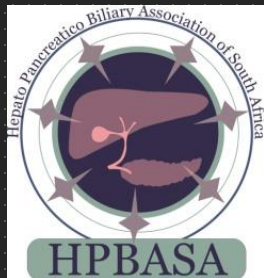




**10th Gastro Foundation Weekend for Fellows  
10<sup>th</sup> Anniversary Meeting  
Friday 1 – Sunday 3 February 2019  
Spier Hotel & Conference Centre, Stellenbosch**

# An approach to NETS

**Jose Ramos**

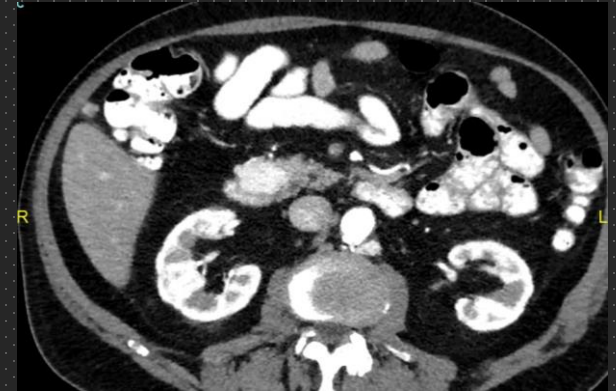


**University of the Witwatersrand  
Donald Gordon Medical Centre**

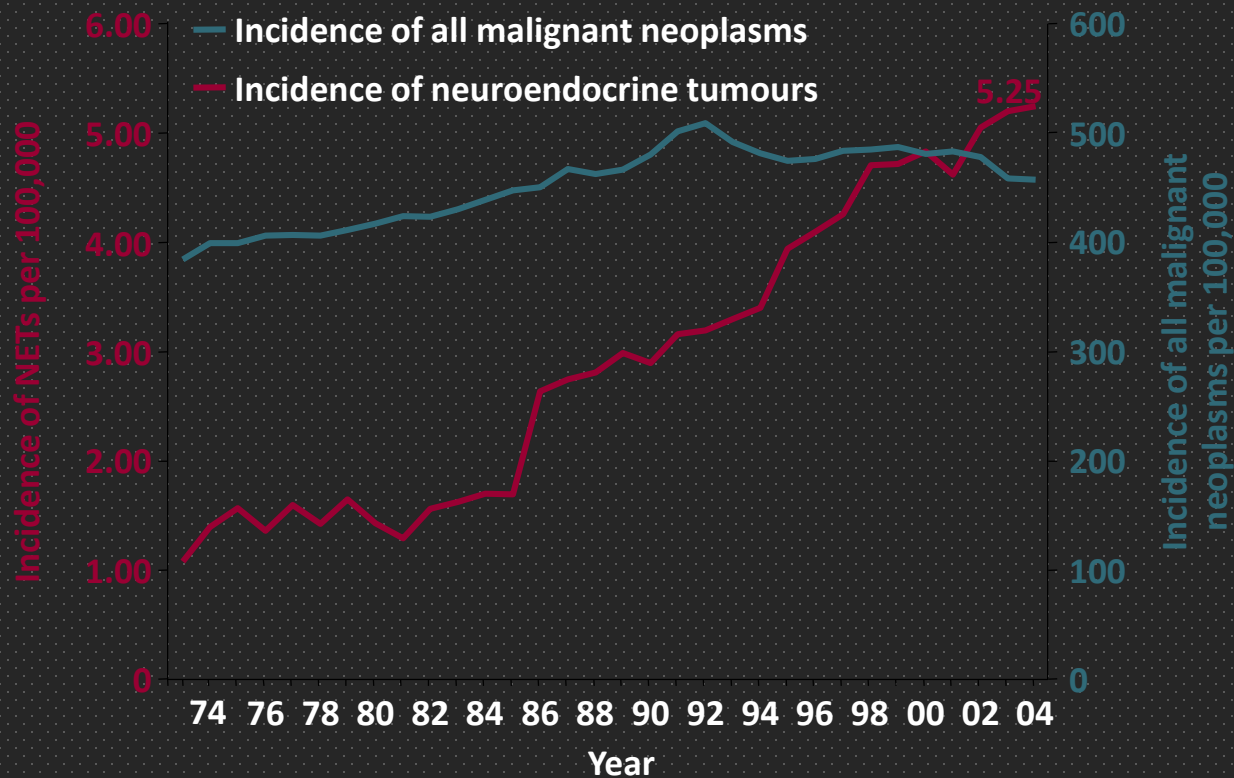


# Epidemiology

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

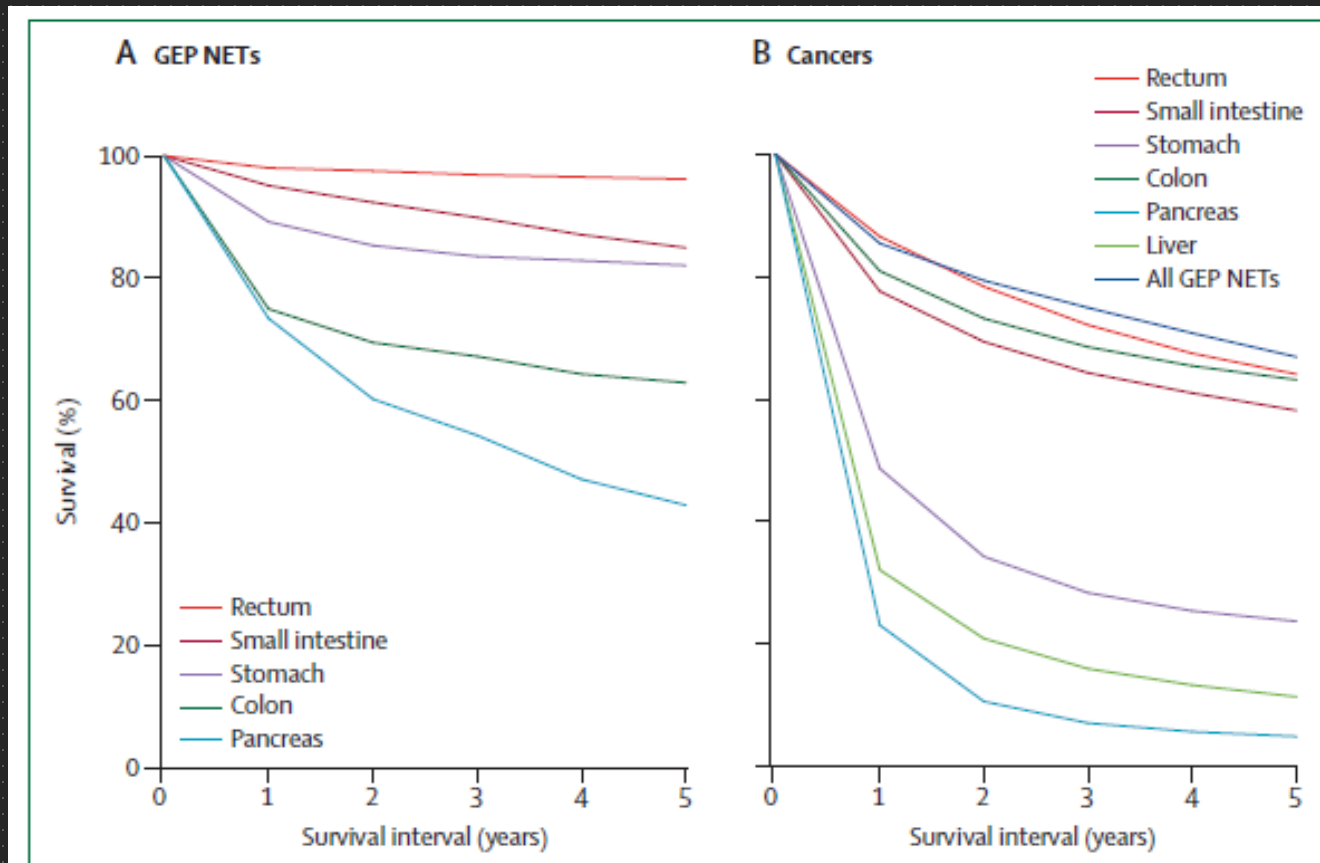


# The Overall Incidence of NET Is Increasing Compared With All Malignant Neoplasms



- The incidence and prevalence of NET has increased approximately 500% over the past 30 years which may be partially due to improved diagnosis

