22nd ANNUAL CONTROVERSIES AND PROBLEMS IN SURGERY SYMPOSIUM 2018

Should small neuroendocrine tumours be treated or observed?

Jose Ramos

Wits Donald Gordon Medical Centre

Epidemiology

- Incidence appears to be increasing
  - True increase probable
  - Improved imaging
  - Incidental finding
- 90% are sporadic
- 10% arise in MEN1
  - Must exclude this – Ca, PTH, gastrin, fasting sugar and insulin, prolactin
- Non-functional vs functional
  - 60% - 90% NF
  - Functional tumours mainly carcinoids, insulinoma and gastrinoma

Natural history of NETs

Biological behaviour and outcome

- Grade
- Stage
- Size
- Organ of origin

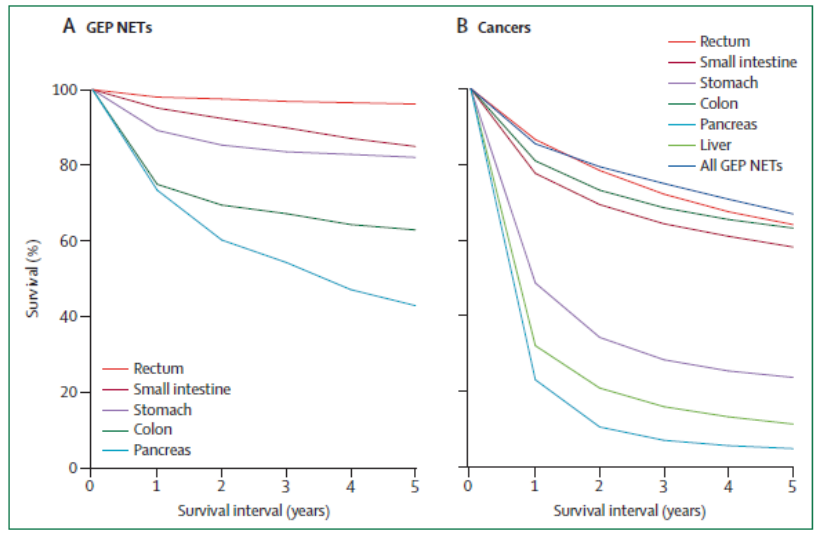
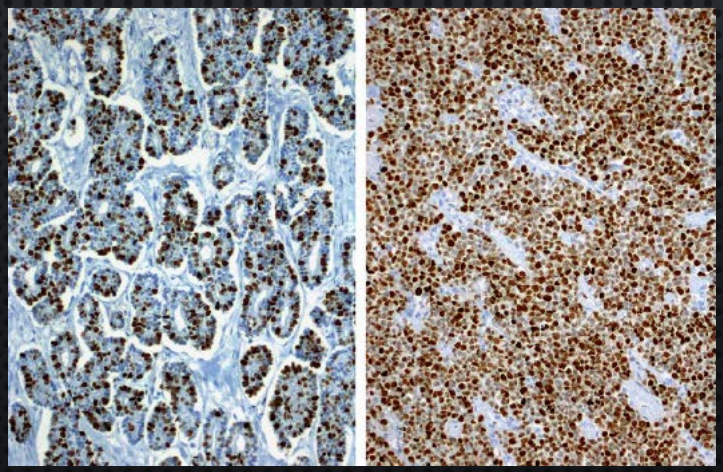
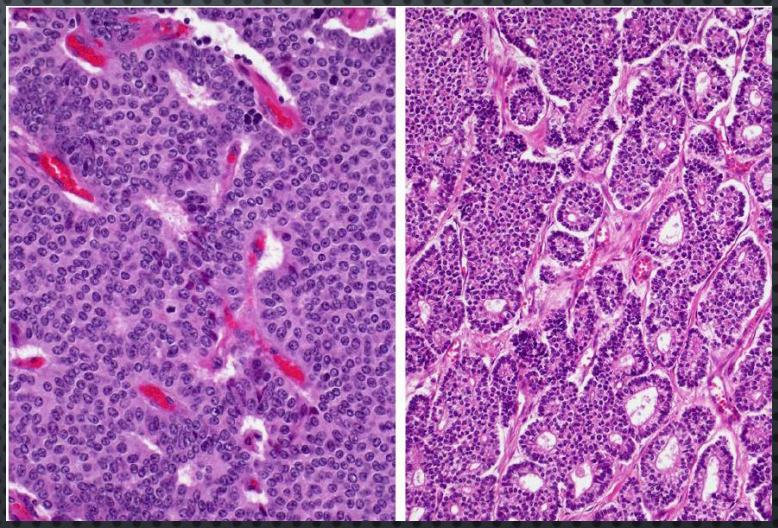


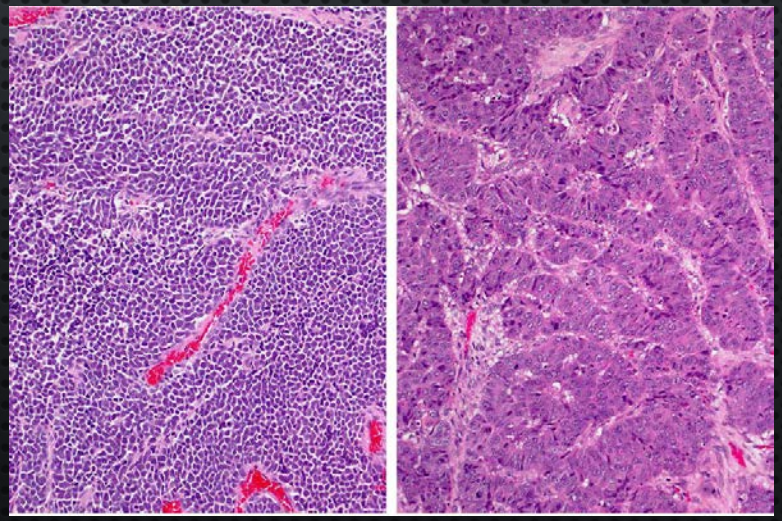
Figure 2: **5 year survival for NETs (A) and gastroenteropancreatic cancers (B)**
Gastroenteropancreatic neuroendocrine tumours (GEP NETs) have a significantly better survival than adenocarcinoma at the same location. The 5 year survival of neuroendocrine liver metastases is less than 50%.[1]

Diagnosis and grading

- FNA adequate for diagnosis in most cases
  - CgA
  - Synaptophysin
- FNA not sufficiently accurate to grade tumours in many cases
- Tissue biopsy preferred for grading







Grading changes

Comparison of the WHO classifications of pancreatic neuroendocrine neoplasms

WHO 1980	WHO 2000/2004	WHO 2010	WHO 2017
Islet cell tumour (adenoma/ carcinoma)	Well-differentiated endocrine tumour/carcinoma (WDET; WDEC)	Neuroendocrine tumour NET G1/G2	Neuroendocrine tumour **NET G1/G2/G3** (Well differentiated neuroendocrine neoplasm)
Poorly differentiated endocrine carcinoma	Poorly differentiated endocrine carcinoma/small cell carcinoma (PDEC)	Neuroendocrine carcinoma NEC G3 large or small cell type	Neuroendocrine carcinoma **NEC G3** (Poorly differentiated neuroendocrine neoplasm), large or small cell type
	Mixed exocrine-endocrine carcinoma MEEC	Mixed adeno-neuroendocrine carcinoma MANEC	Mixed neuroendocrine-nonneuroendocrine neoplasm **MiNEN**
Pseudotumour lesions	Tumour-like lesions (TLL)	Hyperplastic and preneoplastic lesions	

WHO 2010 Grading System

World Health Organization Classification 2010 for Neuroendocrine Neoplasms

Well differentiated NENs	Ki67index|	Mitotic index
Neuroendocrine tumour (NET) G1	≤ 2 %	<2/10 HPF
Neuroendocrine tumour (NET) G2	3-20 %	2-20/10 HPF
Poorly differentiated NENs		
Neuroendocrine carcinoma (NEC) G3*	>20 %	>20/10 HPF
Mixed adenoneuroendocrine carcinoma (MANEC)		

*"NET G3" has been used for this category but is not advised since NETs are by definition well differentiated

