

Top Ten List of Things You Need to Know About Neuroendocrine Tumors



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Objectives

- » overview of GI-NETs
- » recognize the changing paradigm of oncological surgical therapy in NETs
- » understand the role you as a GI specialist plays in the treatment of NETs

Format



Gastric NETs

PNETs

Small Bowel NETs

Appendix NET

Rectal

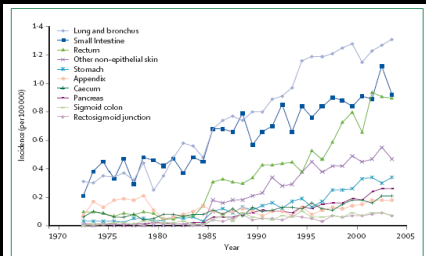


Figure 2: Increased incidence of carcinoid tumours, US population 1973-2005
 Overall increase recorded for all primary sites during this period. Data from SEER database, US National Cancer Institute.

Yao JC *et al* *J Clin Oncol* 26;2008
 Frilling A *Endo Relat Cancer et al* 19;2012

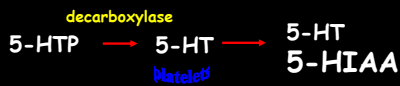
Classification of 'Carcinoid' Tumors

- » Foregut
 - » lung, thymus, gastric, pancreas
- » Midgut
 - » jejunum, ileum, appendix, Rt colon
- » Hindgut
 - » Transverse & Lt colon, rectum

Williams & Sandler *Lancet* 1;1963

Biochemical

Typical (midgut)



Atypical (foregut, hindgut)



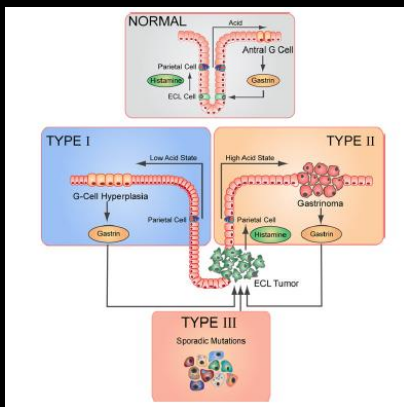
5-HT = serotonin

Terminology

- » Neuroendocrine tumors (NET)
- » differentiation
- » *Ki67*, mitoses
- » site of origin
- » endocrinopathy
- » 'Carcinoid' tumors
- » arise in the small bowel (midgut)
- » produce Carcinoid syndrome

Top Ten Need to Know about NETs

10.Type 1 gastric NETs - endoscopic surveillance



Gastric NETs Type I

- » ECL cells response to gastrin
- » multi-centric, benign
- » > 2cm in malignant potential
- » 5-year survival - 98%

*Anti-parietal AntiB, CgA,
uHistamine, EndoUS*

Gastric NETs Type II

- » associated with ZES/MEN I (30%)
- » metastases to lymph nodes - 30%
- » distant - 10%
- » 5-year survival - 90%

*confirm ZES (pH<2, gastrin>1000)
MENIN testing,
HPT (Ca, Po, PTH)
CT / Octreotide / EndoUS*

Gastric NETs Type III

- » most aggressive (5-year - 20%)
- » regional nodes 20 - 50%
- » distant metastases - 65%
- » Carcinoid Syndrome 5 - 30%
- » histamine mediated

oncological work-up, R/O function

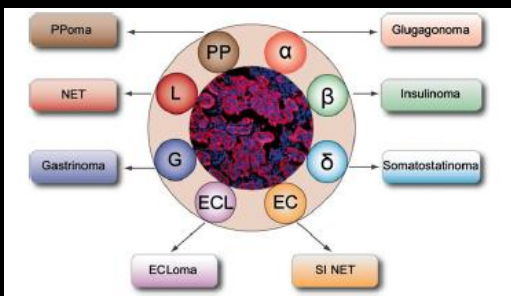
Top Ten Need to Know about NETs

- 8. Survival benefit 70% reduction in Hepatic NETs
- 9. Small nonfunctioning PNETs can be observed
- 10. Type 1 gastric NETs - endoscopic surveillance

