Carcinoid/NETs
A Brief Review & Comments on Recent Developments

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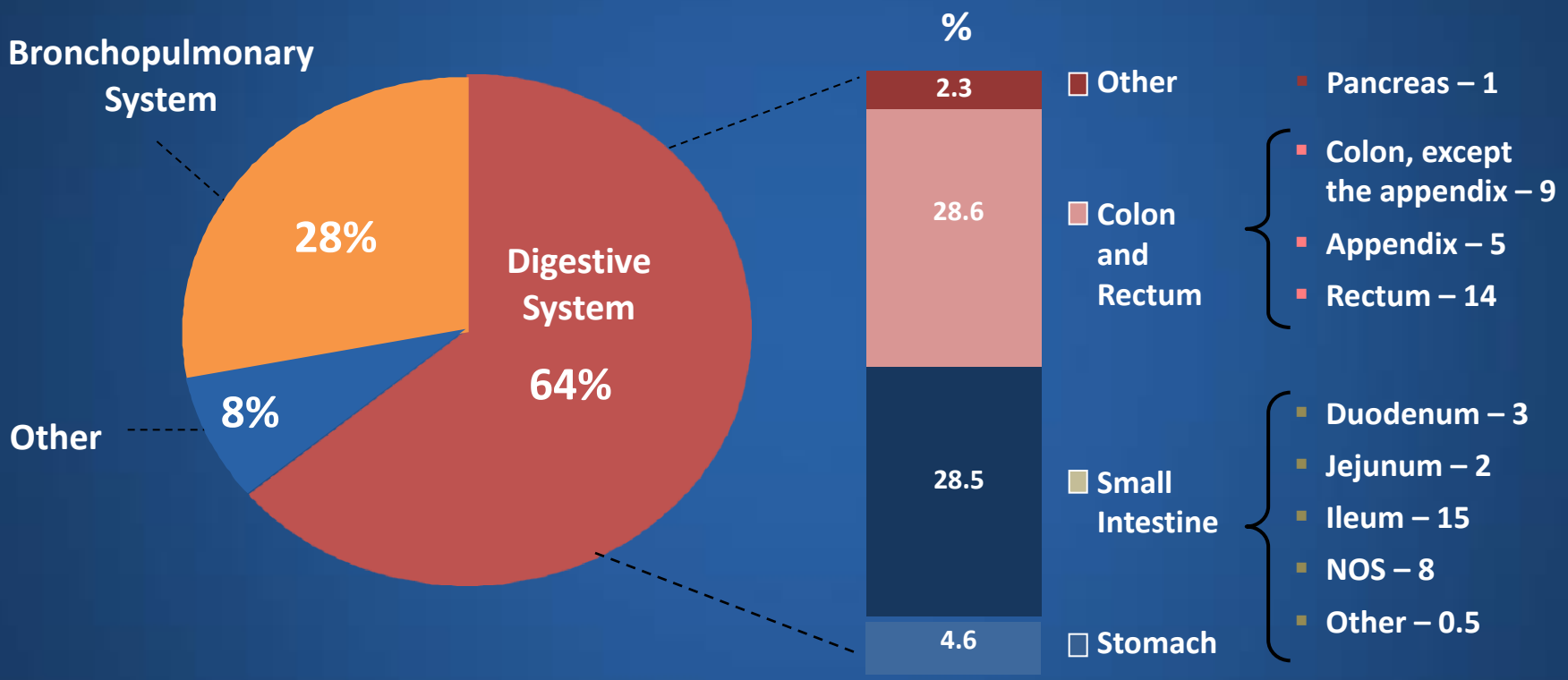
GEP-NETs

Tumor	Peptide	Symptoms/Syndrome
Carcinoid	Serotonin Tachy and bradykinins	Carcinoid syndrome
Insulinoma	Insulin	Hypoglycemia
VIPoma	VIP	Verner-Morrison
Glucagonoma	Glucagon	DM, NME*, cachexia
Somatostatinoma	Somatostatin	Bile stones, steatorrhea, DM
GRFoma	GH releasing factor	Acromegaly
Gastrinoma	Gastrin	Zollinger-Ellison Syndrome: Abdominal pain, diarrhea, GERD, ulcers

