL hyperplasia; gastrin; **autoimmune gastritis** (Type 1; exclude in Type 2)
Gastric acid axis: **gastrin** (up in T1&2, low/normal in 3) and **gastric acid secretion** (low in Type 1, high in Type 2, low in type 3)
Imaging: **EUS (type 1&2's>1cm, all type 3's)** for depth of invasion; panc/duo MEN1 lesions in Type 2s; **CT/Octreoscan: mets**
Biochem screening for MEN1 in ?ZES: Ca2+, PTH, GH, PL, IGF-1, insulin, proinsulin, PP, c-peptide, glucagon
Urine: check **urinary MelmAA if atypical carcinoid** symptoms/signs

TYPE 1 GASTRIC NETS

80% of gastric NETS; older (mean 65yo); 75% female
Pathology: arise in **ECL cells in 1% of CAG Type A** (autoimmune); if long duration of raised gastrin
Site: Size: **usually <2cm**; can be few mm
-**fundus/body**
-**multicentric** (multiple small polyps); if microscopic with one obvious tumour, seem solitary
Macro: **sessile polyps**; some ulcerate/bleed; red/yellow (depending on depth)
**difficult to distinguish from hyperplastic polyps (common in CAG)

Pathogenesis:
CAG Type A (autoimmune)→**antral mucosal atrophy**→pentagastrin-resistant achlorhydria (50% have P. anaemia)
Low gastric acid→ Gastrin(antral G cells)→**Hypergastrinaemia**→ECL hyperplasia→ dysplasia/aplasia/neoplasia

Spread
Slow growth
Local: Small= benign, low risk of invasion beyond submucosa; Large(>1cm)= benign, 10% invade muscularis propria
Mets: Lower incidence of mets than other gastric NETS (nodes 5%, distant 2%)

Clinical Features
Incidentaloma at OGD (esp for anaemia)
(a)Features of **CAG Type A: B12 deficiency/P.A symptoms**
(b)Larger tumours may **mimic gastric carcinoma** (including mass effect, anaemia, N&V, pain etc)
(c)Atypical **carcinoid** due to liver mets
pain due to obstruction, ischaemia, invasion

INVESTIGATIONS
(a)Bloods: **serum gastrin elevated**/**serum CgA elevated**/check for **autoimmune gastritis**
***gastrin and CgA elevated in low-acid conditions eg PPI use ***
(b)**Low gastric acid secretion**
(c)OGD + biopsies: **atrophy of antral** oxyntic mucosa; **ECL hyperplasia in fundus/body**
MEN1 gastrinoma has no atrophy accompanying high gastric acidity/gastrin
(d)Imaging: EUS to **assess invasiveness** (plan surveillance suitability/resection strategy); CT/Octreoscan: mets

TREATMENT:
May spontaneously disappear
Small (<1cm) multicentrics: annual OGD
Large (>1cm) without invasion: EMR/multiple band mucosectomy
Invasive (will be >1cm): local excision, extensive resection as needed,
Antrectomy for recurrent/multicentrics : reduced hypergastrinaemia → ECL hyperplasia regresses

TYPE 2 GASTRIC NETS
6-8% of gastric NETs; middle-age (mean 40-50); ESI

Pathology: **MEN1 with gastrinoma (ZES)** (gastric NETS only in MEN1/ZES, not sporadic ZES; not MEN1 w/o ZES)
-hypergastrinaemia seems to be essential to develop gastric NETs from ECL hyperplasia
Site: **Fundus/body**; **multicentric** Size: **Small (<1cm)**; often **larger than type 1**
Pathogenesis: **ECL hyperplasia in 80% of MEN1/ZES** → fundic gastric NETS in 30% of these
Antral oxyntic mucosal thickness increased *(cf type 1 with atrophy)*
Hyperplasia – dysplasia – neoplasia sequence (greater malignant potential than Type 1s)

Spread
Slow growth; 10% breach submucosa; mets (nodes 30%, liver 10-20% but due to other MEN1 tumours too)

Clinical features
(a)Features of **MEN1 endocrinopathies** and **peptic ulcer disease**
(b)Larger tumours may **mimic gastric carcinoma** (including mass effect, anaemia, N&V, pain etc)
(c)Atypical **carcinoid** due to liver mets
pain due to obstruction, ischaemia, invasion

Investigations
(a)Bloods: **serum gastrin elevated**/biochem screening: **MEN1 endocrinopathies**/exclude autoimmune gastritis
Gastric acid secretion: **High gastric acidity** *(unlike Type 1s)*
OGD + biopsies: Increased antral oxyntic mucosal thickness; ECL-cell hyperplasia/dysplasia
(d)Imaging: EUS to **assess invasiveness** + **panc/duo MEN1**(surveillance suitability/resection strategy); **CT/Octreoscan: mets**

Treatment
1.Medical: treat gastrin excess in MEN1 with **PPI**
2.Surgery:
(a) **remove source of hypergastrinaemia** (mobilise pancrease/duodenotomy: find gastrinomas/panc MEN1 lesions)
(b) **excision of gastric NETs** (>1cm requires local excision; EMR if EUS precludes musc propria invasion ie submucosal)
(c)**Gastric resection/gastrectomy** + regional lymph node clearance for large tumours

Prognosis
Generally depends on the other MEN1 tumours but favourable
Can get highly malignant neuroendocrine gastric carcinomas with poor prognosis