WHO 2017 Grading System

TABLE 1

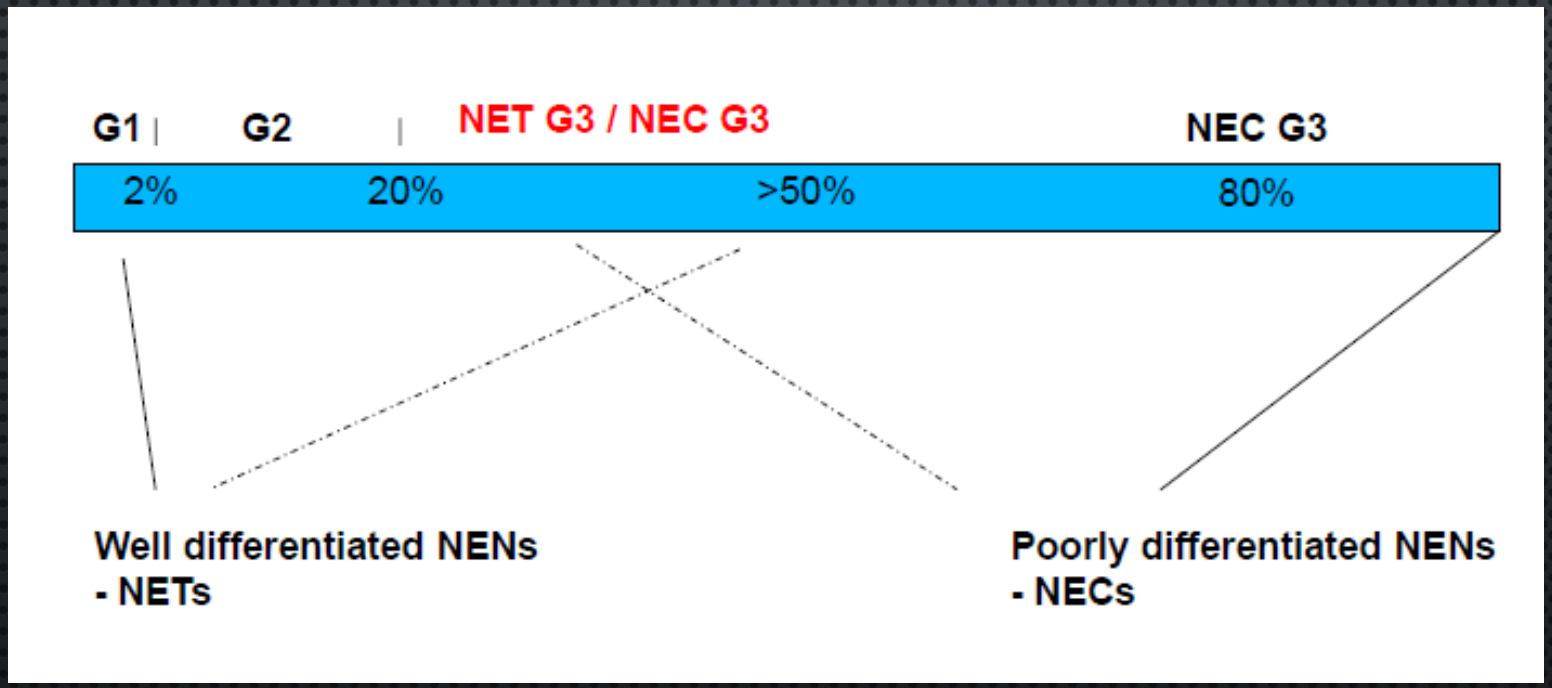
World Health Organization Classification 2017 for Pancreatic Neuroendocrine Neoplasms

Well differentiated NENs	Ki67index*|	Mitotic index
Neuroendocrine tumour (NET) G1	<3 %	<2/10 HPF
Neuroendocrine tumour (NET) G2	3-20 %	2-20/10 HPF
Neuroendocrine tumour (NET) G3	>20 %	>20/10 HPF
Poorly differentiated NENs		
Neuroendocrine carcinoma (NEC) G3 Small cell type Large cell type	>20 %	>20/10 HPF
Mixed neuroendocrine-nonneuroendocrine neoplasm (MiNEN)		

* Ki67 index is based on at least 500 cells in areas of higher nuclear labeling ("hot spots"); mitoses in 50 high power fields (HPF, 0.2mm^2) in areas of higher density and expressed per 10 HPF (2.0 mm^2); the final grade based on which ever index (mitotic rate or Ki67) places the tumor in the highest grade category. For assessing Ki67, casual visual estimation ("eyeballing") is not recommended; manual counting of printed images is suggested {25412850}.

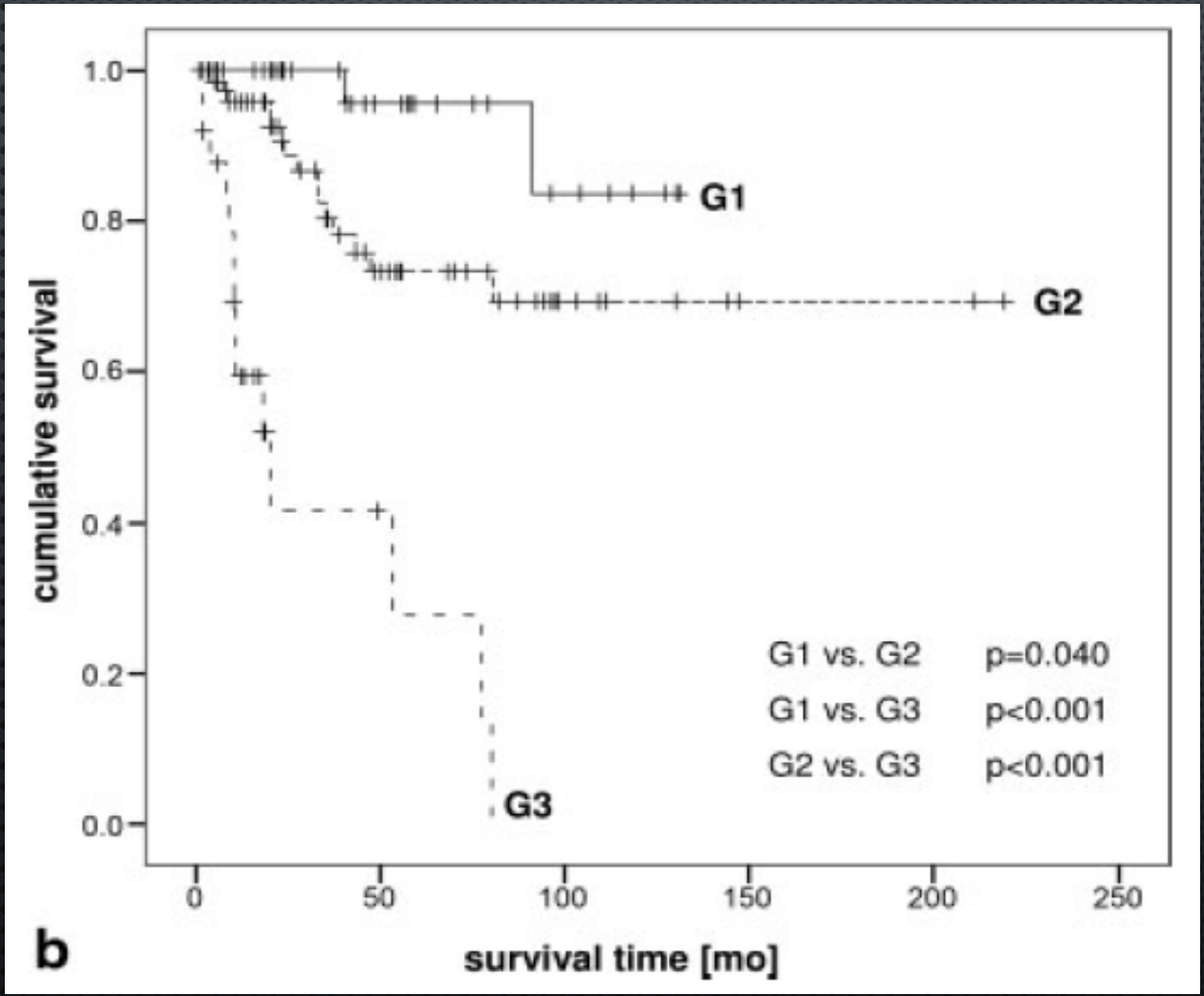
PNETs with ki67>20% - Strong evidence that not just ki67/mitotic rate but also morphological differentiation is important.

