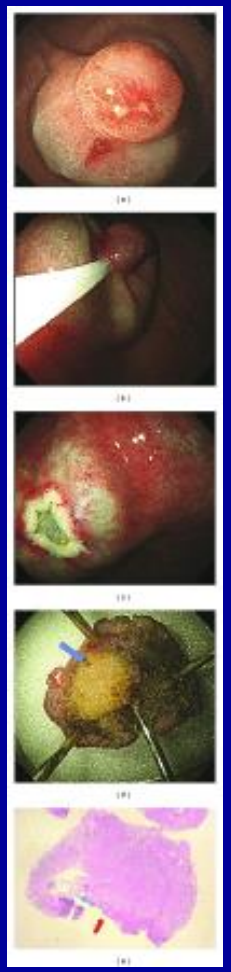
Investigations	Type I	Type II	Type III
Gastrin	Raised	Raised	Normal
Chromogranin-A	Raised	Raised	Normal / Raised
Auto-antibodies (anti-parietal & anti-intrinsic factor)	Positive	Negative	Negative
Ca, PTH	Normal	Raised	Normal
Upper GI endoscopy	Recommended	Recommended	Recommended
E U S	**Only** if resection is planned (for invasion)	**Only** if resection is planned (for invasion)	For assessment of regional lymph nodes
CT / MRI	**Only** if resection is planned (for completion of staging)	For restaging of Gastrinoma	**Always** (for completion of staging)
Somatostatin Receptor Scintigraphy	**Only** if resection is planned (for completion of staging)	**Only** if resection is planned (for completion of staging)	**Always** (for completion of staging) FDG PET in G3 tumours

Endoscopic resection in G-NETs

Snare polypectomy, Endoscopic Mucosal Resection (EMR) or Endoscopic Submucosal Dissection (ESD) ?



- 33 pts, (polyps 2 – 20 mm), 45% polypectomy with snare.
- 63.6% had recurrence (within 8 months).

Merola et al, Neuroendocrinology 2011

- 62 pts had either EMR or ESD.
- **The overall ESD complete resection rate was higher than that of the EMR rate** (94.9% versus 83.3%, *P* value = 0.174).
- **A statistically lower vertical margin involvement rate was achieved when ESD was performed** compared to when EMR was performed (2.6% versus 16.7%, *P* value = 0.038).
- The complication rate was not significantly different between the two groups.

Kim et al, Gastroenterol Res Pract 2014

Somatostatin analogues in gastric NETs

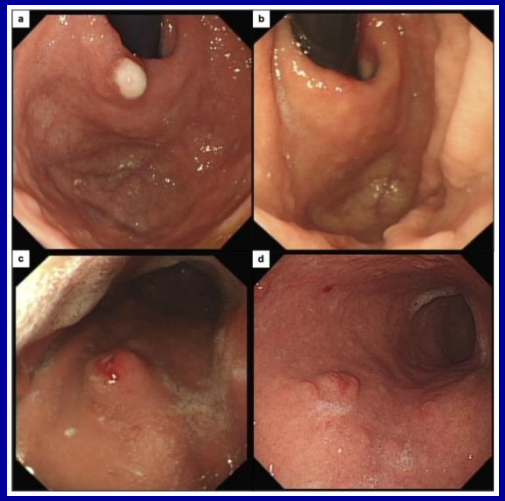
	No of pts	Type	Tumour size	Biochemical response	Endoscopic response
Tomassetti et al	3	II	≤ 1 cm	Yes	Reduction in 6 m Regression in 12m
Fykse et al	5	I	1cm	Yes	Reduction of tumour number > 50%
Campana et al	9	I	< 1 cm	Yes	Regression in12 m
Grozinsky –Glasberg et al	15	I	9/15 : < 1cm 6/15 : ≥ 1cm	Yes	11/15 complete regression 3/15 reduction of size