* Necrolytic migratory erythema

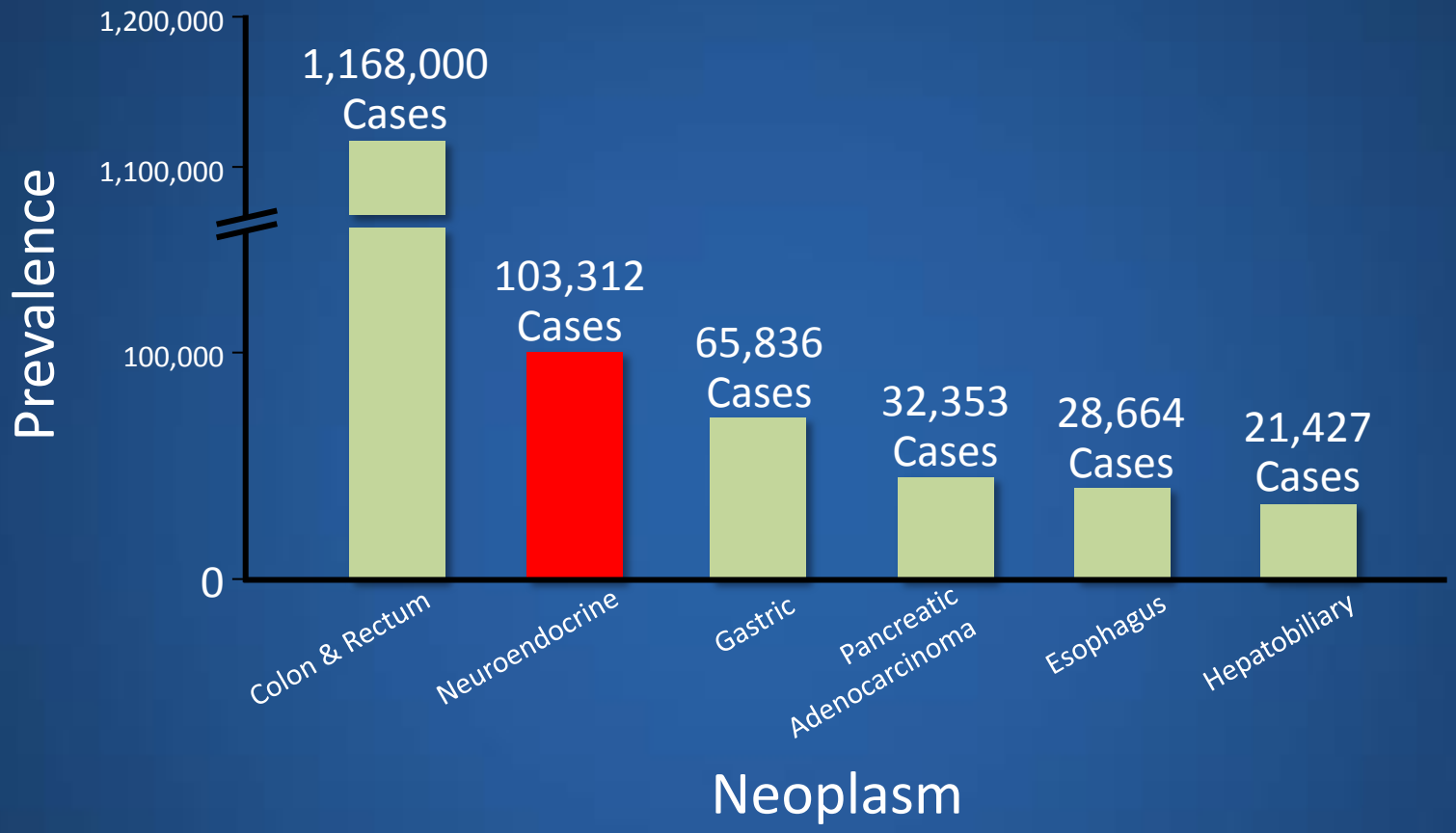
Distribution of Carcinoid Tumors by Site



NOS, not otherwise specified.