PNENs and Ki-67

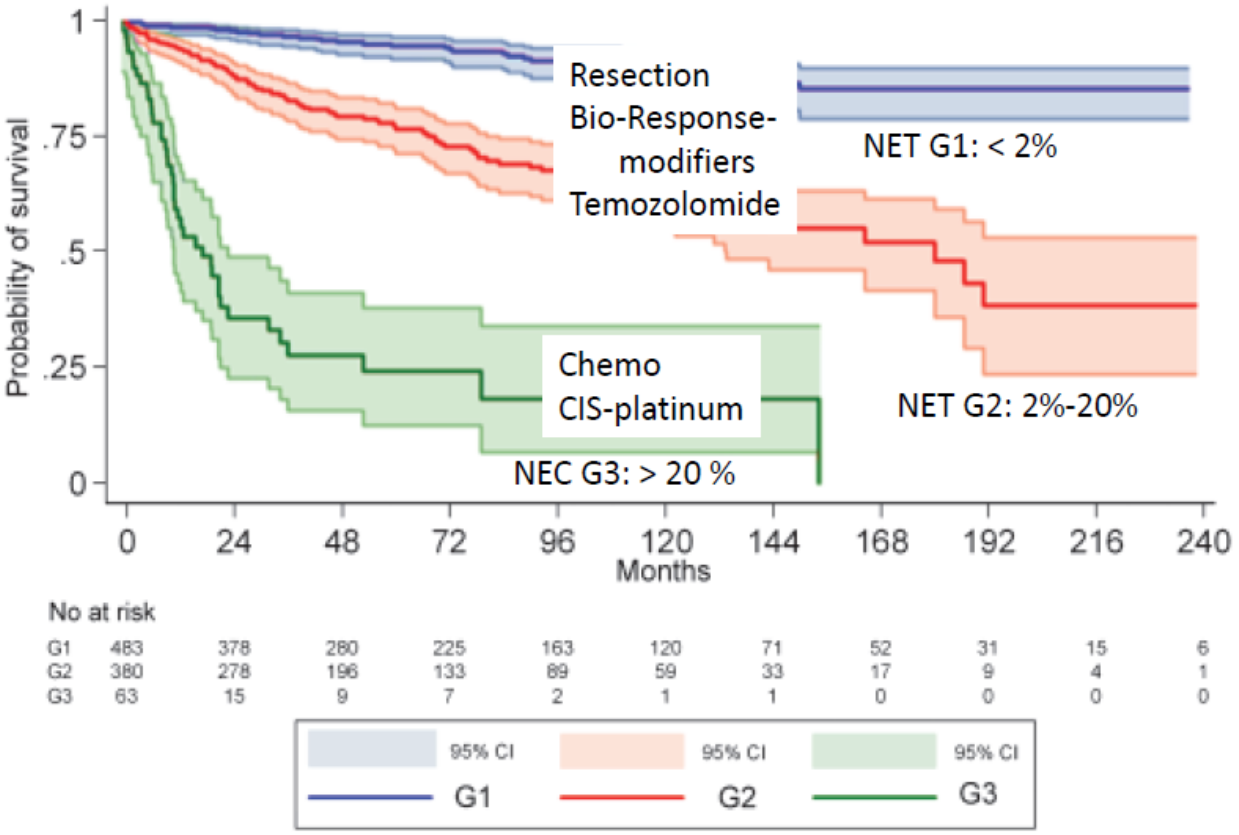


Determinants of Survival

Survival correlates with grade



Relevance of grading

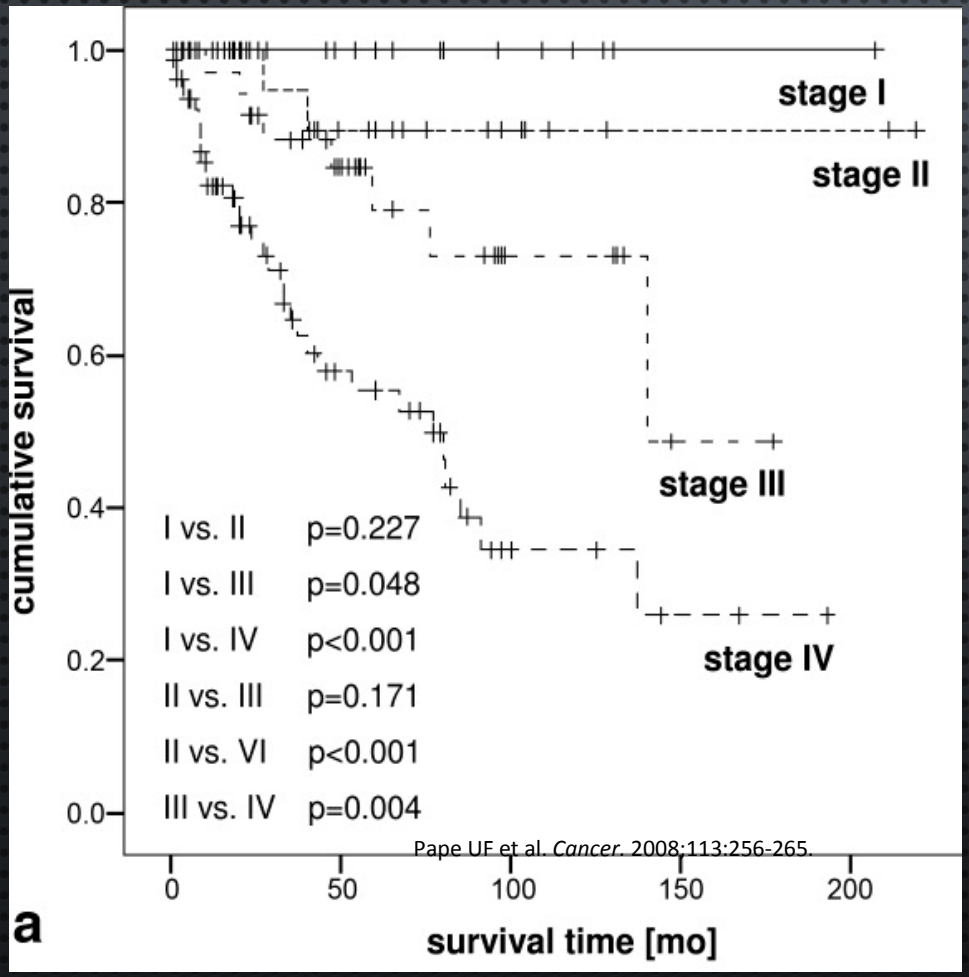


Klinikum rechts der Isar
Technische Universität München

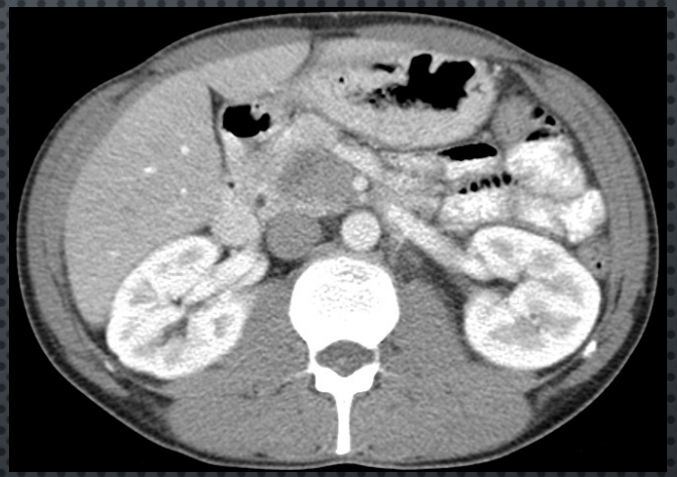
Rindi et al, JNCI 2012

Technische Universität München

Staging of Upper Digestive NENs According to ENETS/WHO/AJCC



Pape UF et al. *Cancer*. 2008;113:256-265.