Pancreatic NETs

- » 1/100,000
- » 1-2% pancreatic neoplasms
- » MEN I and vHL
- » 2/3 endocrinopathy
- » 1/3 non-functioning
- » Cg A elevated in 60 -80%

Pancreatic islet cell



PNETs

Functional screen

history, exam
gastrin, insulin/glucose, glucagon,
pancreatic polypeptide, CgA

Anatomical imaging

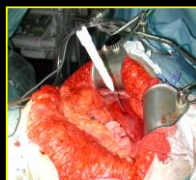
CT or MRI
Octreotide, +/- mIBG
+/- EndoUS

Surgery for Functioning PNET

- » resuscitate the patient FIRST
- » adhere to oncological principles
 - » head - Whipple procedure
 - » body/tail - en bloc +/- spleen
 - » small < 2 cm - enucleation
- » debulking can reduce endocrinopathy

Metastatic Functional PNETs

- » cytoreduction
- » endocrinopathy can be life-threatening

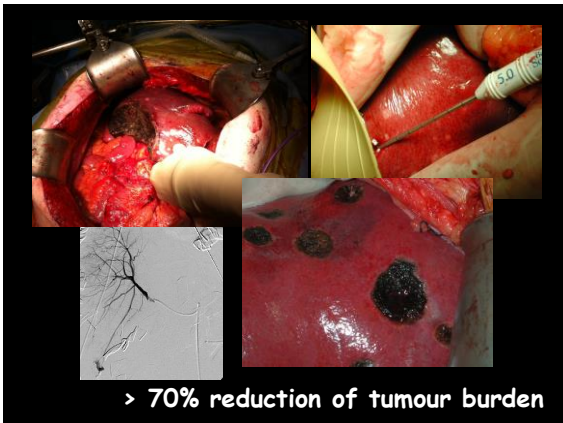


Hepatic resection for NET mets

- » cytoreduction - ↓ endocrinopathy
biochemical response
- » improves symptoms / palliation
- » improves survival
74% 5-yr 51% 10-y*



Chamberlain J *Am Coll Surg* 190;2000
 Norton JA *Surgery* 134;2003
 Sarmiento JM *J Am Coll Surg* 197;2003
 Mayo SC *et al Ann Surg Oncol* 17;2010*
 Saxena A *et al Surg Oncol* 21;2012*



> 70% reduction of tumour burden

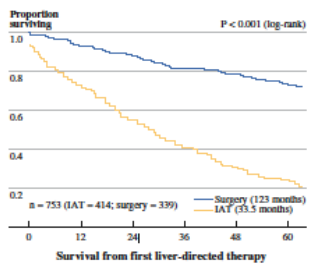


FIG. 1 Overall survival of patients with NELM stratified by receipt of surgery versus intra-arterial therapy (IAT) (P < 0.001)

Mayo SC *et al Ann Surg Oncol* 18;2011

Non-Functioning NET of Pancreas

- » 1/3 of pancreatic NET
- » incidental finding - small or large
- » Dx on biopsy and serum CgA, PP
- » ?surgical debulking impacts disease*

Cusati D *et al* J Am Coll Surg 215;2012

Non Functioning Pancreatic NET

- » overall median survival - 3.2 years
 - » complete resection - 7 yr
 - » locally advanced unresectable 5 yr
 - » unresectable metastatic - 2 yr
- » < Ro resection - no survival benefit

Solorzano C *et al* Surg 130;2001

Cytoreduction of Pancreatic NET

- » metastatic disease
resection G1/G2
5-yr 70% 10-yr 42%*
- » ? facilitate other therapies

Cusati D *et al* J Am Coll Surg 215;2012
Saxena A *et al* Surg Oncol 21;2012*

Canadian Consensus Guidelines PNETs

Small incidental PNETs
observation

<2cm

Low Ki67% (G1/2)