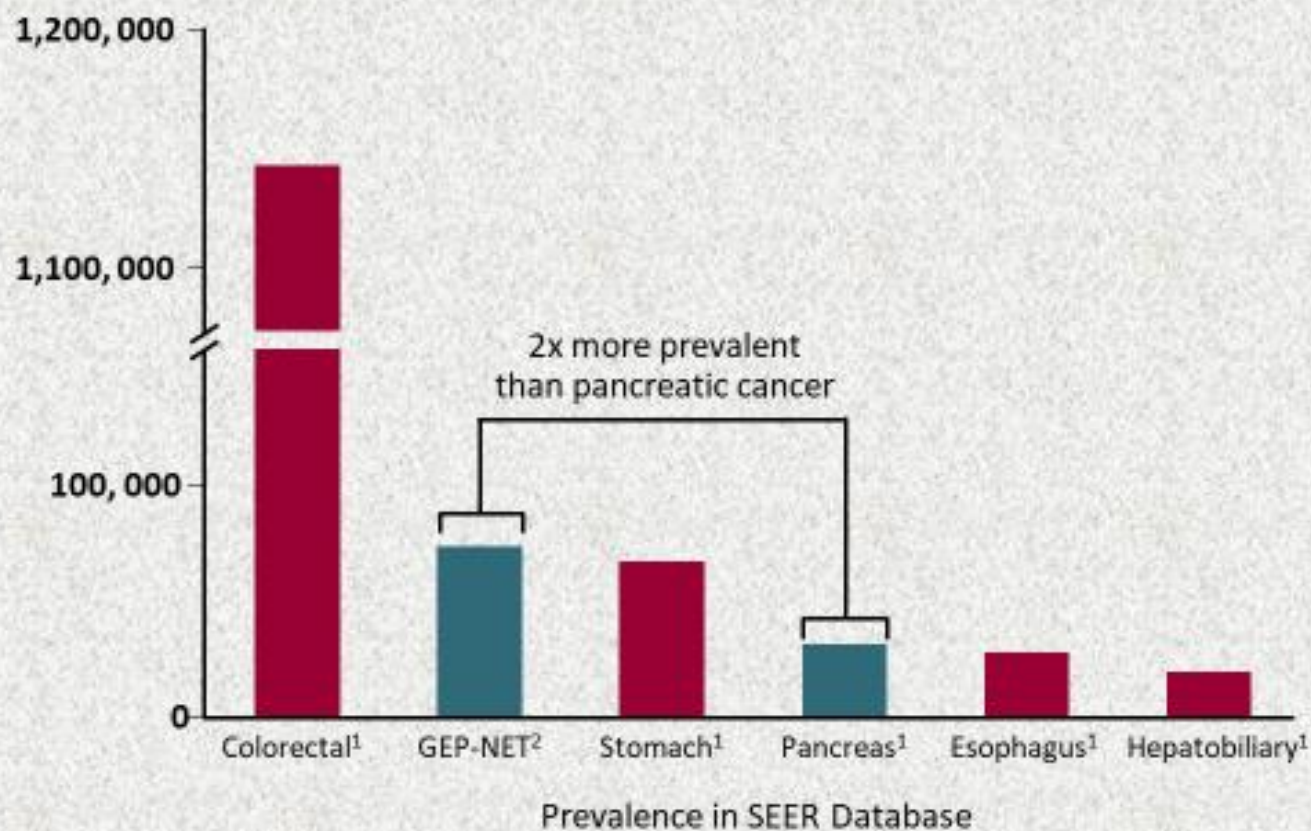
# GEPNETs vs Adenocarcinoma



**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%.<sup>1</sup>

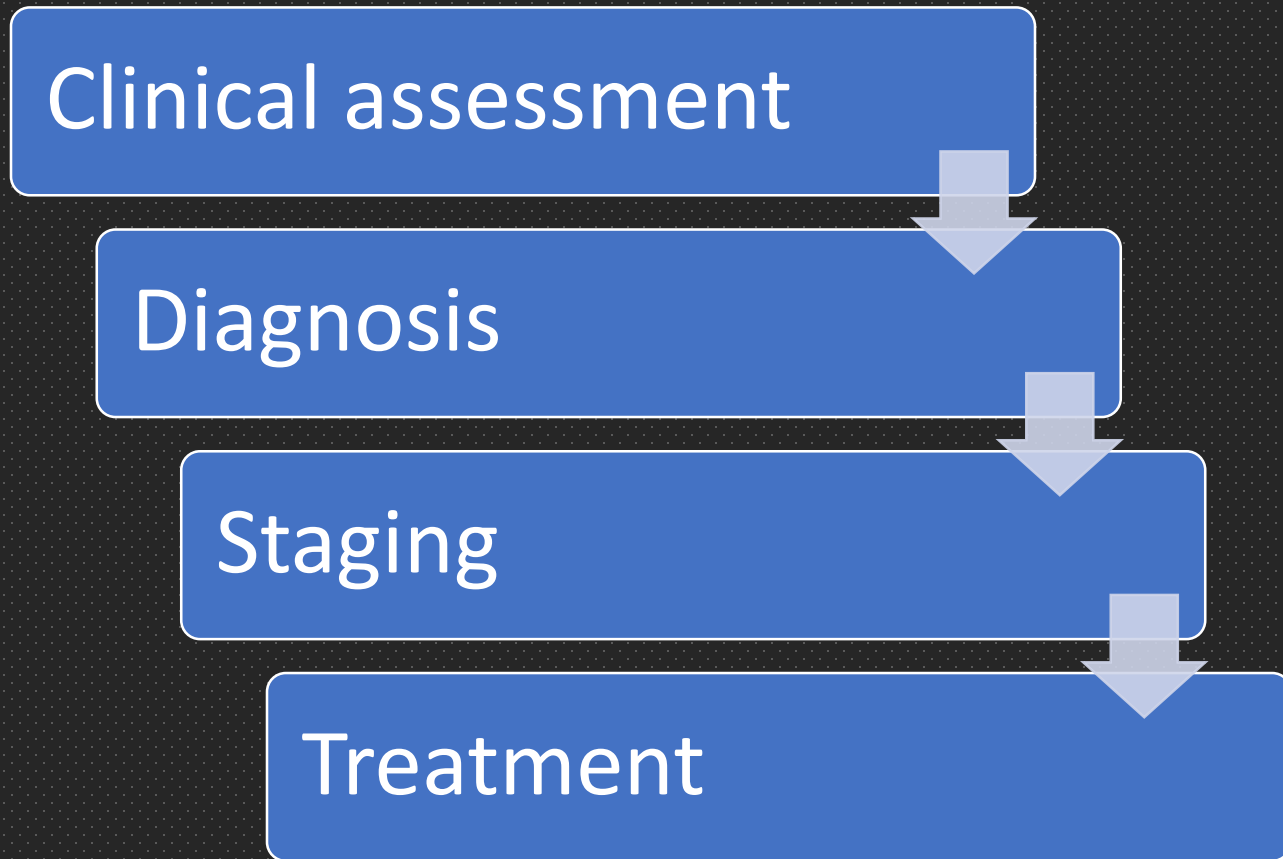
## NET Are the Second Most Prevalent Type of Gastrointestinal Malignancy



1. National Cancer Institute. SEER Cancer Statistics Review, 1975-2004. [http://seer.cancer.gov/csr/1975\\_2004](http://seer.cancer.gov/csr/1975_2004).

2. Modlin IM, Lye KD, Kidd M. *Cancer*. 2003;97(4):934-959.

# Standard approach to malignancy



# Approach to NET

Clinical assessment