ENETS/AJCC TNM Staging Systems

ENET/AJCC Classification Criteria – GI NET			
Stage includes tumour location, size, lymph node involvement/distant metastasis			
Stage I	T1	N0	M0
Stage IIa	T2	N0	M0
Stage IIb	T3	N0	M0
Stage IIIa	T4	N0	M0
Stage IIIb	Any T	N1	M0
Stage IV	Any T	Any N	M1

ENETS = European Neuroendocrine Tumour Society
AJCC = American Joint Committee on Cancer

[1]Rindi G, et al. *Virchows Arch.* 2006;449:395-401. [2]Rindi G, et al. *Virchows Arch.* 2007;451:757-762.
[3]American Joint Committee On Cancer. AJCC Cancer Staging System. 7th ed.

Relevance of tumour size

T1 Tumor limited to pancreas, <2cm
T2 Tumor limited to pancreas, 2-4 cm
T3 Tumor limited to pancreas, >4 cm, or invading duodenum or bile duct
T4 Tumor perforates visceral peritoneum (serosa) or invades other organs or adjacent structures

N0 No regional lymph node metastasis
N1 Regional lymph node metastasis

M0 No distant metastasis
M1 Distant metastasis
M1a Heptatic metastasis only
M1a extraheptatic metastasis only
M1c Heptatic and extraheptatic metastases

	T	N	M
Stage I	T1	N0	M0
Stage II	T2, 3	N0	M0
Stage III	T4	N0	M0
	Any T	N1	M0
Stage IV	Any T	Any N	M1

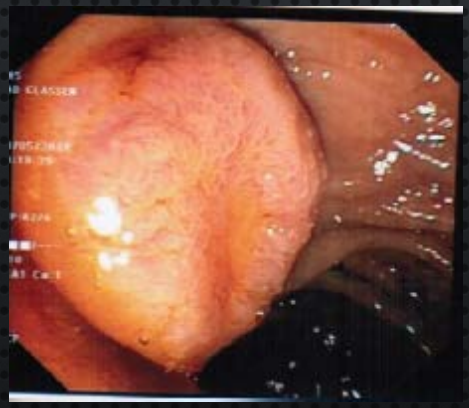
Principles of management of GEPNETs

Surgical / endoscopic resection

- G1 and G2 tumours
- Localised
- Locally advanced but resectable
- Metastatic if primary and metastases resectable

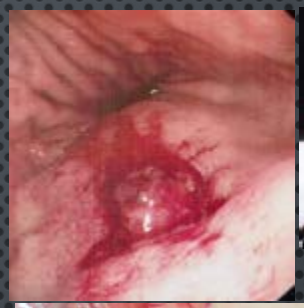
Do all NETs need to be treated?

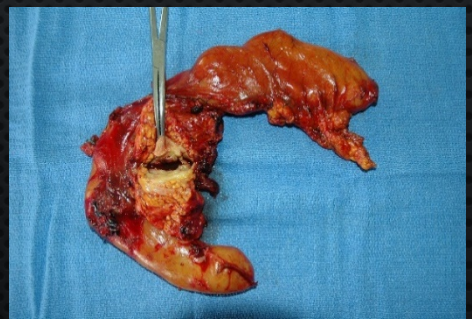
- Most detected incidentally
- Many show benign behaviour
- No symptoms or complications



Factors to be considered

- Symptoms and or complications
- Patient fitness for surgery
- Functional status of the tumour
- Size of tumour
- Grade of tumour
- Stage of tumour
- Site and organ of origin of tumour
- Magnitude of intervention required
  - Endoscopic resection
  - Minor surgery e.g. enucleation, local resect
  - Major surgery





Factors to be considered

Symptoms and or complications

- Resection indicated

Factors to be considered

Symptoms and or complications

Patient fitness for surgery

Functional status of the tumour

- Conservative treatment only for non-functional tumours

Factors to be considered

Symptoms and or complications

Patient fitness for surgery

Functional status of the tumour

Size of tumour

- No evidence-based criteria
- <1cm can be observed
- 1 - 2cm can be considered for observation or treatment

Factors to be considered

Symptoms and or complications

Patient fitness for surgery

Functional status of the tumour

Size of tumour

Grade of tumour

- G1 or low G2 (Ki-67 < 6)

Factors to be considered

Symptoms and or complications

Patient fitness for surgery

Functional status of the tumour

Size of tumour

Grade of tumour

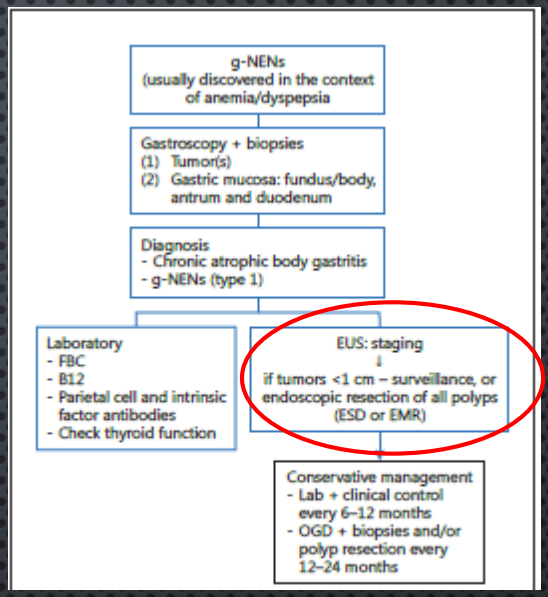
Stage of tumour

- CT, MRI, EUS
- Dotatate-PET/CT
- FDG-PET/CT
- Stage 1 (tumour < 2cm) can be considered for observation

ENETS Guidelines

Gastric NETs

	Type 1	Type 2	Type 3
Proportion among g-NENs, %	70–80	5–6	14–25
Tumor characteristics	Often small (<1–2 cm), multiple in 65% of cases, polypoid in 78% of cases	Often small (<1–2 cm) and multiple, polypoid	Unique, often large (>2 cm) polypoid and ulcerated
Associated conditions	Atrophic body gastritis	Gastrinoma/MEN-1	None
Pathology	G1–G2 NET	G1–G2 NET	G3 NEC
Serum gastrin levels	↑	↑	Normal
Gastric pH	↑↑	↓↓	Normal
Metastases, %	2–5	10–30	50–100
Tumor-related deaths, %	0	<10	25–30