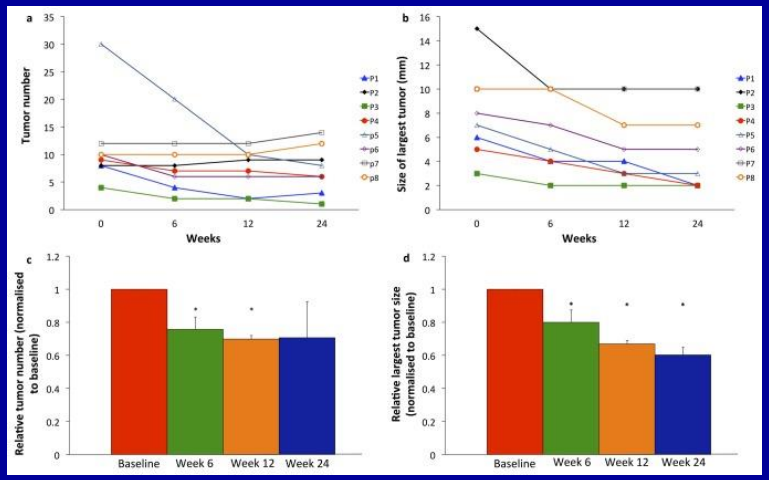
Disease recurrence or progression is noted in patients who underwent only a 12-months treatment (study with 5 years endoscopic follow-up)

Jianu et al, Scand J Gastroenterol, 2011

Tomassetti et al, NEJM 2000
Fykse et al, Scand J Gastroenterol 2004
Campana et al, Endocrine Rel Cancer 2008
Grozinsky – Glasberg et al, Eur J Endocrinol 2008

Netazepide : a gastrin/CCK-2 receptor antagonist for type I gastric NETs





- Oral agent.
- No adverse effects.
- Data for 34 patients, to date.
- Regression of tumour number & size.
- Duration of treatment up to 52 weeks, to date.
- Relapse of tumours, if discontinued.

Fossmark et al, Neuroendocrinology 2012
Moore AR et al, PLoS One 2013
Sagatun L, Eur J Gastr & Hepatol 2016
Boyce M et al, Br J Clin Pharmacol 2017

Surgical intervention in type I G-NETs

- **Local resection** *+/- antrectomy*

  a) in polyps > 2 cm (may hide adenocarcinoma)

  b) 1 – 2 cm, if : *i) invasion beyond submucosa ii) vascular invasion and tumours G2 or G3 iii) not significant co-morbidities*

- **Antrectomy**

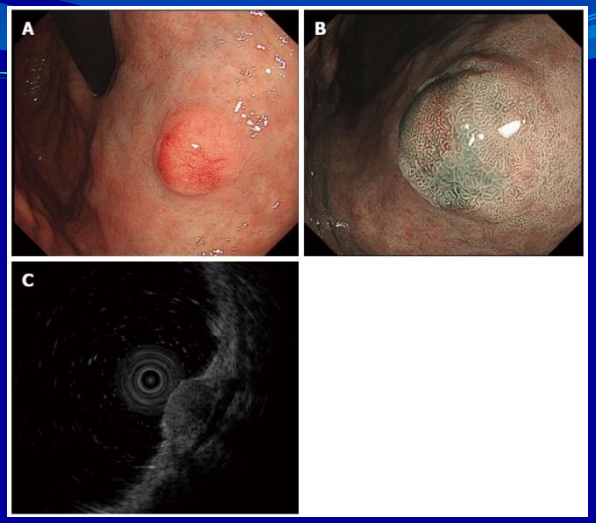
PROS	CONS
➢90% reduction of serum gastrin within 5 months ➢ Tumour regression in 70 and 85% within 3 and 5 years, respectively	• Hypergastrinaemia may relapse • Same results with somatostatin analogues