```
graph TD; A[Clinical assessment] --> B[Diagnosis]; B --> C[Grading]; C --> D[Staging]; D --> E[Treatment];
```

Diagnosis

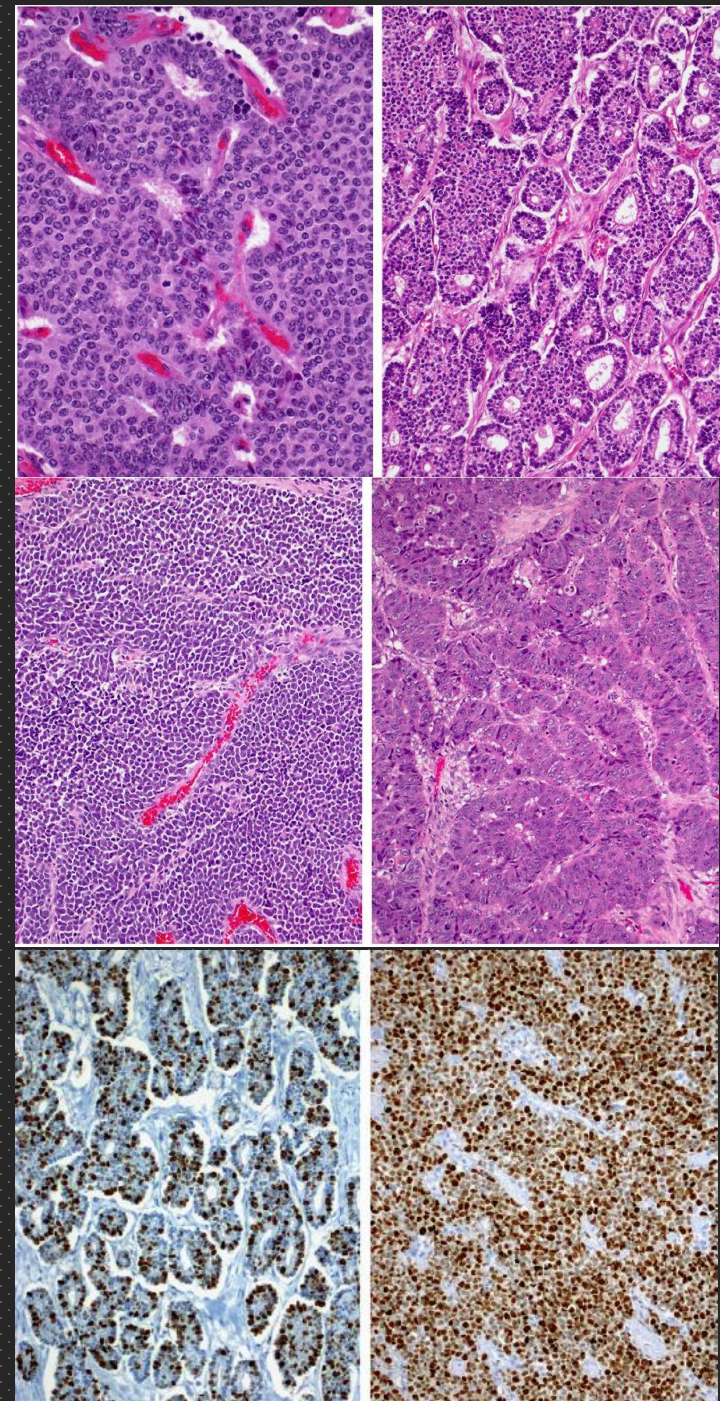
Grading

Staging

Treatment

# How do we confirm diagnosis and grade?

- FNA adequate for diagnosis in most cases
  - CgA
  - Synaptophysin
- FNA not sufficiently accurate to grade tumours in many cases
- Core biopsy preferred for grading
- Grade of metastases may be higher than that of primary





# Grading WHO 2017

- Ki-67
- Mitotic index
- Cell morphology (2017)