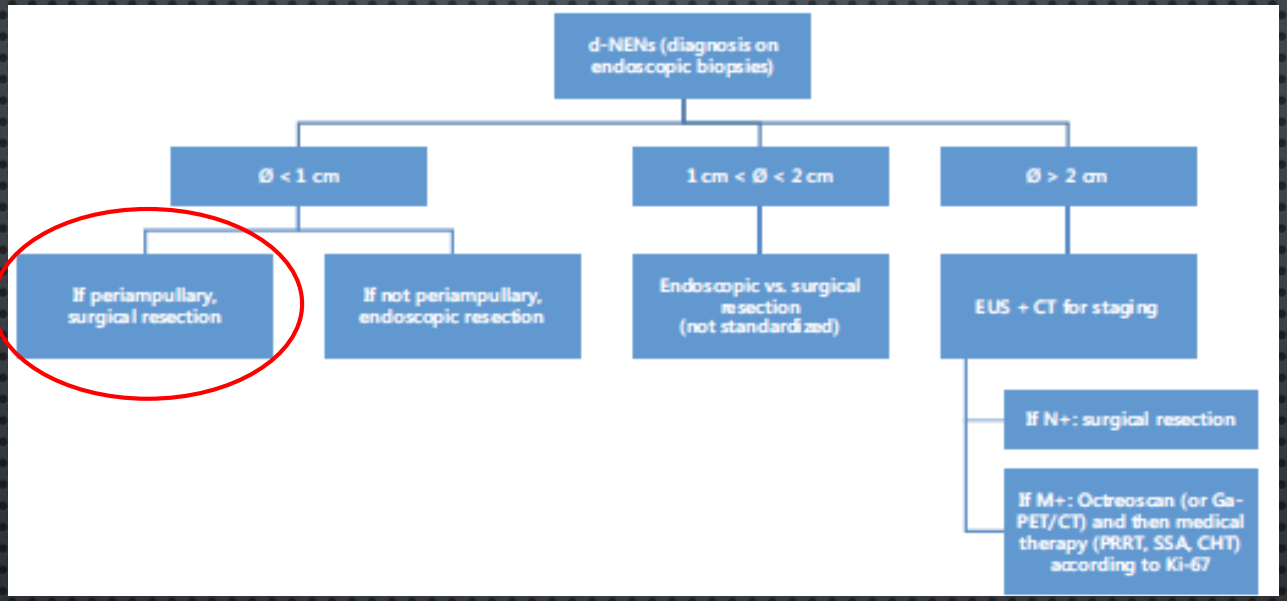


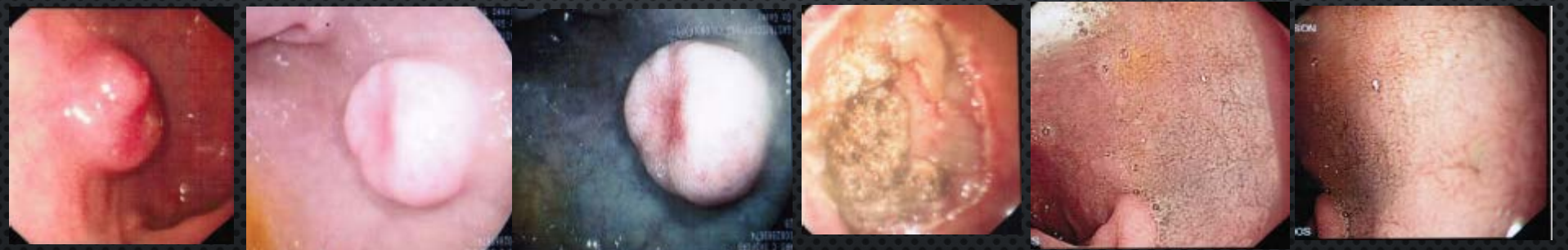
Type 1
Observe <1cm

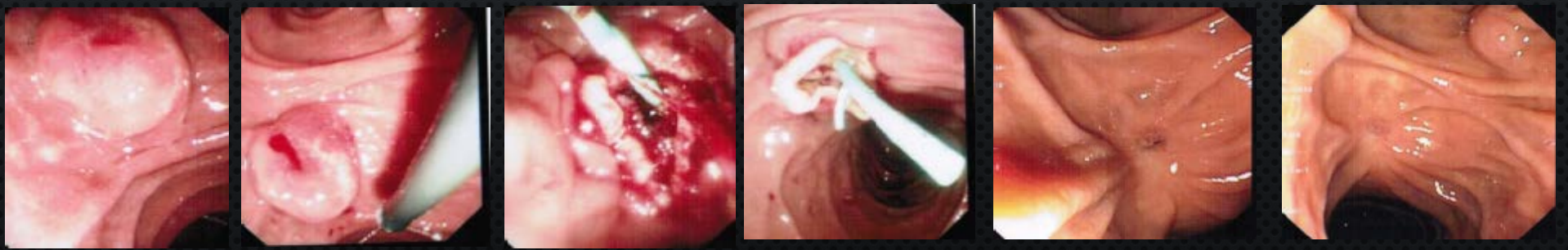
Type 2
Endoscopic/surgical resection

Type 3
Surgical resection

Duodenal NETs







Small bowel NETs

Disease	Localized	Regional	Distant		
Stage	**I/II**	**III**	**IV**		
TNM	T1–3N0M0	T4N0M0 T1–4N1M0		TxNxM1	
Surgical treatment	**Radical resection**		**Radical resection with curative intent**	**Palliative resection**	**No resection**
	Local radical open (or in selected pts) laparoscopic resection* of • primary tumor(s)** • lymph nodes (dissection along the superior mesenteric root)		Local radical open resection of • primary tumor(s) • lymph nodes (dissection along the superior mesenteric root) In combination with: • mets (liver)	Local radical open (in selected pts) laparoscopic resection of • primary tumor(s) • lymph nodes (dissection along the superior mesenteric root)	Due to: • local inoperability • comorbidity
Aim	Free from tumor		Free from tumor	• To avoid local complications (obstruction, bleeding etc.) • To possibly improve prognosis*	

Fig. 2. Therapeutic algorithm for Si-NENs. Pts = Patients; mets = metastasis. *For details, see the text. **Caution: multiple primaries.

- Majority have multifocal disease, 1/3 present with stage III disease.
- 40-50% of SB NETs < 10mm in size have nodal mets
- All SB NETs should be aggressively resected unless inoperable

Appendiceal NETs

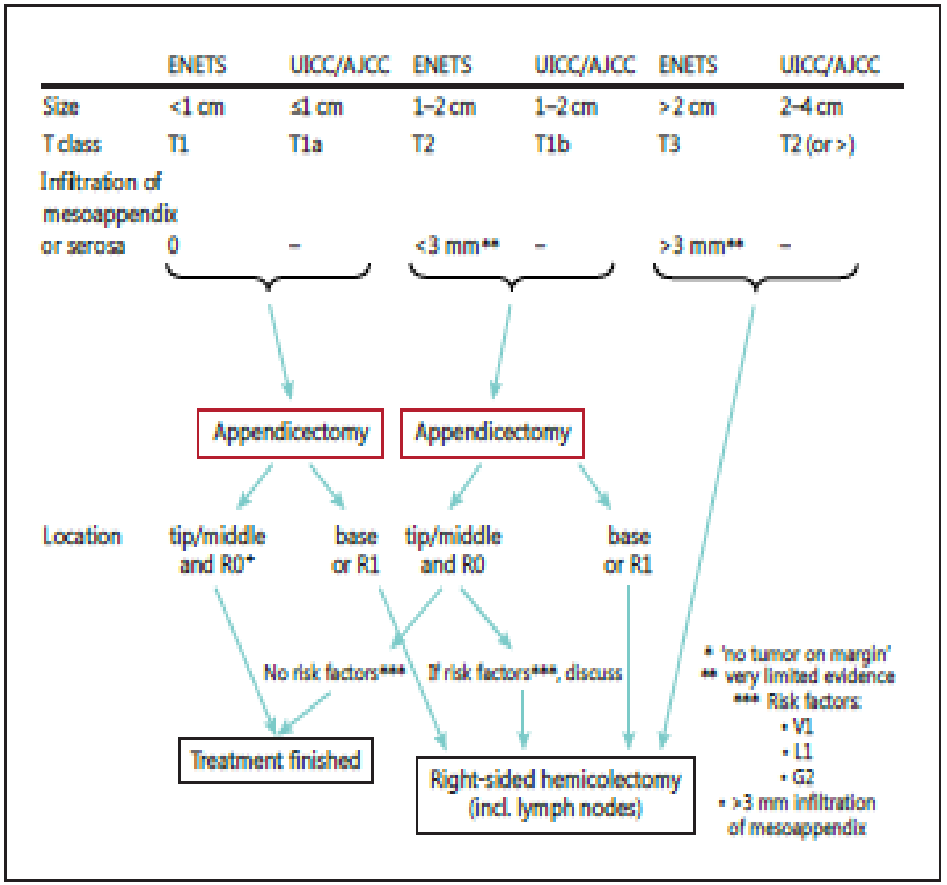
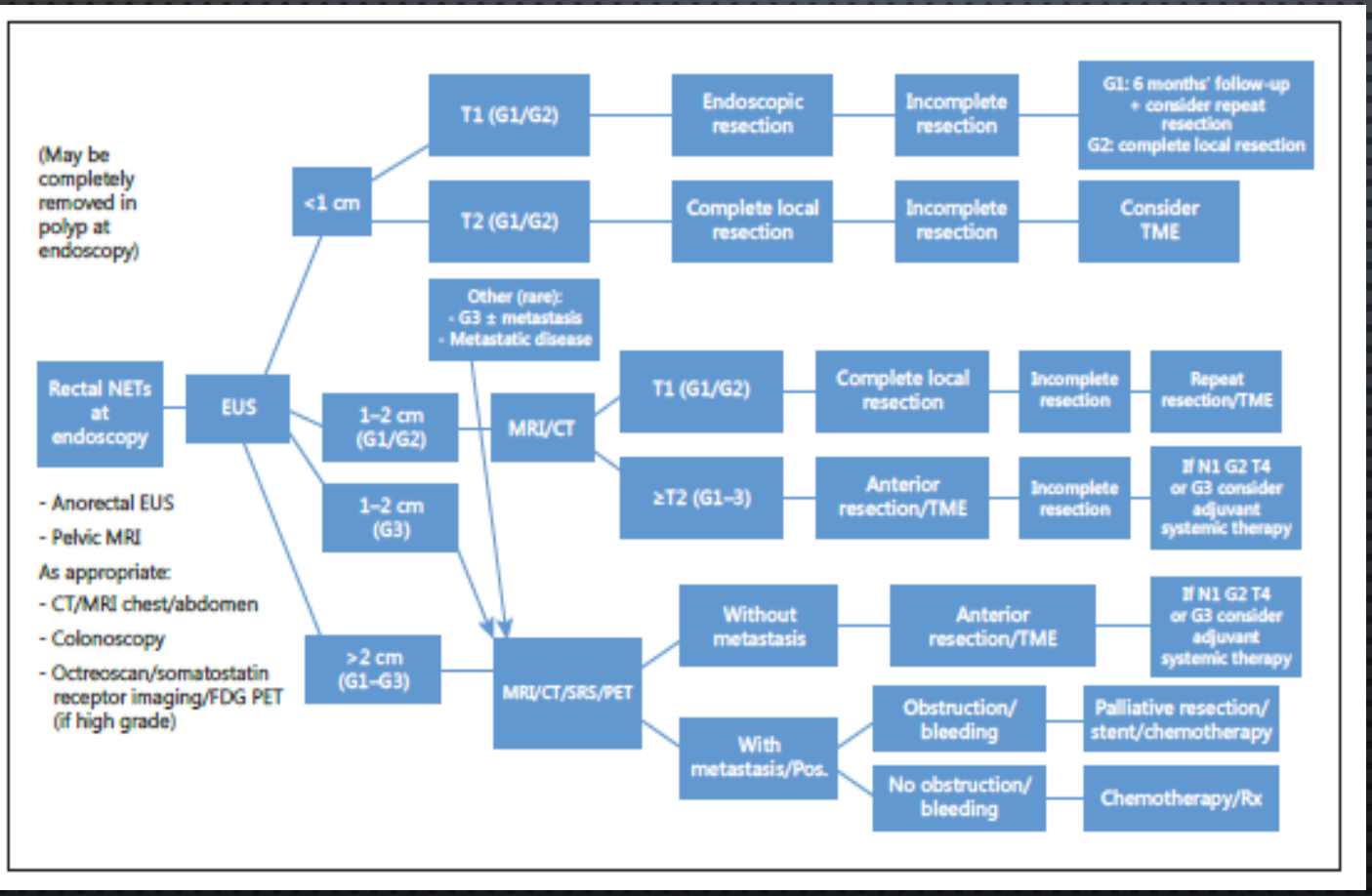