Locally advance
selective multivisceral Sx

Metastatic disease - resection G1/G2

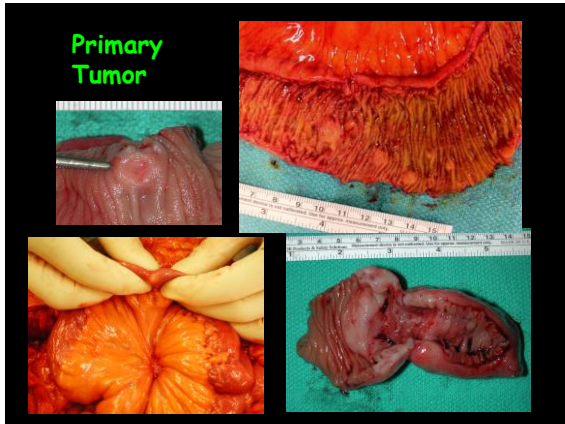
Singh S et al Ann Surg Oncol epress 2015

Top Ten Need to Know about NETs

7. SBNET both the primary and mesenteric disease must be addressed
8. Survival benefit 70% reduction in Hepatic NETs
9. Small nonfunctioning PNETs can be observed
10. Type 1 gastric NETs - endoscopic surveillance

Small Bowel NETs

- » 2nd most common 30 - 42%
- » 1.65 - 2 per 100,000 annually
- » Carcinoid syndrome - 30%
- » multiple tumors 30 - 50%
- » 2nd primary malignancy 20 - 30%






- » retrospective review of 84 NET
- » 60 had 1^o resected vs 24 without
- » median progression free (56 vs 25 m)
- » mean survival (159 vs 47 m)
- » ? Tumor propagation factors

Givi B et al Surgery;140:2006

» multivariate analysis of 360 pt


» age, *Ki67*, resection of 1^o 
independent predictors of survival

Ahmed A *et al* *Endocrine-Related Cancer* 16;2009

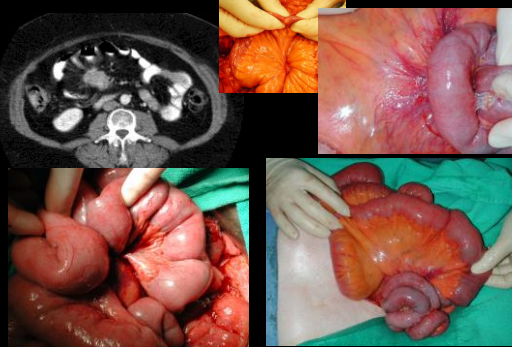
» 579 SB NETs
» median survival 10.9 years
vs. 2.65 not resected

Norlen O *et al* *World J Surg* 35;2011


Capurso G *et al* *Br J Surg* 99;2012



Mesenteric Disease



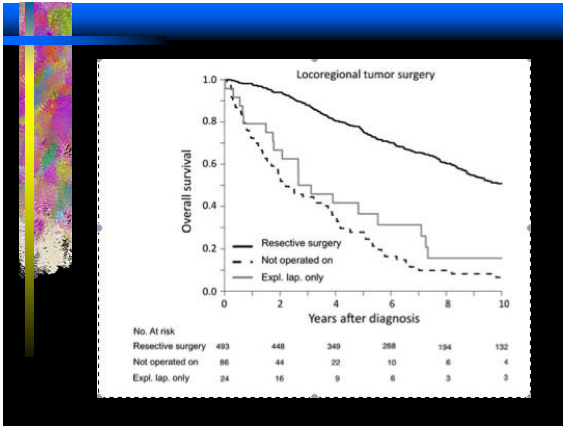
**Mesenteric resection
In Midgut Carcinoids**