TYPE 3 GASTRIC NETs

15-20% of gastric NETs; middle-age (mean age 50); 75% male

Pathology: originate in argyllophyllic ECL cells/EC and other cell types (cf Type 1&2 ECL lesions)
Found in atrophic gastric mucosa with no ECL cell proliferaton
No association with hypergastrinaemia (cf T1&2)
Site: fundus/body; solitary (*cf T1&2*)
Size: large (70% are >1cm) *(cf T1&2)*
Macro:
Micro: well-differentiated generally (often grade 2 with Ki67 index >2%)
Spread: much more aggressive than Type 1 & 2s; 66% musc prop, 50% breach; mets: 71% nodes, liver 69%

Clinical features

Atypical carcinoid syndrome (5-10%, histamine)
Flushing/cutaneous oedema/itching/bronchospasm/salivary gland swelling/lacrimation

Investigations

Bloods: **normal serum gastrin**
Gastric acid secretion: normal (low if atrophic)
Urine: **MelmAA** (histamine metabolite methylmidazole-acetic acid) may serve as a tumour marker
Most gastric NETs deficient in L-amino acid decarboxylase and only few have elevated serotonin so urinary 5-HIAA is less appropriate as a tumour marker but may be elevated in some disseminated sporadic NETs
OGD + biopsies: **larger tumour** likely to be sporadic
Imaging: **EUS for all Type 3 lesions** for assessment of depth of invasion ; **CT/Octreoscan: mets**

Treatment

Gastric resection and regional lymph node clearance
Gastrectomy if >2cm/gastric wall invasion/local mets/atypical histology
Carcinoid: tumour debulking /excise liv mets/hep art embolization/chemoemb/RF ablation of liver mets
Octreotide may help palliate symptoms in carcinoid syndrome
Chemotherapy less useful when proliferation index >5% (response rate 20-40%) but can combine it with other treatment modalities

Prognosis: 50% 5 year survival; distant mets = 10% 5 year survival

POORLY DIFFERENTIATED NECs

Highly malignant neoplasms with extensive local invasion and mets
Elderly (60-70 mean); male predominance
Atrophic gastritis in 50% but only a few have hypergastrinaemia
Site: fundus/body 80-90%; may occur in antrum Size: Large (4-5cm)
Macro: deeply invading; ulcerated/fungating || Micro: EMVI and perineural invasion in nearly all
Micro: high degree of atypia/high mitotic number
Tumour staining (high Ki67 index 20-40%)
Sparse immunoreactivity to Chromogranin A (unlike well-differentiated gastric NETs)
Immunoreactivity to synaptophysin/NSE/PGP9.5 may differentiate from exocrine gastric carcinomas
Treatment: rarely suitable for radical surgical and high recurrence if operate
Prognosis: dismal, median survival 8 months

OESOPHAGEAL NETs

Extremely rare (<1% of NETs); mean age 60; male
Mostly lower 1/3 of oesophagus or GOJ
Non-specific symptoms; rarely exhibit carcinoid syndrome
Lymph node mets in 50% at time of diagnosis
Survival correlates with stage of disease; overall is poor

DUODENAL NETs

So rare that it is difficult to identify prognostic factors/determine optimum treatment strategies
<5mm: enucleate with overlying mucosa
Larger: excise with full thickness of duodenal wall and may need nodal clearance around pancreatic head

GASTRINOMAS

60% of duodenal NETs
G- cell tumour
15-30% of these cause ZES and the remainder are clinically silent
40-60% of ZES-causing gastrinomas are in duodenum
Mostly D1/2
Small (5mm or less)
Multifocal in 90% of MEN1/ZES
Slow-growing in ZES thus indolent
Early mets to Node (up to 70%)
Mets to liver are late

Duodenal gastrinoma is potentially curable entity of ZES, especially non-MEN1 ZES
In both sporadic and MEN1 ZES, resection of duodenal gastrinoma confers favourable prognosis (85% 10 year survival)

SOMATOSTATIN-RICH NETs

15-20% of duodenal NETs
Most non-hormonally functioning
Associated with von Recklinghausen's NF Type 1 and phaeochromoctyoma
1-2cm nodule (only occasionally larger, polypoid or ulcerated)
Mostly at Ampulla of Vater → obstructive jaundice/pancreatitis/bleeding
Glandular growth pattern (unlike conventional NETs)
Immunoreactivity with Chromogranin A
50% have regional nodes or liver mets
Depending on size/stage: pancreatico-duodenectomy

GANGLIOCYTIC PARAGANGLIOMAS

Almost exclusively in D2
Associated with NF Type 1
mixture of paraganglioma, ganglioneuroma, NET tissue
Reactivity for PP and Somatostatin
Benign generally and usually incidental or discovered due to UGI bleeding
Excellent prognosis following surgical excision

OTHERS

Mainly D1
Multiples raise suspicion of MEN1
Mainly excisable (<2cm, with no invasion) but larger ones require segmental resection or pancreatico-duodenectomy
Peri-ampullary tumours behave in malignant fashion so need more radical surgery
Metastasising duodenal NETs may still survive for years so seem to be less aggressive than adenocarcinomas

PANCREATIC NETs

We covered this shit elsewhere; fitted in with duodenal NETs to account for 2% of NETs
Exceptionally stain intensely for serotonin
Histologically appear as classic GEP-NETs but few associated with carcinoid syndrome
Managed as for other endocrine pancreas malignancies
Hepatic mets and carcinoid syndrome can be treated with octreotide/chemotherapy/interferon if there is a higher proliferation rate