1. Modlin IM *et al.* A 5-decade analysis of 13,715 carcinoid tumors. *Cancer* 2003;97:934–959.

Prevalence of GI Cancers

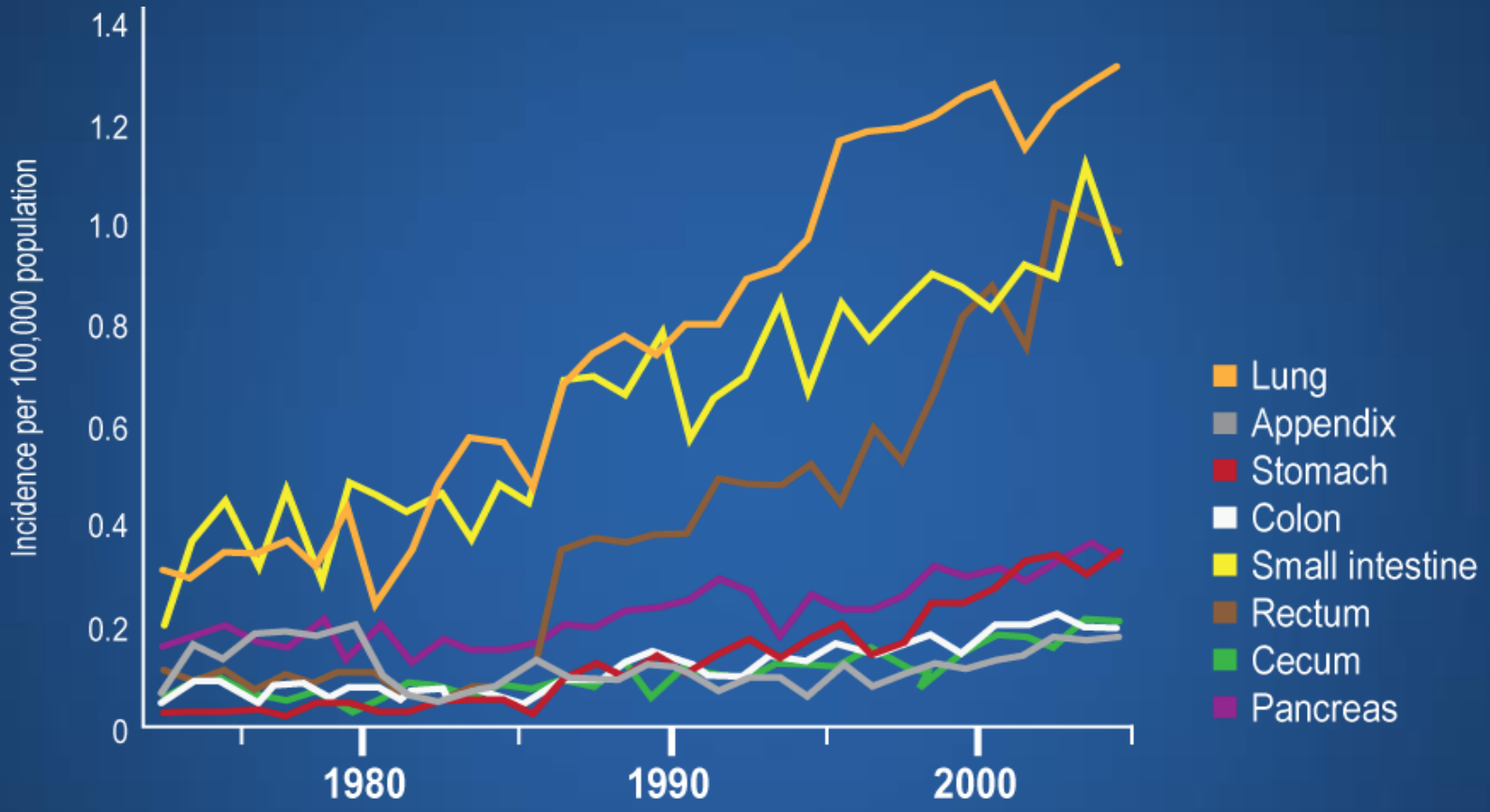


- Prevalence of GI NETs is more than three times greater than pancreatic adenocarcinoma[1]

Column 1 = SEER data for 2005; all other columns = 29-year prevalence analyses based on SEER data for 2004.