## 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

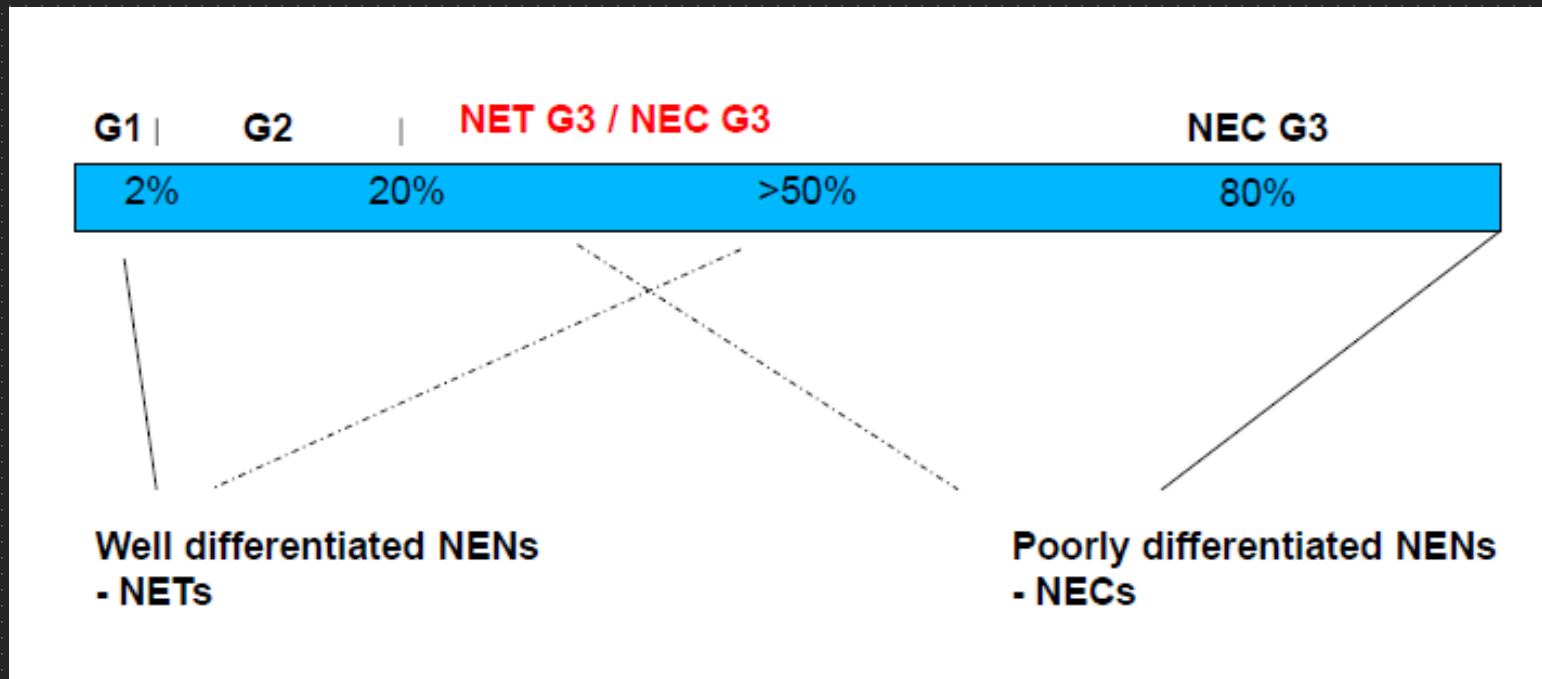
Neuroendocrine carcinoma (NEC) G3	>20 %	>20/10 HPF
Small cell type		
Large cell type		

### Mixed neuroendocrine-nonneuroendocrine neoplasm (MiNEN)

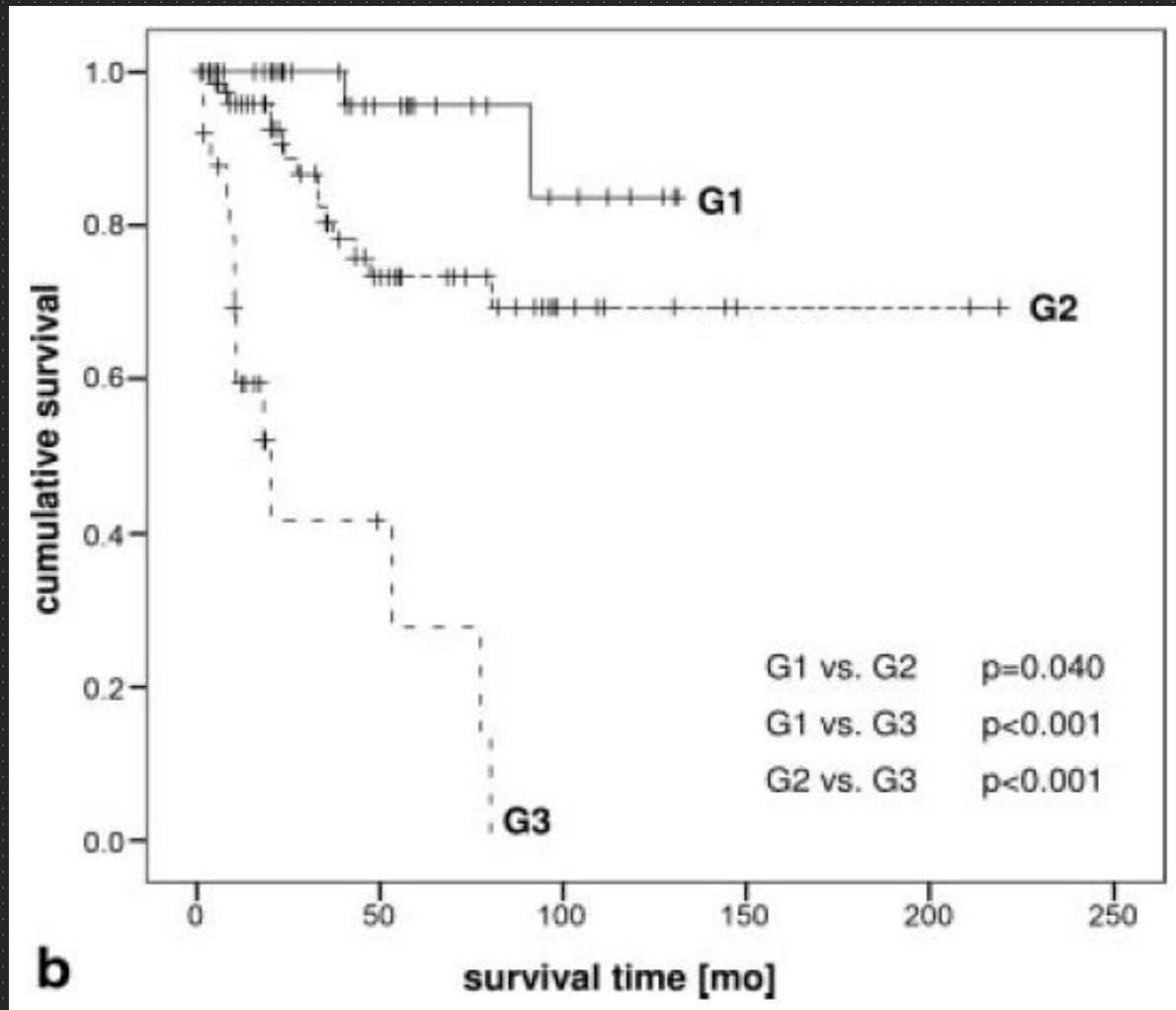
\* Ki67 index is based on at least 500 cells in areas of higher nuclear labeling ("hot spots"); mitoses in 50 high power fields (HPF, 0.2mm<sup>2</sup>) in areas of higher density and expressed per 10 HPF (2.0 mm<sup>2</sup>); the final grade based on which ever index (mitotic rate or Ki67) places the 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.