- Total gastrectomy rarely indicated

Zhang et al, World J Surg 2011

Fendrich & Bartsch, Langenbecks Arch Surg 2011

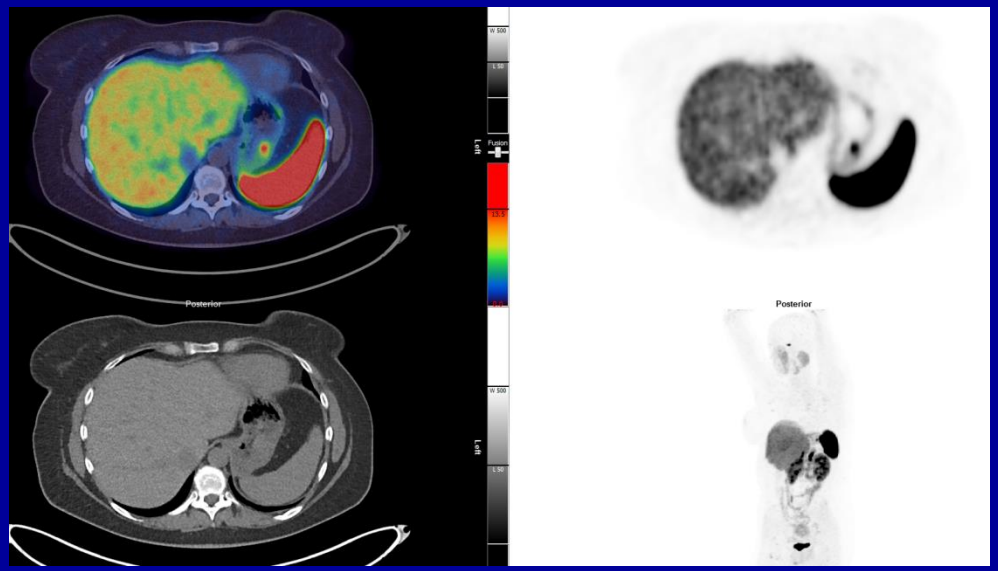
Type I G-NET



- 45 years old male
- Hypothyroidism
- Asthma

- Atrophic gastritis
- G1 NET
- Raised gastrin, Chromogranin-A
- Positive auto-antibodies

- One of the polyps is measuring 1.7 cm



3rd Question to the Audience

What would be the appropriate management?

- Endoscopic polypectomy ?

The overall metastatic risk is low in type 1 g-NENs and has been directly correlated with tumor size (**10 mm appearing to be the cut-off**)
Therefore, the minimal approach **should be to resect tumors ≥ 10 mm.**
Resection should be performed by experienced endoscopists
in gastric tumors using either *Endoscopic Mucosal Resection or Endoscopic Submucosal Dissection (ESD);*
the latter has the benefit of an en bloc resection for complete histological appraisal.

Delle Fave et al, ENETS Consensus Guidelines, Neuroendocrinology 2016

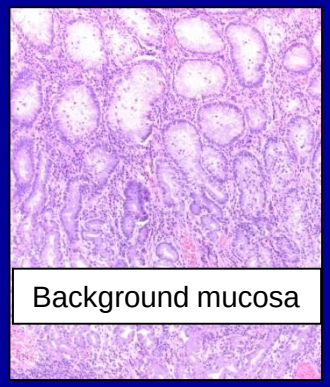
Questions to the Panel

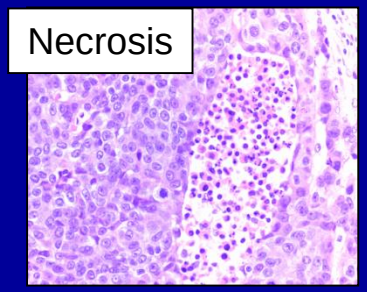
- Can EUS be misleading in terms of depth of invasion?
- Which makes you choose between EMR or ESD ?
- Would you be concerned if it is proved to be a R1 endoscopic resection or the tumour grade is G2?