Fig. 1. Therapeutic algorithm for small appendiceal NET. V1 = Vascular invasion; L1 = lymphatic invasion; G2 = grade 2 tumor (Ki-67: 3–20%).

All should be resected

Rectal NETs


(May be completely removed in polyp at endoscopy)
<1 cm
T1 (G1/G2)
Endoscopic resection
Incomplete resection
G1: 6 months' follow-up + consider repeat resection
G2: complete local resection
T2 (G1/G2)
Complete local resection
Incomplete resection
Consider TME
Other (rare):
- G3 ± metastasis
- Metastatic disease
Rectal NETs at endoscopy
EUS
1–2 cm (G1/G2)
MRI/CT
T1 (G1/G2)
Complete local resection
Incomplete resection
Repeat resection/TME
≥T2 (G1–3)
Anterior resection/TME
Incomplete resection
If N1 G2 T4 or G3 consider adjuvant systemic therapy
1–2 cm (G3)
- Anorectal EUS
- Pelvic MRI
As appropriate:
- CT/MRI chest/abdomen
- Colonoscopy
- Octreoscan/somatostatin receptor imaging/FDG PET (if high grade)
>2 cm (G1–G3)
MRI/CT/SRS/PET
Without metastasis
Anterior resection/TME
If N1 G2 T4 or G3 consider adjuvant systemic therapy
With metastasis/Pos.
Obstruction/ bleeding
Palliative resection/ stent/chemotherapy
No obstruction/ bleeding
Chemotherapy/Rx

Pancreatic NETs

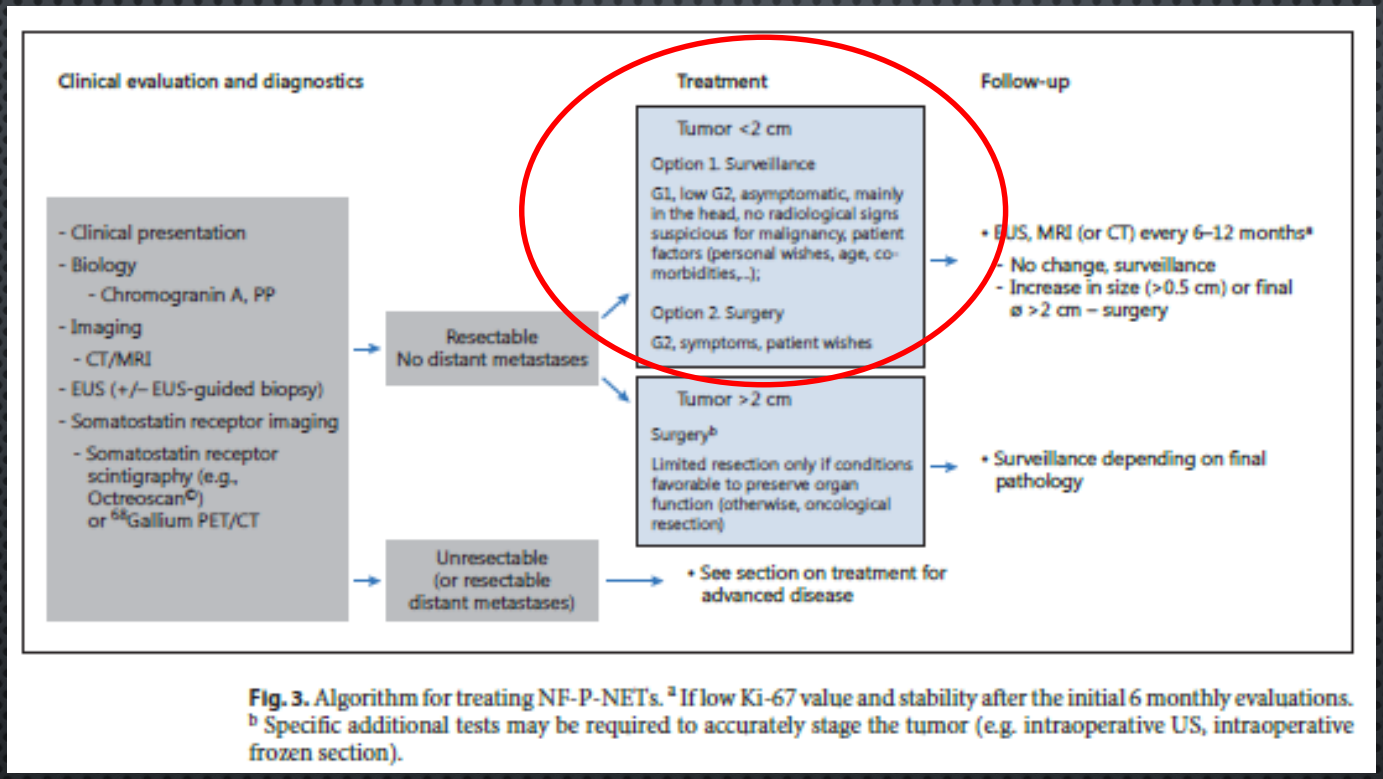
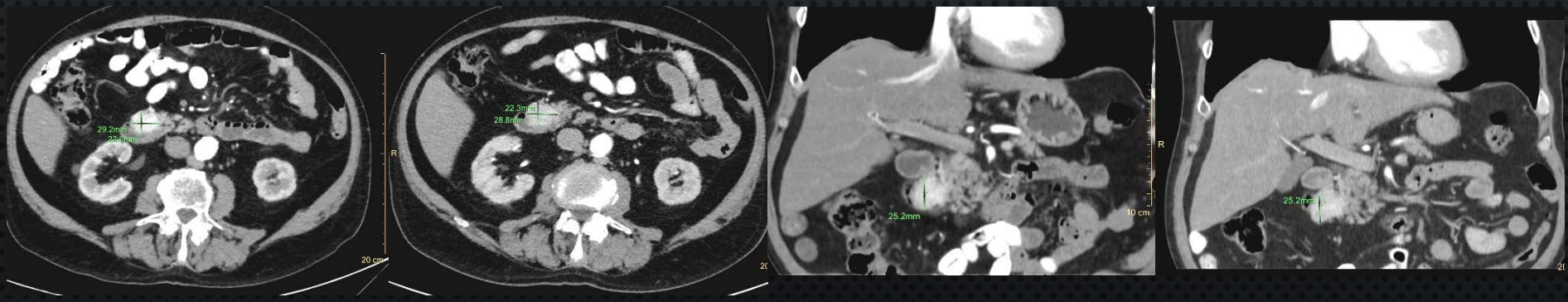
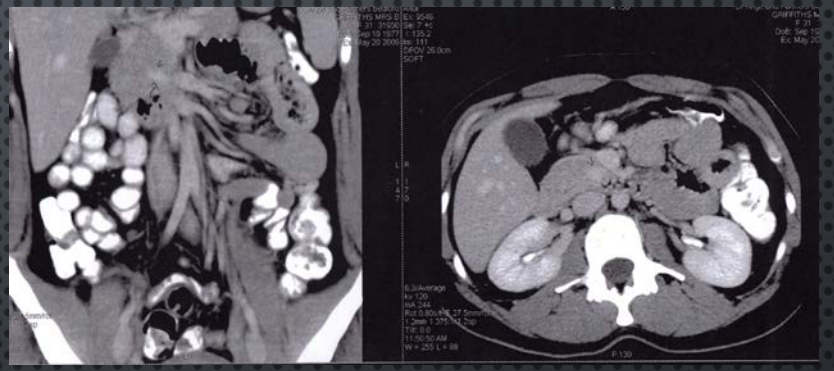