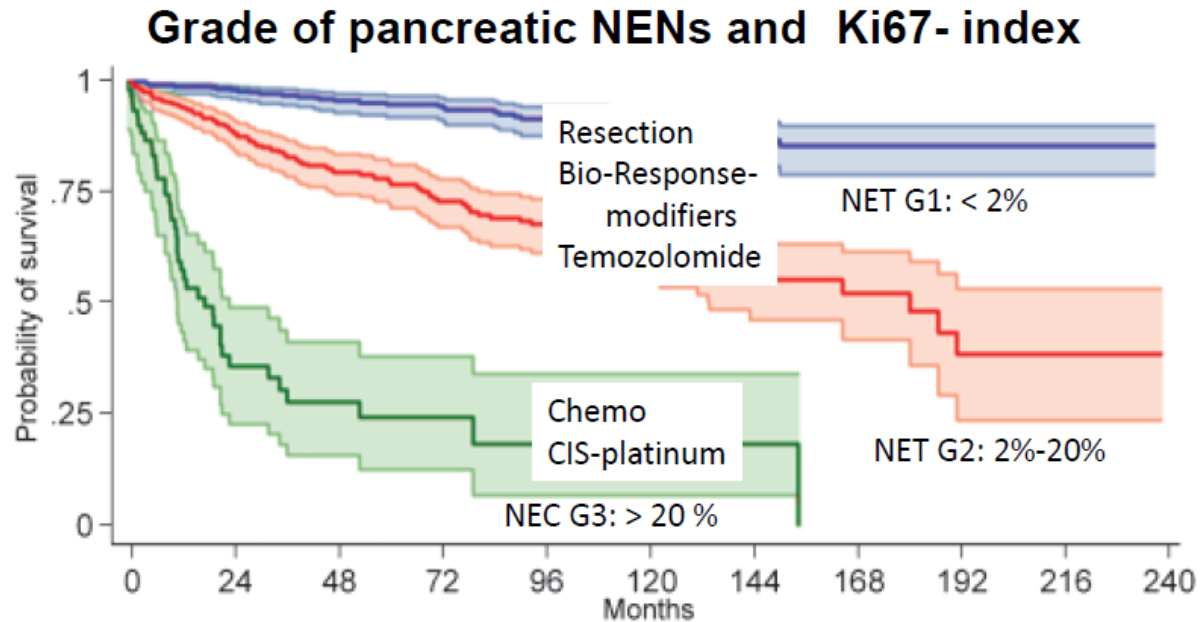
# PNENs and Ki-67



# Survival correlates with grading



# Relevance of grading



No at risk

G1	483	378	280	225	163	120	71	52	31	15	6
G2	380	278	196	133	89	59	33	17	9	4	1
G3	63	15	9	7	2	1	1	0	0	0	0



Staging

# Staging of GEP-NENs According to ENETS/WHO/AJCC

## ENETS/AJCC TNM Staging Systems

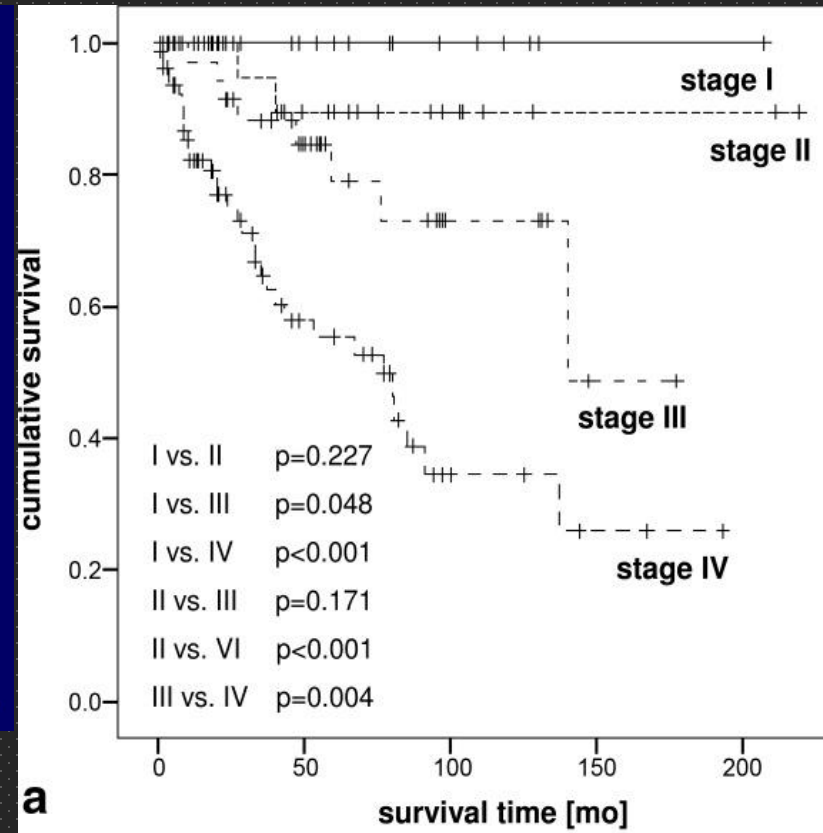
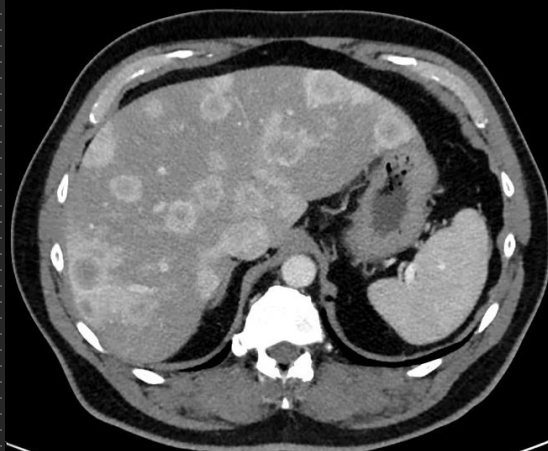
### ENET/AJCC Classification Criteria – GI NET