» 493 resected locoregional disease
» 75% 5-years overall survival

» 110 unresected locoregional disease
» 28-37% 5-year

Norlen O *et al* *World J Surg epress*; 2012



Mortality from Small Bowel NETs

- » > 50% die of ischemic / SBO
- » 33% die of Carcinoid heart disease
- » 15% end-organ disease

Surgery for Small Bowel NETs

- » improved QOL
- » improves symptoms / palliation
- » delays onset of ischemic / SBO
- » prolonged survival

Hellman P *et al* World J Surg 26;2002
 Akerstrom G *et al* J Surg Oncol 89;2005
 Chambers A *et al* Surgery 144;2008
 Norlen O *et al* World J Surg 35;2011

Top Ten Need to Know about NETs

6. Rt hemi is for prognostication in appy NETs
7. SBNET 1^o and mesenteric disease must be addressed
8. Survival benefit 70% reduction in Hepatic NETs
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Appendiceal NETs

- » most common
- » incidental finding (0.3 % of appendectomies)
- » 70 - 90% < 1 cm
- » Carcinoid syndrome - rare
- » multiple tumours - 4%
- » 2nd primary malignancy - 13%
- » 5-yr survival 99%



Pathological Features

- » size
- » positive nodes
- » angio / lymphatic invasion
- » mesoappendix involvement
- » margins
- » serosal invasion
- » proliferation index
- » Goblet cell



Treatment of Appendiceal NETs

Size	Risk of Lymph Nodes	Treatment
≤ 1 cm	0%	appendectomy
1 - 2 cm	1 - 10%	pathology
≥ 2 cm	20 - 30%	Right hemicolectomy

916 1-2cm appendiceal NET
 42% appendectomy / 58% Rt Hemi
 22% lymphovascular invasion
 Positive LN 25% vs 28%

No survival benefit Rt hemicolectomy
Nussbaum DP et al J AM Coll Surg 220;2015

213 pediatric cases with invasion
 81 - Rt Hemi vs 132 appy only
 No documented recurrences

Henderson L et al J Ped Surg 49;2014

Treatment of Appendiceal NETs

Size	Risk of Lymph Nodes	Treatment
≤ 1 cm	0%	appendectomy
1 - 2 cm	1 - 10%	segmental resection
≥ 2 cm	20 - 30%	<i>prognosticating</i> Right hemicolectomy

Top Ten Need to Know about NETs

- 5. Rectal NETs are size dependant
- 6. Rt hemi is for prognostication in appy NETs
- 7. SBNET 1^o and mesenteric disease must be addressed
- 8. Survival benefit 70% reduction in Hepatic NETs
- 9. Small nonfunctioning PNETs can be observed
- 10. Type 1 gastric NETs - endoscopic surveillance

Rectal NETs

- » 3rd most common 16%
- » 1 - 3% of all rectal tumors
- » rectal bleeding or incidental
- » Carcinoid syndrome - rare
- » multiple tumors 0 - 3%
- » 2nd primary malignancy 7 - 32%
- » size dependent prognosis

History / exam

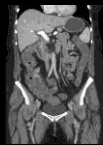
EndoRectal US

~~u5~~ HIAA

CgA

Anatomical imaging - MRI

Octreotide scan



Endoscopic and MRI surveillance
Stage II and III

Anthony L et al Pancreas 39;2010

Treatment of Rectal Carcinoids

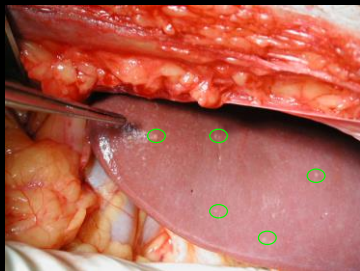
Size	Risk of Lymph Nodes	Treatment
≤ 1 cm	7% transanal	
1 - 2 cm ?	individualize	
> 2 cm	90%	TME