Fig. 3. Algorithm for treating NF-P-NETs. [a] If low Ki-67 value and stability after the initial 6 monthly evaluations. [b] Specific additional tests may be required to accurately stage the tumor (e.g. intraoperative US, intraoperative frozen section).



MEN1

- Present in up to 10% of PNETs
- Primary hyperparathyroidism (95%–100%)
- Functional pNET (F-pNET) (0-20%)
  - Gastrinomas 20% - 61%
  - Insulinomas 7% - 31%
  - Glucagonomas 3% - 4%
  - VIPomas, GRFomas, Ssomas < 2%
- NF-pNET (80%–100%)
- Multiple NETs typical
- NF-pNETs occur microscopically in 80% to 100% of patients with MEN1
- Functional/nonfunctional pituitary tumors
- Adrenal adenomas/carcinomas (27%–36%), carcinoids [gastric (7%–35%), lung, and thymic (0%–8%)], and thyroid adenomas



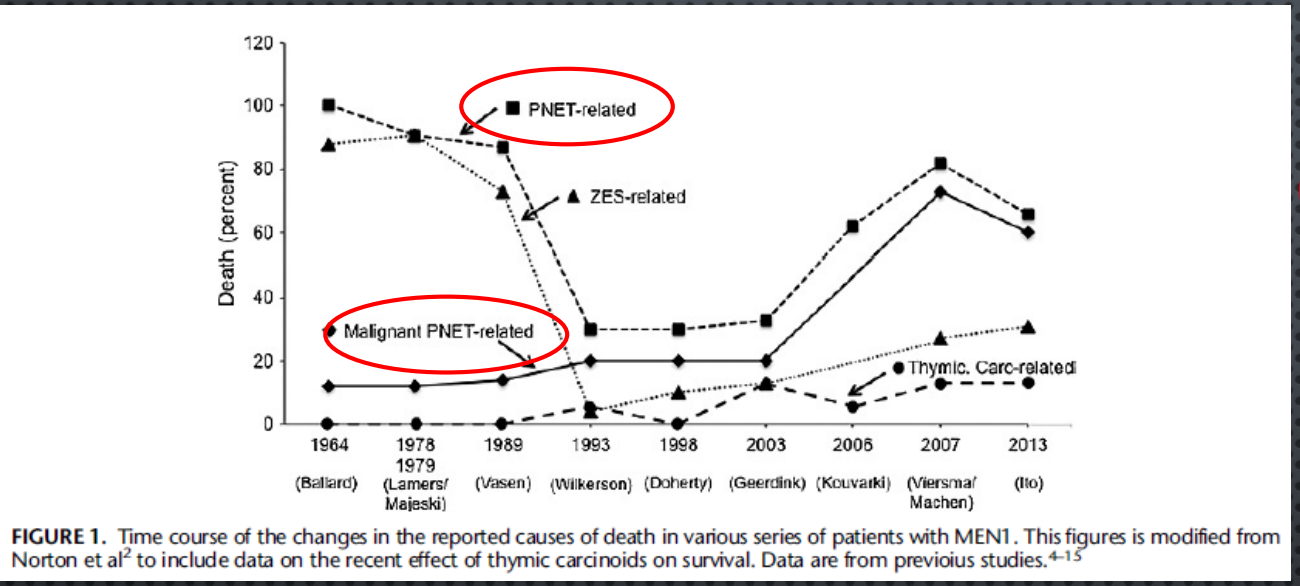


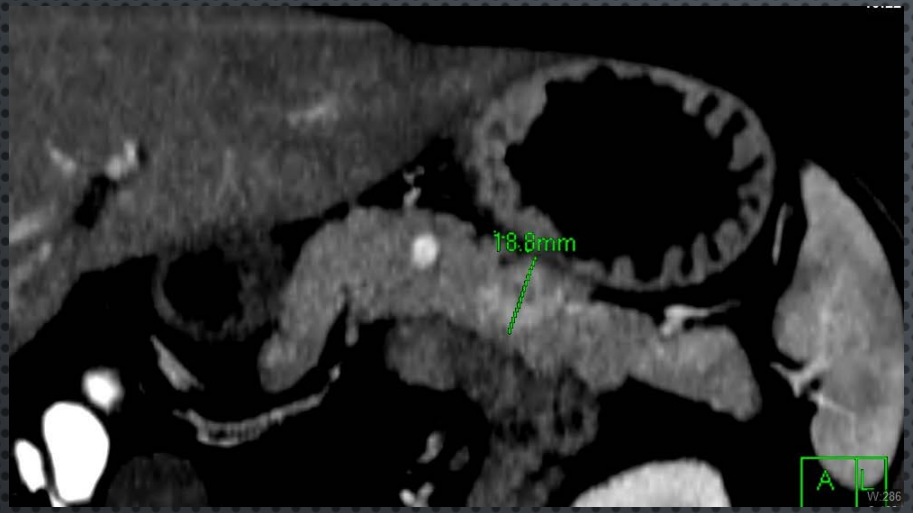
FIGURE 1. Time course of the changes in the reported causes of death in various series of patients with MEN1. This figures is modified from Norton et al[2] to include data on the recent effect of thymic carcinoids on survival. Data are from previoius studies.[4–15]

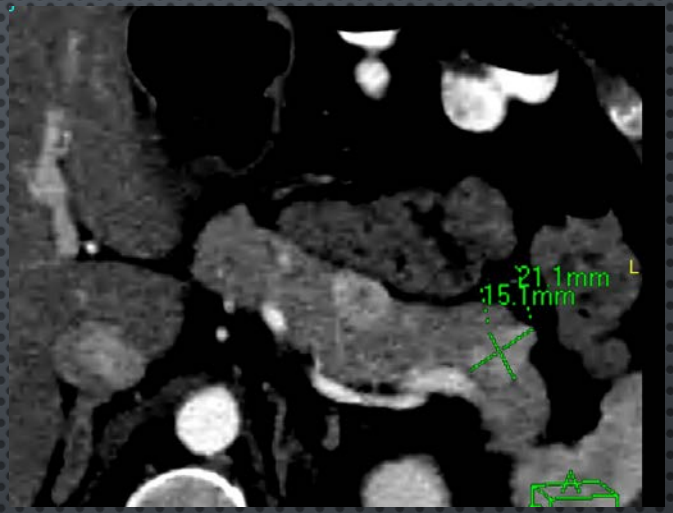
TABLE 1. Causes of Death in Patients With MEN1 From Recent Series