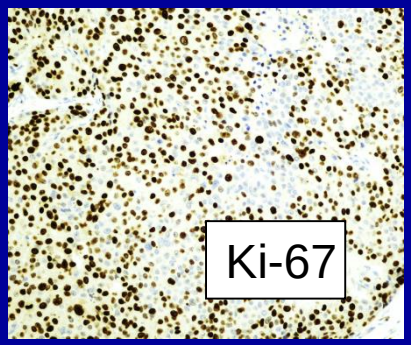
Type III gastric NET

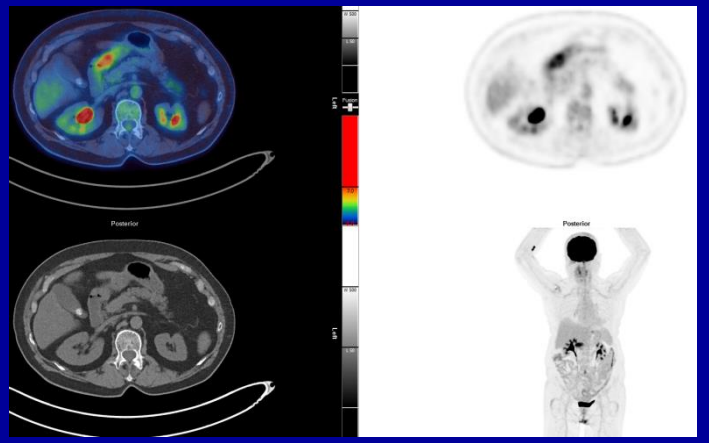
- 58 years old female
- Dyspepsia, weight loss

- Normal Gastrin, CgA
- No *Helicobacter Pylori*
- Negative autoantibodies
- Chronic gastritis









Poorly differentiated NEC with Ki67: 60%

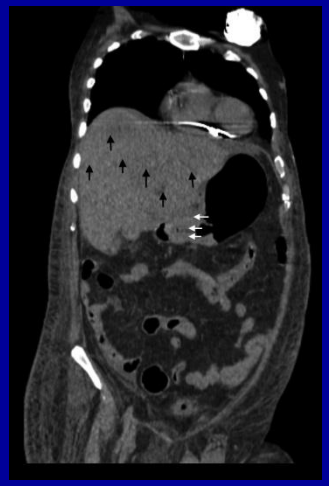
Management suggestions

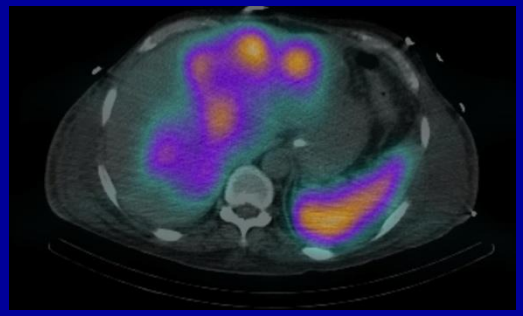
- Endoscopic polypectomy ?
- Commencement of systemic treatment?
- Gastrectomy ?

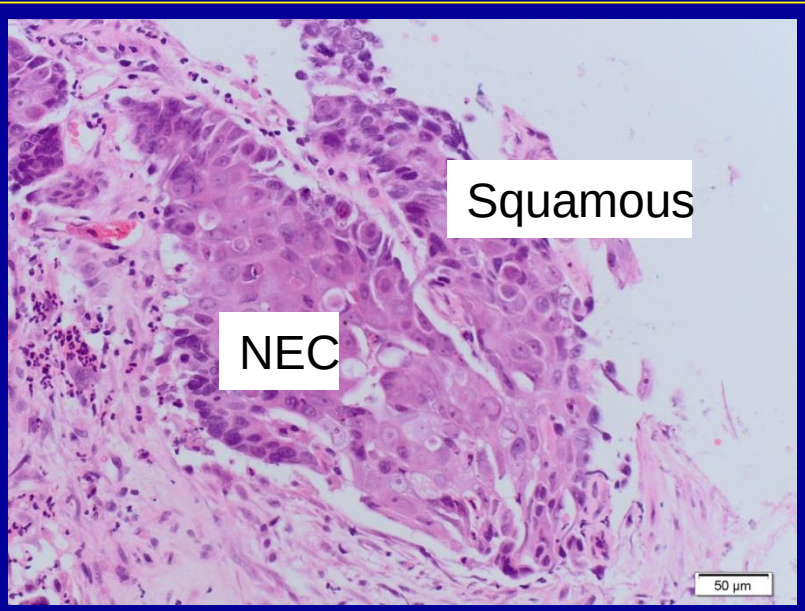
In patients with **localized type 3 g-NENs, surgical treatment** remains the recommended option and follows the strategy employed for gastric adenocarcinomas (partial or total gastrectomy with lymph node dissection).