Overall 5-yr survival 70 - 85%

Top Ten Need to Know about NETs

4. Conventional imaging underestimated 35% NETs
5. Rectal NETs are size dependant
6. Rt hemi is for prognostication in appy NETs
7. SBNET 1^o and mesenteric disease must be addressed
8. Survival benefit 70% reduction in Hepatic NETs
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10. Type 1 gastric NETs - endoscopic surveillance

- » SB NETs patients with clinical Carcinoid Syndrome had negative preoperative imaging of their liver

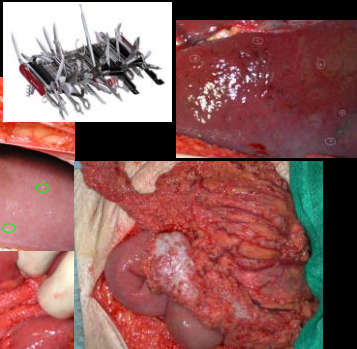


64 SB NETs underwent laparotomy

	Imaging CT, MRI, mIBG Octreotide scan	@OR
Mesenteric	47 (73%)	56 (88%)
Hepatic	42 (66%)	49 (77%)
Peritoneal	4 (6%)	16 (25%)

Chambers A et al J Am Coll Surg 211:2010

Be Prepared



Top Ten Need to Know about NETs

3. Somatostatin analogues mainstay Rx in NETs
4. Conventional imaging underestimated 35% NETs
5. Rectal NETs are size dependant
6. Rt hemi is for prognostication in appy NETs
7. SBNET 1^o and mesenteric disease must be addressed
8. Survival benefit 70% reduction in Hepatic NETs
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Somatostatin Analogues

- > inhibits release of hormones and growth factors
- > anti-proliferative effect
 - > *sst 2*
- > induces apoptosis
- > peri-tumoral veins high affinity *sst*
 - > ? angiogenesis effect

Hormonal therapy

- > *somatostatin analogs*
 - > 70% biochemical
 - > 60 - 80% symptomatic (QOL)
 - > 8% tumor (40% stabilization)
- > tachyphylaxis (median 12 months)

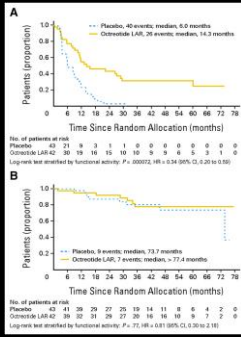
Appetecchia M. J Exp & Clin Cancer Res 29;2010

PROMID Study

- >> 85 Mid-gut NET pts randomized LAR or placebo
- >> Median time to progression 14 vs. 6 months
- >> Stable disease @ 6 months 67% vs. 37%

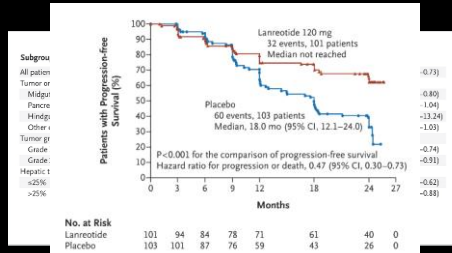
Rinke A *et al* J Clin Oncol 27;2009

PROMID



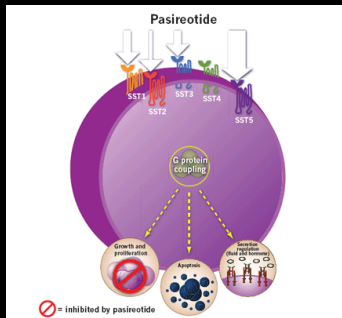
Rinke A J Clin Oncol et al 27;2009

CLARINET Study Lanreotide vs. Placebo GI-NET



Caplan M et al/NEJM 371:2014

Pasireotide SMO-230



Top Ten Need to Know about NETs

2. Chemotherapy / Targeted Rx increasing role
3. Somatostatin analogues mainstay Rx in NETs
4. Conventional imaging underestimated 35% NETs
5. Rectal NETs are size dependant
6. Rt hemi is for prognostication in appy NETs
7. SBNET 1^o and mesenteric disease must be addressed
8. Survival benefit 70% reduction in Hepatic NETs
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10. Type 1 gastric NETs - endoscopic surveillance