1. Yao JC *et al.* One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol* 2008;26:3063–3072.

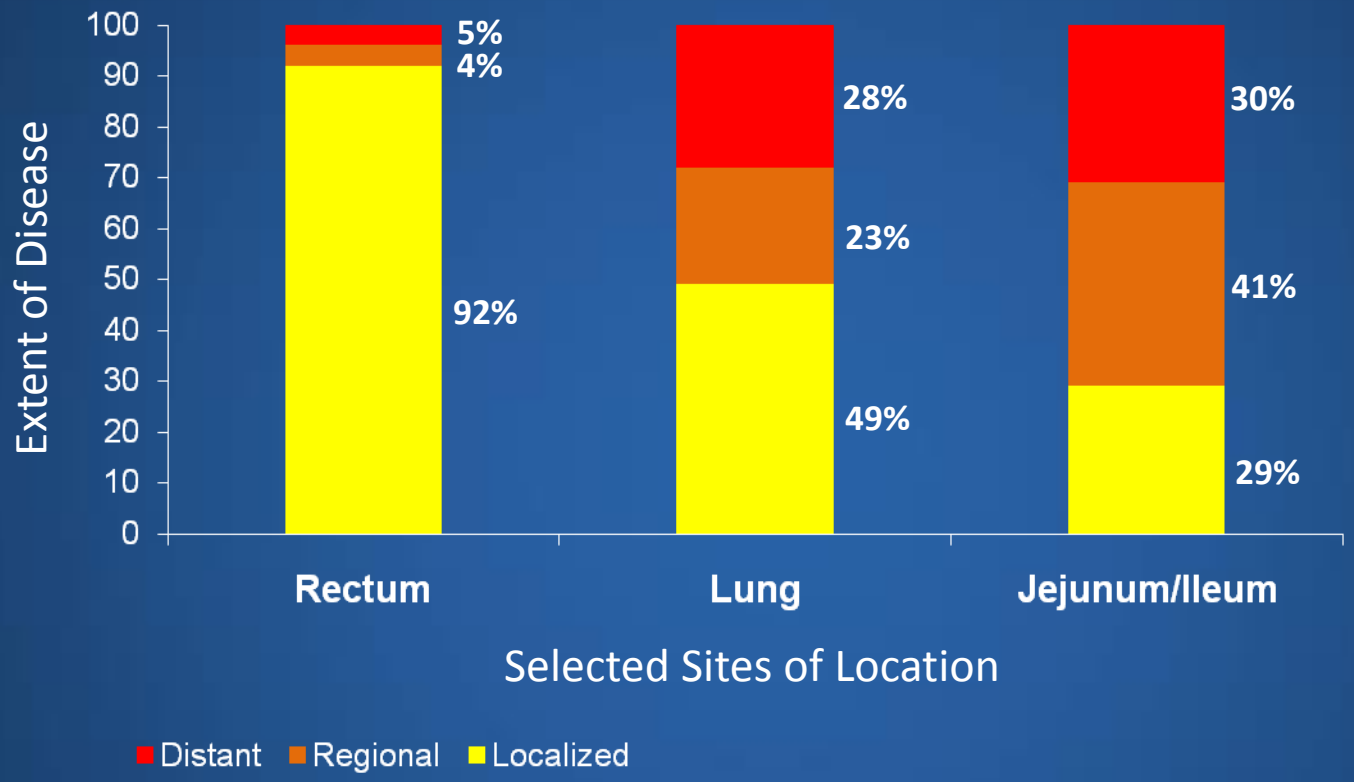
Incidence of NETs by Location



- Although the incidence of all NETs is increasing, the largest increase has been seen in the diagnosis of lung and small intestinal NETs[1]

1. Reprinted from *Lancet Oncology,* 9, Modlin IM *et al.* Gastroenteropancreatic neuroendocrine tumors. Pages 61–72, Copyright 2008, with perssion from Elsevier