Delle Fave et al, ENETS Consensus Guidelines, Neuroendocrinology 2016

Mixed Adeno NEuroendocrine Carcinoma (MANEC)

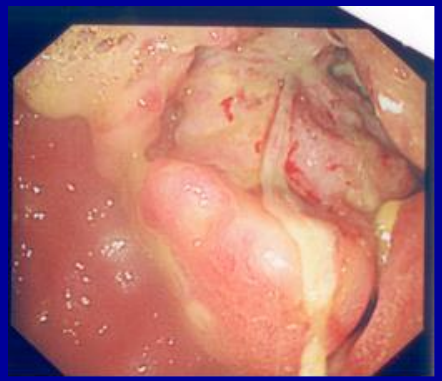


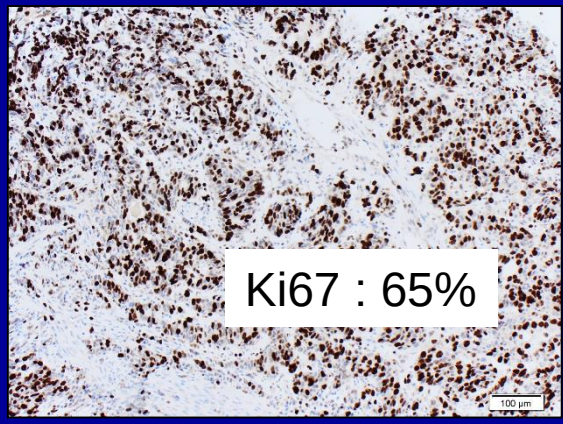




83 years old male
Multiple co-morbidities

Ulcerated tumour in gastric antrum
Multiple hepatic metastases

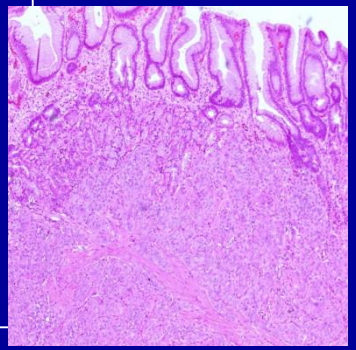


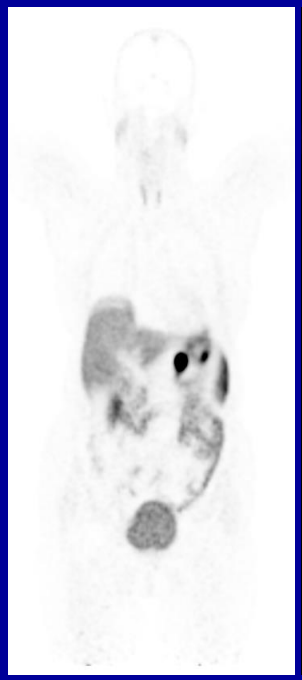


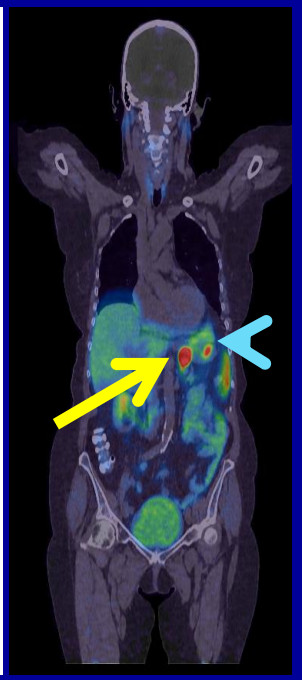
Type III gastric NET

- 65 years old female
- PMH : Arterial hypertension
- **Screening colonoscopy** : rectal Ca.
- **Staging CT** : a left gastric lymph node.
- **EUS + FNA** : 3 cm left gastric node
- **FNA cytology** : well-differentiated NET with Ki67< 1%.
- **OGD :** tumour at the greater curvature.
- **Gastric tumour biopsy** : well-differentiated NET with Ki67< 1%.

Normal Gastrin, CgA
No *Helicobacter Pylori*
Negative autoantibodies
Chronic gastritis







Questions to the Panel

What surgical approach would you consider ?

In patients with **localized type 3 g-NENs, surgical treatment** remains the recommended option and follows the strategy employed for gastric adenocarcinomas (partial or total gastrectomy with lymph node dissection).