Tyrosine Kinase Inhibitors

Sunitinib

17% response rate
68% stable disease

Kulke MH et al J Clin Oncol 26;2008

mTOR inhibitors

Everolimus + LAR

20% response
70% stable disease
3-yr survival 78%

Yao JC et al J Clin Oncol 26;2008

Chemotherapy

Capecitabine and Temozolomide

70% response rate
Median PFS - 18 months
OS of 92% at 2 years

Strosberg JR et al Cancer 117;2011

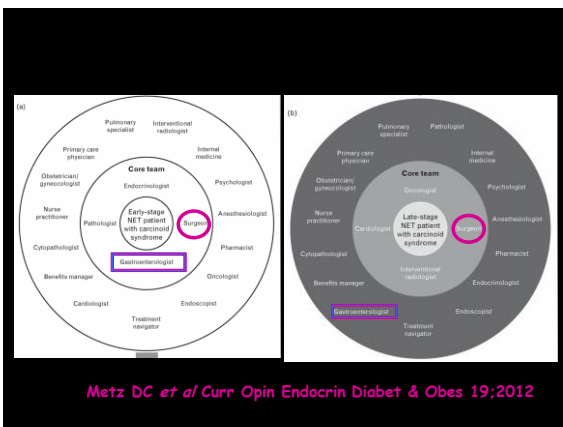
63 tumors

Cisplatin + etoposide
42% observed response
Duration 9 months

Hainsworth JD et al J Clin Oncol 24;2006

Top Ten Need to Know about NETs

1. Multidisciplinary approach is paramount
2. Chemotheapy / Targeted Rx increasing role
3. Somatostatin analogues mainstay Rx in NETs
4. Conventional imaging underestimated 35% NETs
5. Rectal NETs are size dependant
6. Rt hemi is for prognostication in appy NETs
7. SBNET 1⁰ and mesenteric disease must be addressed
8. Survival benefit 70% reduction in Hepatic NETs
9. Small nonfunctioning PNETs can be observed
10. Type 1 gastric NETs - endoscopic surveillance

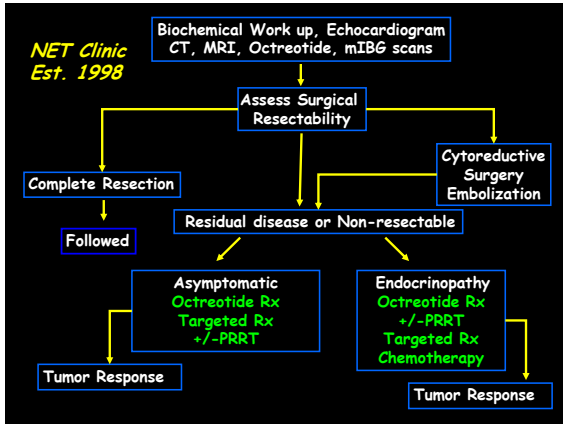


Multidisciplinary NET Clinic


- > endocrine surgeon
- > hepatobiliary surgeon
- > endocrinologist
- > medical oncologist
- > GP Oncologist
- > nuclear radiologist
- > nurse clinician

- > pathologist, gastroenterologists, interventional radiologists, palliative care, psychosocial support





Top Ten Need to Know about NETs



1. Multidisciplinary approach
2. Chemotherapy has a limited role in NETs
3. Somatostatin analogs are the mainstay of medical therapy in 35% NETs
4. Conventional chemotherapy is not effective in NETs
5. Rectal NETs are the most common site of origin
6. Rt hemi-gastrectomy is not indicated for NETs
7. SBNET (small bowel NET) is the most common type of NET disease
8. Survival is significantly better for pancreatic NETs compared to other NETs
9. Small number of NETs are observed in the liver
10. Type 1 neuroendocrine tumor (NET) requires surveillance