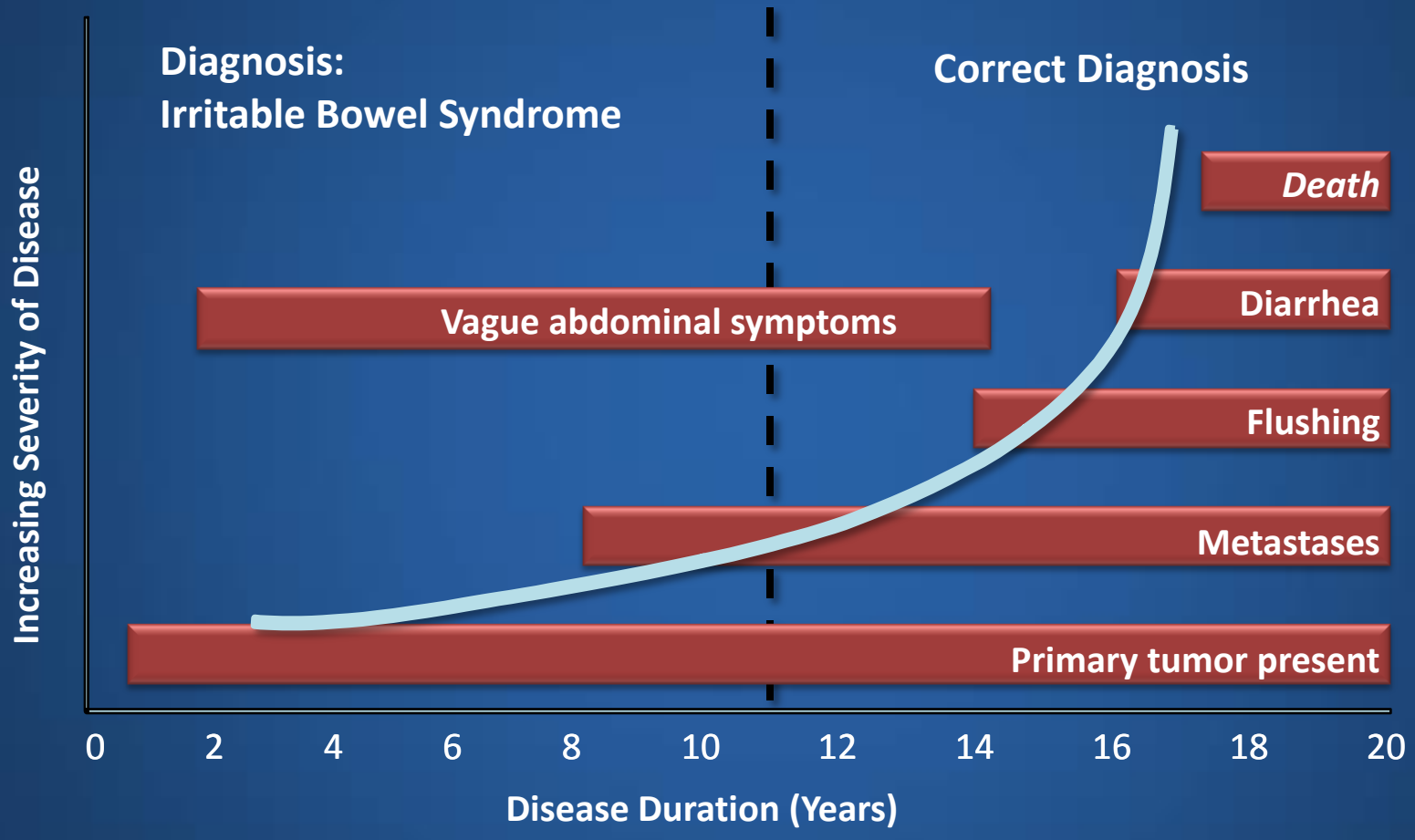
Extent of Disease at Diagnosis[1]