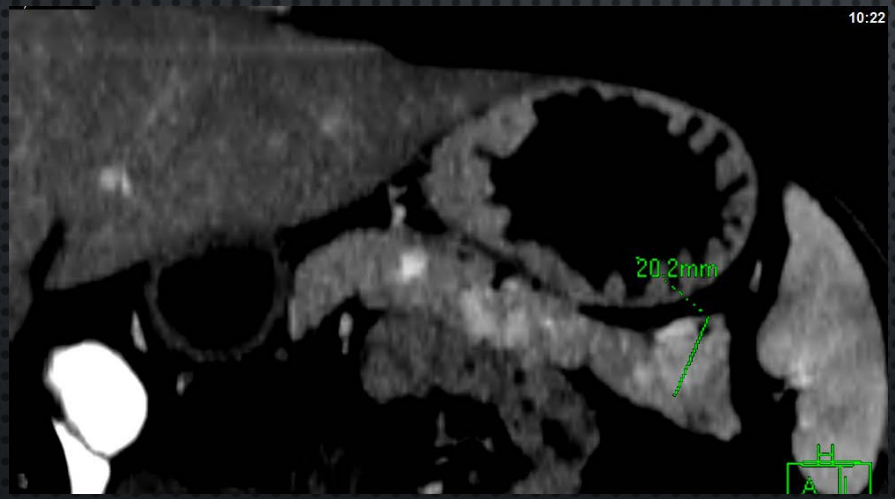
	% of Deceased Patients
Death due to:	**Mean (range)**
I. MEN1 related	
MEN1-related disease	60 (28–81)
pNET	38 (19–62)
ZES	20 (9–38) = 38
Acid related	4 (0–11)
Gastrinoma related	10 (7–38)
Malignant pNET	31 (10–62)
Thymic carcinoid	8 (0–24)
Hyperparathyroidism	2 (0–5)
Pituitary tumor	0.8 (0–3)
Lung carcinoid/tumor	0.7 (0–5)
Gastric carcinoid	0.4 (0–10)
Other MEN1 related causes*	3 (0–9)
II. Non–MEN1-related	36 (6–72)
III. Unknown cause of death	4.5 (0–13)

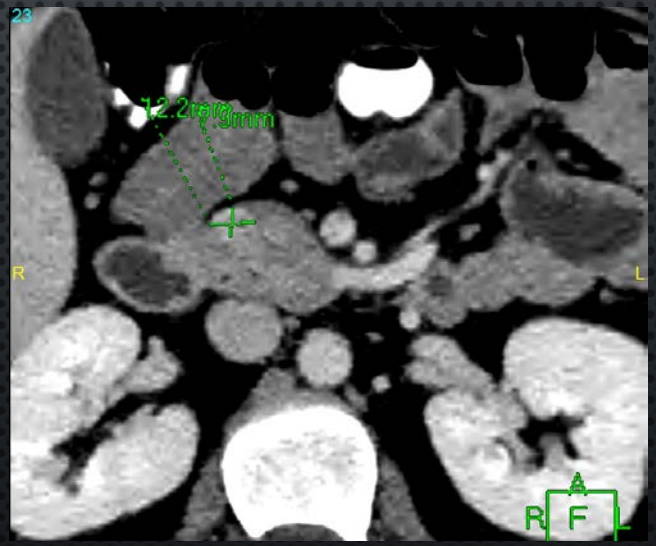
Pancreas • Volume 46, Number 5, May/June 2017

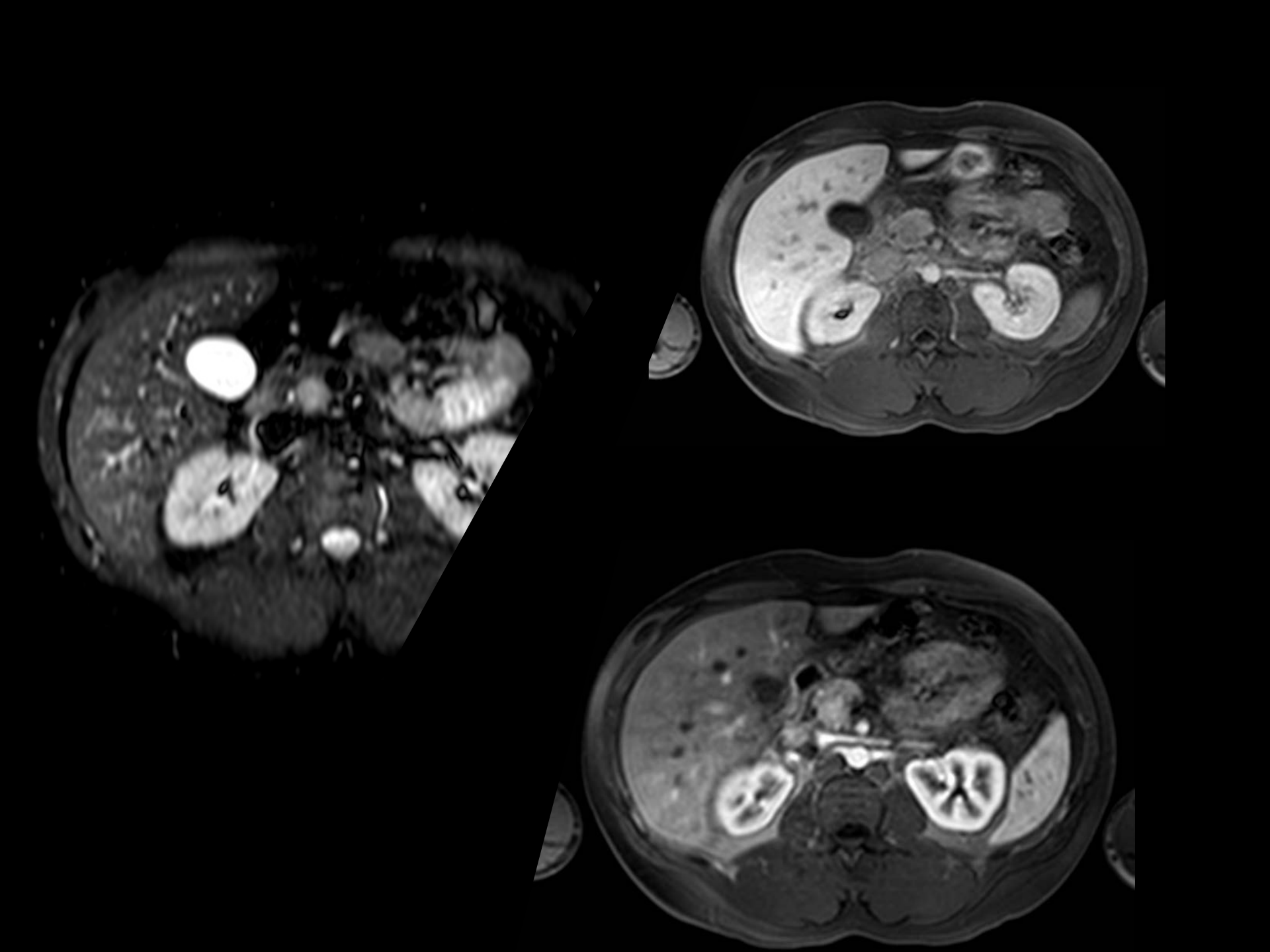
- In general, pNETs are slow growing in patients with MEN1
- Up to 15% of patients with MEN1/ZES have a pNET that demonstrates aggressive growth.
- NIH study of patients with MEN1/ZES with pNETs < 2 cm without surgery no deaths in pts followed for up to 15 years
- Following existing conservative guidelines for managing patients with MEN1 with NF-pNETs and MEN1/ZES may extend survival


18.8mm
A
L


21.1mm
15.1mm
L


10:22
20.2mm
A


23
12.2mm
9mm
R
L
A
R
F
L



Surveillance

- 1-2 yearly
- Endoscopy
- US
- CT/MRI
- EUS

Summary

- NET incidence is increasing
- Most detected incidentally on endoscopy and/or imaging
- Majority are non-functional
- All functional, symptomatic or complicated NETs should be resected
- Management options must be fully discussed with patient
- Observation only appropriate for small G1 or low G2 NETs, Stage 1
  - Type 1 gastric NETs
  - (Duodenal NETs)
  - Pancreatic NETs
  - MEN-1 related pancreatic NETs
  - (Rectal NETs)
- Surveillance essential