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

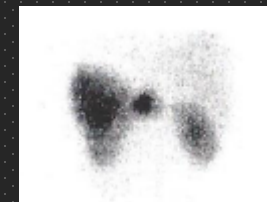
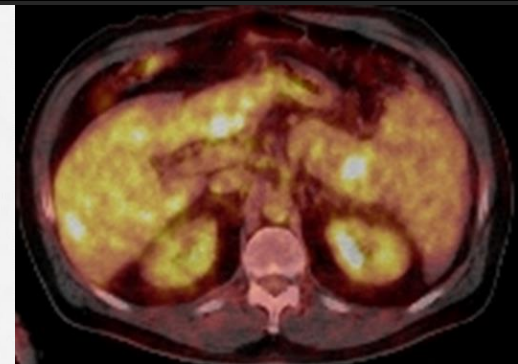
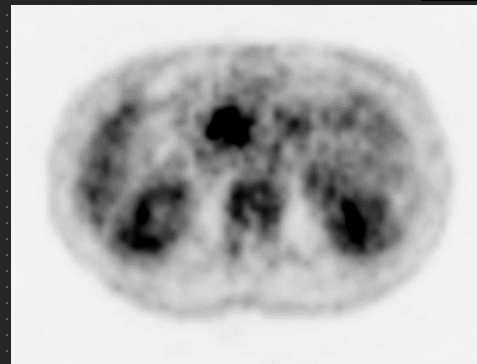
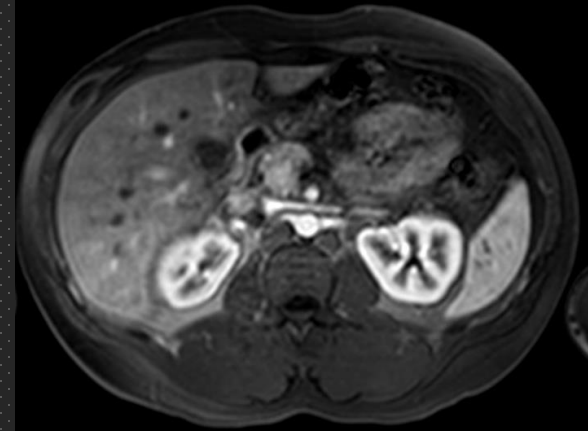
<sup>1</sup>Rindi G, et al. *Virchows Arch.* 2006;449:395-401. <sup>2</sup>Rindi G, et al. *Virchows Arch.* 2007;451:757-762.  
<sup>3</sup>American Joint Committee On Cancer. *AJCC Cancer Staging System.* 7<sup>th</sup> ed.



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

# How to stage?

- General
  - CAT scan
  - MRI
- Somatostatin receptor imaging
  - Gallium PET/CT (Dotatate, Dotatoc etc)
    - G1 and low G2
    - Ki-67 < 10%
  - Octreoscan
  - Tektrotyd scan
- FDG PET
  - G2 and G3
  - Ki-67 > 10%
  - Does not depend on SS receptor



Primary and metastases may have different grading

Management



# NET Treatment Options

Modality	Disciplines Involved
• Surgical Resection	Surgery
	Anaesthesiology
	Intensive Care
• Chemotherapy	Oncology
• Targeted Therapy	Oncology
• Biological Therapy - Somatostatin Analogs (SSA)	Oncology
• Radiotherapy	Radiation Therapy
• Ablation – RFA or MWA	Interventional Radiology
• Transarterial embolisation / radioembolisation	Interventional Radiology Radiation Therapy
• Peptide Receptor Radiation Therapy (PRRT)	Nuclear Medicine
• Hormonal control	Endocrinology

A multidisciplinary disease requires  
a Multi-Disciplinary Team in a  
Multi-Disciplinary Referral Centre

The diagram features a central white text box with a black border. Surrounding this box are several blue circles, each containing the name of a medical discipline. The circles are arranged in a roughly circular pattern, with some overlapping. The disciplines listed are: Radiation Therapy, Diagnostic Radiology, Interventional Radiology, Nuclear Medicine, Endocrinology, Surgery, and Gastroenterology. There are also several empty blue circles visible in the diagram.