Delle Fave et al, ENETS Consensus Guidelines, Neuroendocrinology 2016

- What are the pros and cons of a "less-aggressive" surgical approach?
- What would be the optimal follow-up post-surgery?

Type III gastric Neuroendocrine Neoplasms: moving towards less-extensive resections in selected cases?

UKI NETS, 2019

- **Aim:** To assess whether advanced endoscopic excision [Endoscopic Mucosal Resection (EMR) or Endoscopic Submucosal Dissection (ESD)] or localized surgical approach (wedge resection) is sufficient and not associated with disease recurrence at follow-up.
- **Methods: Thirty five patients with type III g-NEN of grade 1 and 2 were included**

- **Results:** Average follow-up was 41.5 months.
- Mean tumour size was 1.77 cm and most common location was gastric body (80%). Most tumours (91%) had Ki67 $\leq$ 10%.
- **In 6/35 (17%) with mean tumour size 1.3 cm and Ki67<10%, EMR or ESD was performed**. No recurrence was noted at follow-up (average: 35.6 months).
- **Wedge resection was performed in 15/35 (43%) patients.** In 14 patients, no recurrence has been noted (average follow-up 42.1 months). Hepatic metastases were detected and resected in 1 patient, with tumour size > 2cm, 96 months post-wedge resection. This patient has been tumour-free, 36 months post-hepatectomy.
- Tumour size (p: 0.0018), but not tumour grade, seemed to be associated with lymph nodal metastases, detected post-resection in 38% patients.

- ***Conclusions:*** *A proportion of type III g-NEN seems be associated with less-aggressive biologic behavior. In type III g-NEN, measuring less than 2 cm with Ki67 $\leq$ 10%, either EMR/ESD or wedge resection, seems sufficient. Larger series are needed to identify more accurately: a) patients who are suitable just for endoscopic excision and b) further risks factors for lymph-nodal or distal metastases.*

Biopsies of surrounding mucosa
Serum Gastrin

No atrophic gastritis
Normal serum gastrin
TYPE III

Atrophic gastritis
Hypergastrinaemia
TYPE I

No atrophic gastritis
Hypergastrinaemia
TYPE II

- **In localized disease**
  Surgical resection
- **In advanced disease**
  Systemic treatment

> 2 cm

1 -2 cm

< 1 cm

> 1 cm

Invasion beyond Submucosa
? Lymph nodes

No vascular invasion
No deep invasion
G1

Resection, if symptomatic or Somatostatin analogues

Local resection
+/- antrectomy or
+/- somatostatin analogues

Endoscopic resection

Annual endoscopic surveillance

Neuroendocrine Tumour Unit & Multidisciplinary Team
ENETS Centre of Excellence

Royal Free – University College of London NET Academy

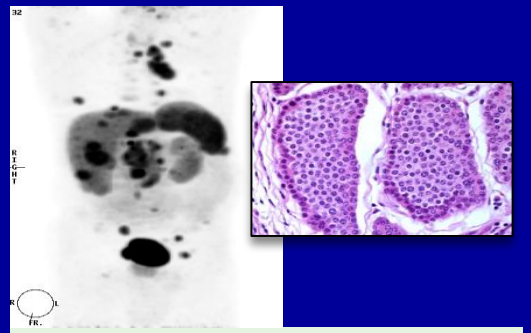
27-29th April 2020

A "Hands-on" learning opportunity for 15 Clinicians, 10 Radiologists and 5 Histopathologists with interest in NETs

Attendance of outpatients' NET clinic (50 patients) and Multi-Disciplinary-Team (MDT) meeting (40 cases), including NETs of several types

Lectures with updates on diagnosis and treatment of NETs

Symposium in **"Translational Medicine" in NETs**



Live reporting of cross-sectional & molecular imaging, and histopathology slides

- **Limited places available**

For more information please contact the Course Moderator :Dr Christos Toumpanakis

Or Course Administrator : Mr Mohmaduvesh Mullan

****Course Fees** : £ 400 covering accommodation for 3 nights (4 star Hotel), lunches, coffee breaks, and dinners