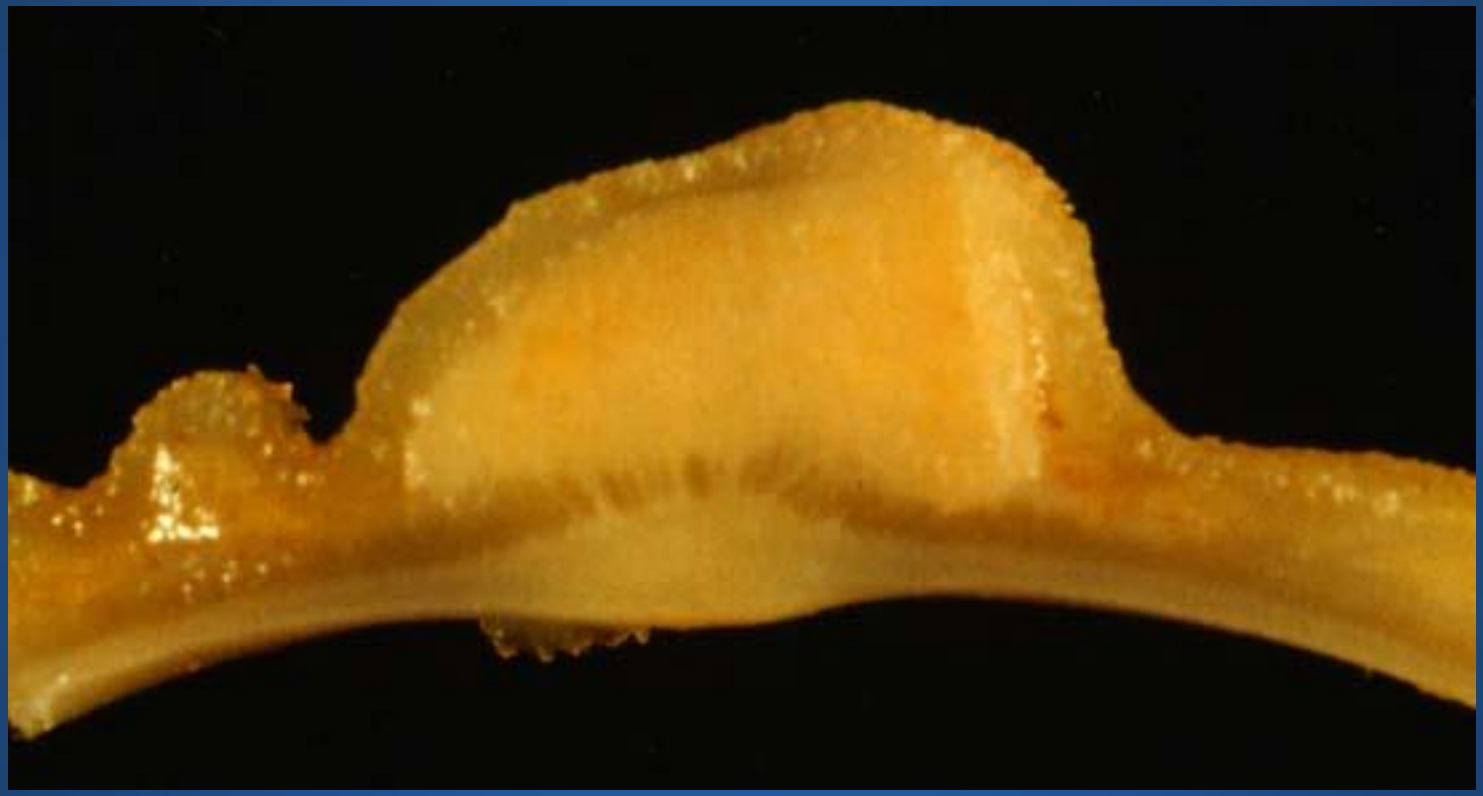
- Diagnosis is often delayed 5 to 7 years on average, and the probability of metastatic disease at diagnosis is increased[2]

1. Yao JC *et al.* One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol* 2008;26:3063–3072.
2. Modlin IM *et al.* Gastroenteropancreatic neuroendocrine tumours. *Lancet Oncol* 2008;9:61–72.

Natural History of NET



1. Adapted from Vinik A *et al.* Use of somatostatin analog in management of carcinoid syndrome. *Dig Dis Sci* 1989;34(suppl):14S–27S.



Midgut Carcinoid Tumors Commonest Presenting Features

- Abdominal pain
- Obstruction
- Incidental
- Bleeding
- Mass
- CS

Carcinoid of the Lung Presenting Features

- Incidental finding
- Recurrent infection (pneumonia)
- Hemoptysis
- Chronic Cough
- Distant metastases
- Endocrine syndrome (Carcinoid, Cushing's, etc.)