Radiation  
Therapy

Diagnostic  
Radiology

Interventional  
Radiology

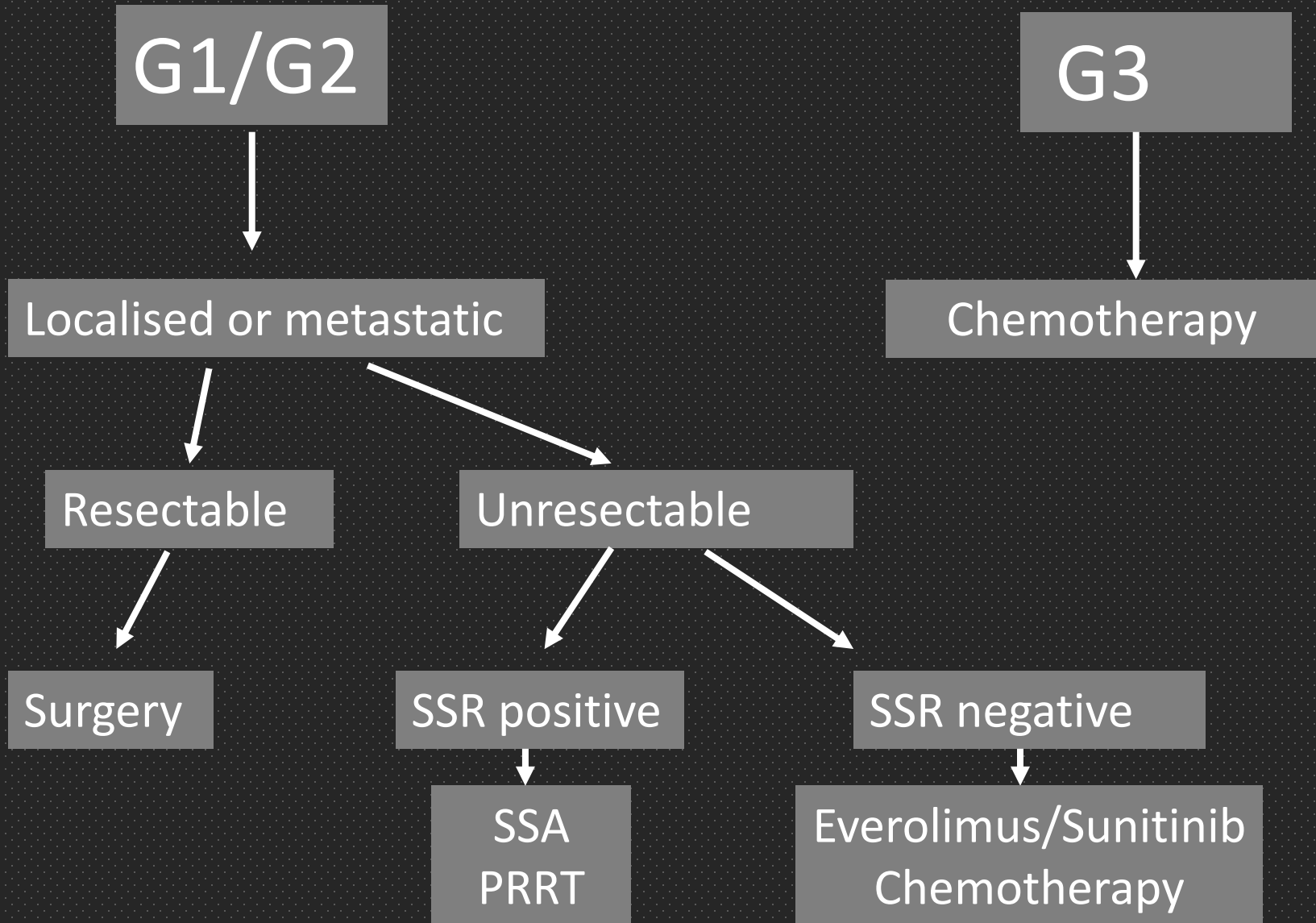
Gastroenterology

Nuclear  
Medicine

Surgery

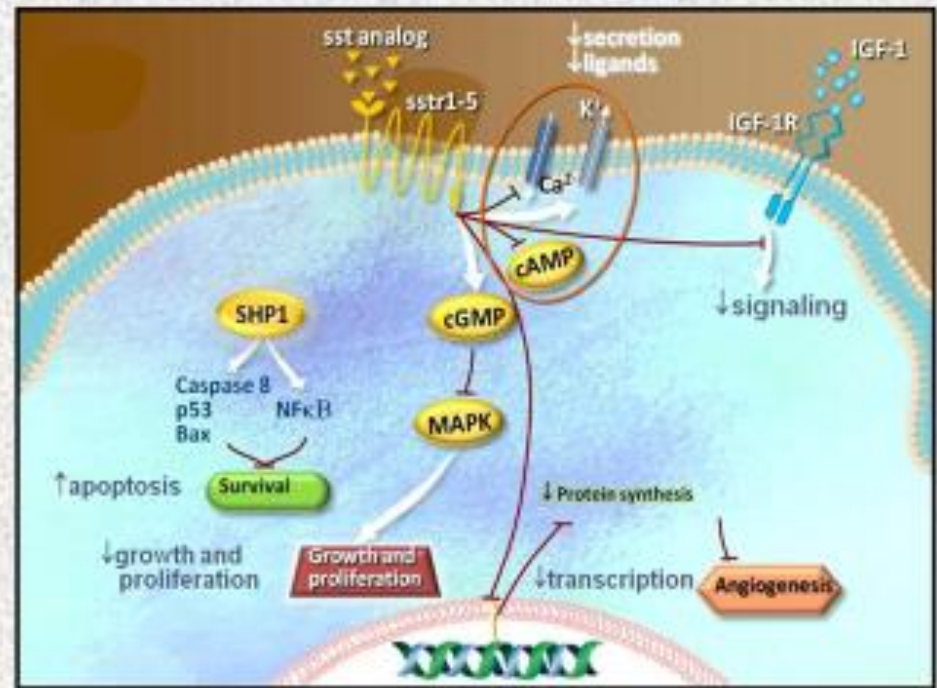
Endocrinology

# Management principles



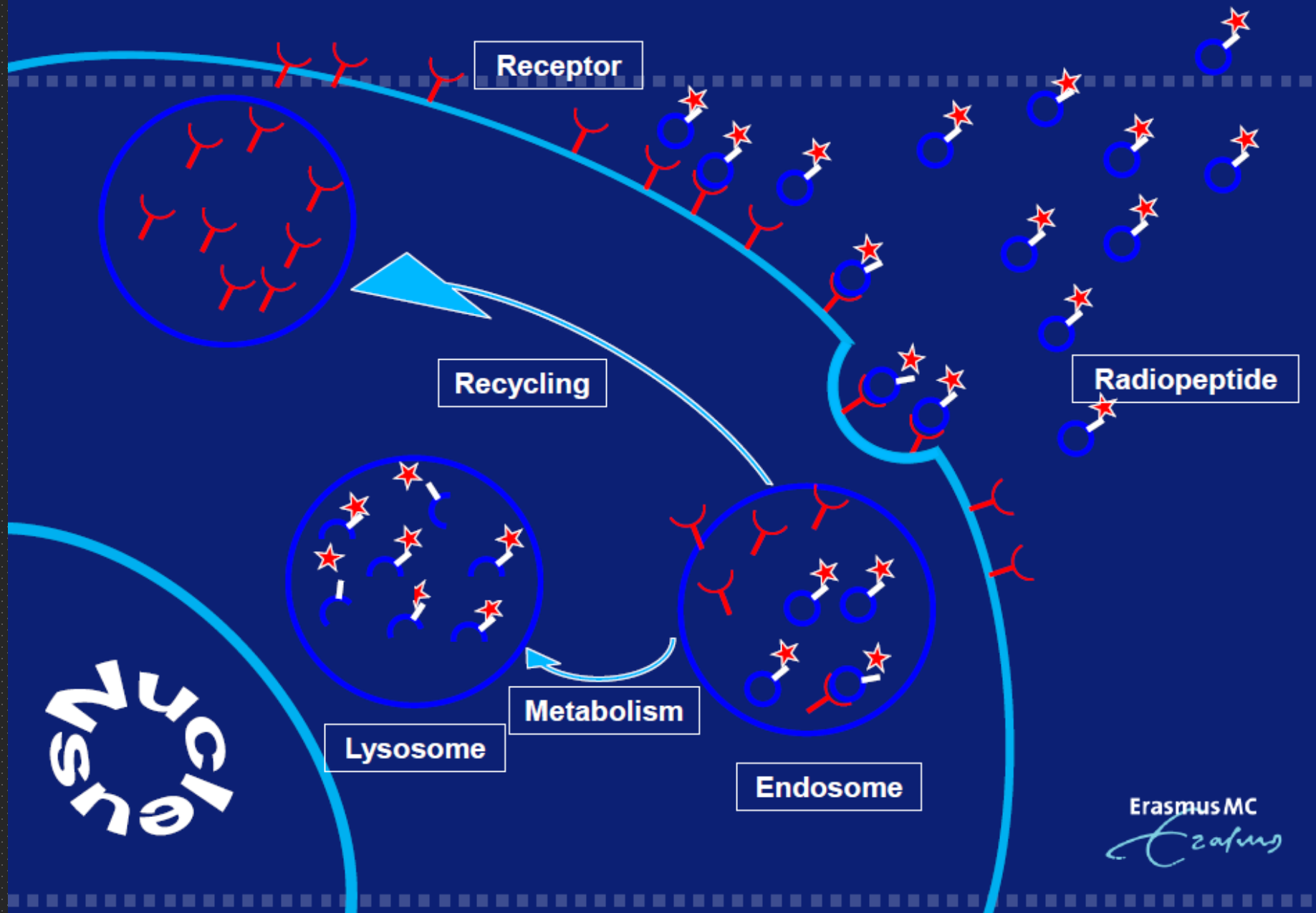
# Somatostatin Receptors and Somatostatin Analogs (SSA) in NETs

- More than 90% of NET express somatostatin receptors<sup>1,2</sup>
  - Somatostatin receptors can be divided into five subtypes, STRs1-5, based on structure and function
  - In NETs, SSTR2, SSTR5, and SSTR1 are most frequently expressed, followed by SSTR4 and SSTR3<sup>3</sup>
- Somatostatin signaling inhibits secretory and proliferative activity<sup>4</sup>; acting on the IGF/PI3K/mTOR pathway<sup>5</sup>
- Octreotide reduces severe diarrhoea and flushing episodes by  $\geq 50\%$  in approximately 74% to 89% of patients with carcinoid syndrome<sup>4,6,7</sup>



IGF = insulin-like growth factor; PI3K = phosphoinositide 3-kinase; mTOR = mammalian target of rapamycin

# PRRT: Mechanism of Action



# Somatostatin analogues (SSA) vs PRRT

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

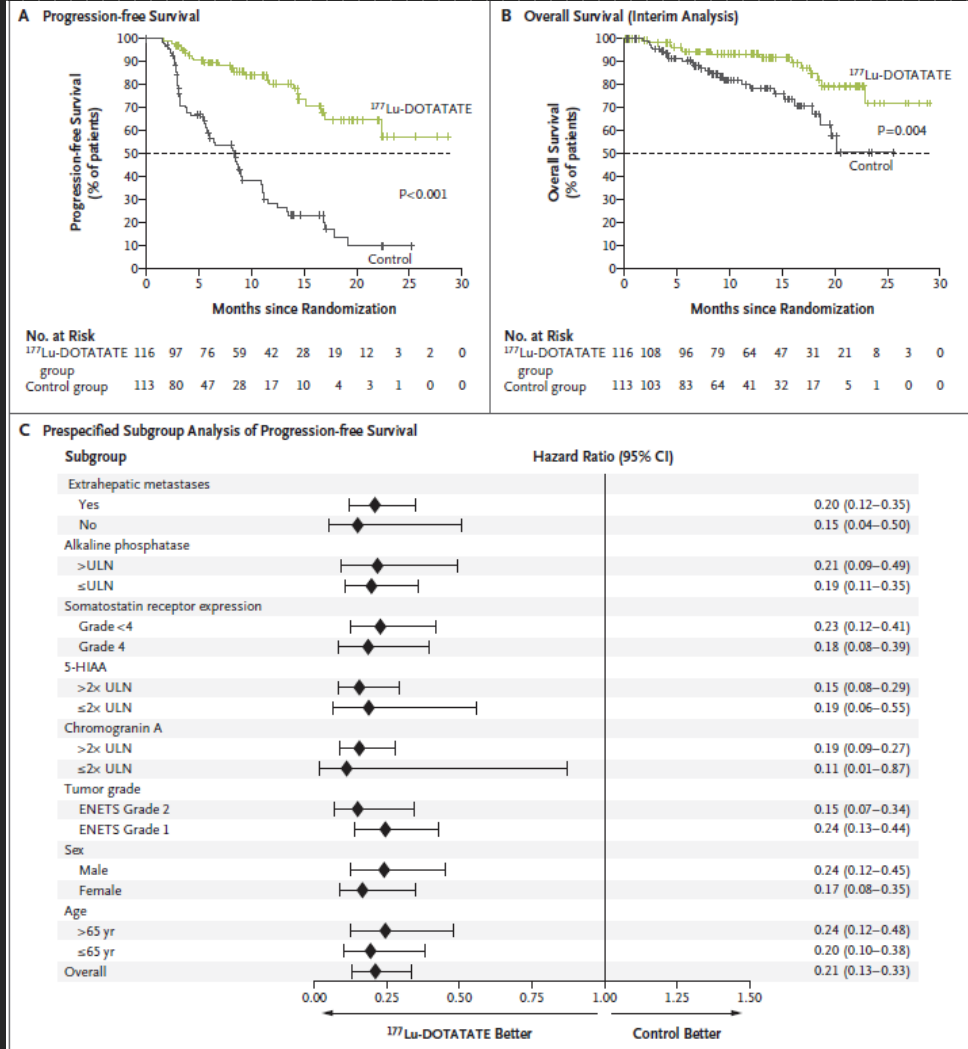
## Phase 3 Trial of <sup>177</sup>Lu-Dotatate for Midgut Neuroendocrine Tumors

J. Strosberg, G. El-Haddad, E. Wolin, A. Hendifar, J. Yao, B. Chasen, E. Mittra, P.L. Kunz, M.H. Kulke, H. Jacene, D. Bushnell, T.M. O'Dorisio, R.P. Baum, H.R. Kulkarni, M. Caplin, R. Lebtahi, T. Hobday, E. Delpassand, E. Van Cutsem, A. Benson, R. Srirajaskanthan, M. Pavel, J. Mora, J. Berlin, E. Grande, N. Reed, E. Seregni, K. Öberg, M. Lopera Sierra, P. Santoro, T. Thevenet, J.L. Erion, P. Ruszniewski, D. Kwkkeboom, and E. Krenning, for the NETTER-1 Trial Investigators\*

N ENGL J MED 376;2 NEJM.ORG JANUARY 12, 2017

## Netter-1 Trial

<sup>177</sup>Lu-Dotatate + Octreotide 30mg/month  
VS  
Octreotide 60mg/month



# Using Gallium-PET and FDG-PET to guide treatment

Gallium-PET Positive FDG-PET Negative	Gallium-PET Positive FDG-PET Positive	Gallium-PET Negative FDG-PET Positive
PRRT SSA	PRRT/SSA plus Everolimus/chemotherapy	Everolimus Chemotherapy

# Summary

- NETs have an increasing incidence and relatively high prevalence
- Survival is dependent on grade and stage of disease
- Grade and stage dictate management
- Surgical resection best treatment for resectable NETs, whether localized or metastatic, if complete resection possible
- Gallium-PET and FDG-PET can be used to guide treatment