Diagnosis of Carcinoid

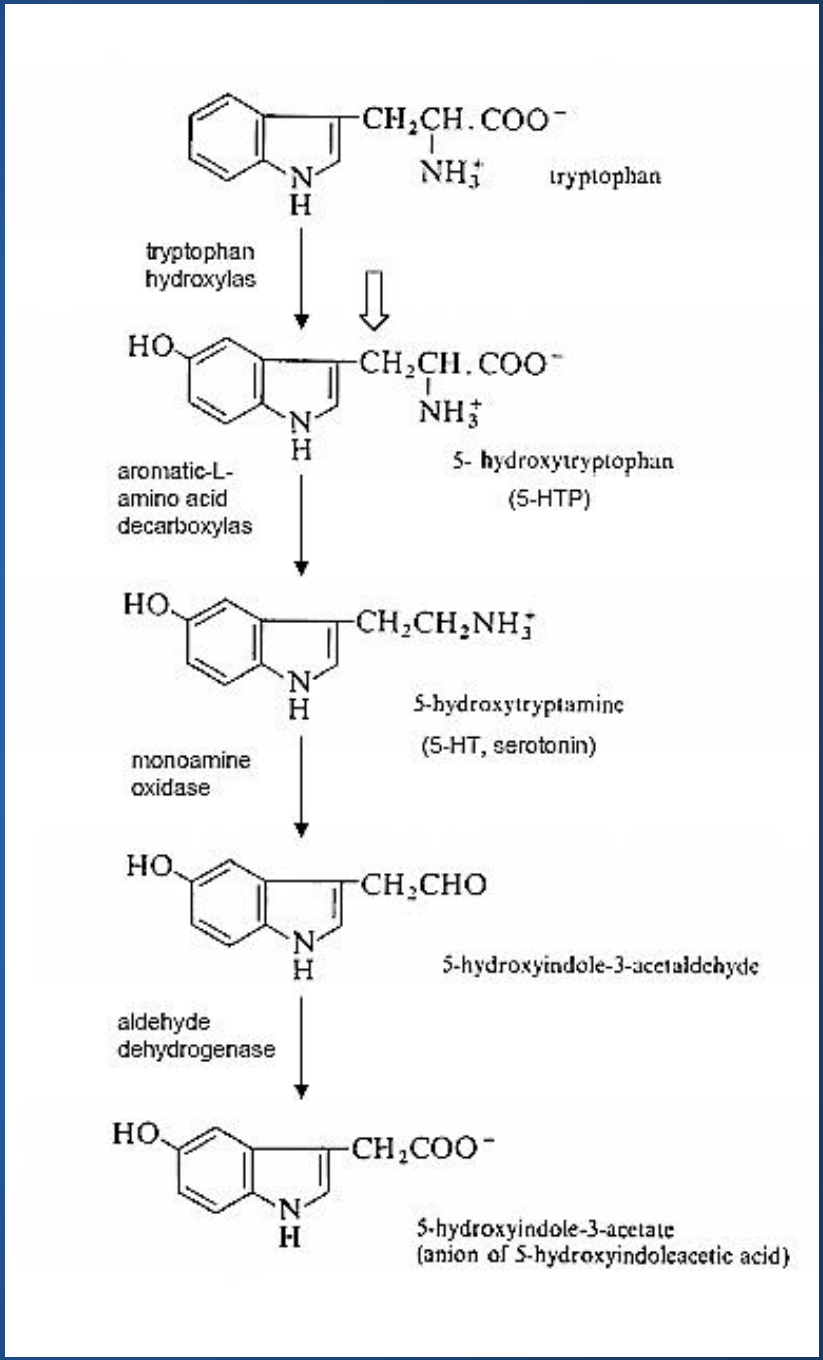
- Suspicion
- Markers
- Imaging
- Biopsy

Carcinoid Tumor Markers (1)

- Urine 5-HIAA
- Serotonin (5-HT)
- Chromogranin A (CgA)

Serotonin Metabolic Pathway

- Tryptophan
  Protein, Nicotinic Acid
- 5-Hydroxytryptophan (5-HTP)
- 5-Hydroxytryptamine
  (5-HT, serotonin)
- 5-Hydroxyindole-3-acetaldehyde
- 5- Hydroxyindoleacetic acid
  (5-HIAA)



Carcinoid Tumor Markers (2)

- Neuron specific enolase (NSE)
- Substance P
- Pancreatic poly peptide (PP)
- Pancreastatin
- Neurokinin A
- α/ß subunits of HCG

Specific NET Markers

- Gastrin
- Insulin and related substances
- VIP
- Glucagon
- Calcitonin
- ACTH
- VMA, Catachole amines, Metanephrines

CgA – Elevated in

- ↓ renal function, ↓ liver function
- PPI
- Eating
- Retained antrum
- Hypergastrinemia (ZES and atrophic gastritis)
- IBD
- Physical stress and trauma

Newly Emerged Diagnostic Techniques

Based on molecular gene and DNA analysis to aid choice of treatment drug

1. Molecular profiling tumors (tissue) using:
   - IHC
   - FISH
   - MA
   - Q PCR

   Commercially Available.
2. Molecular diagnosis (to find origin of metastases, Cancer Type ID) by profiling 92 genes from RNA extracted from fixed paraffin embedded tumor biopsy via QRT-PC Technique. Commercially Available.

Newly Emerged Diagnostic Techniques (continued)

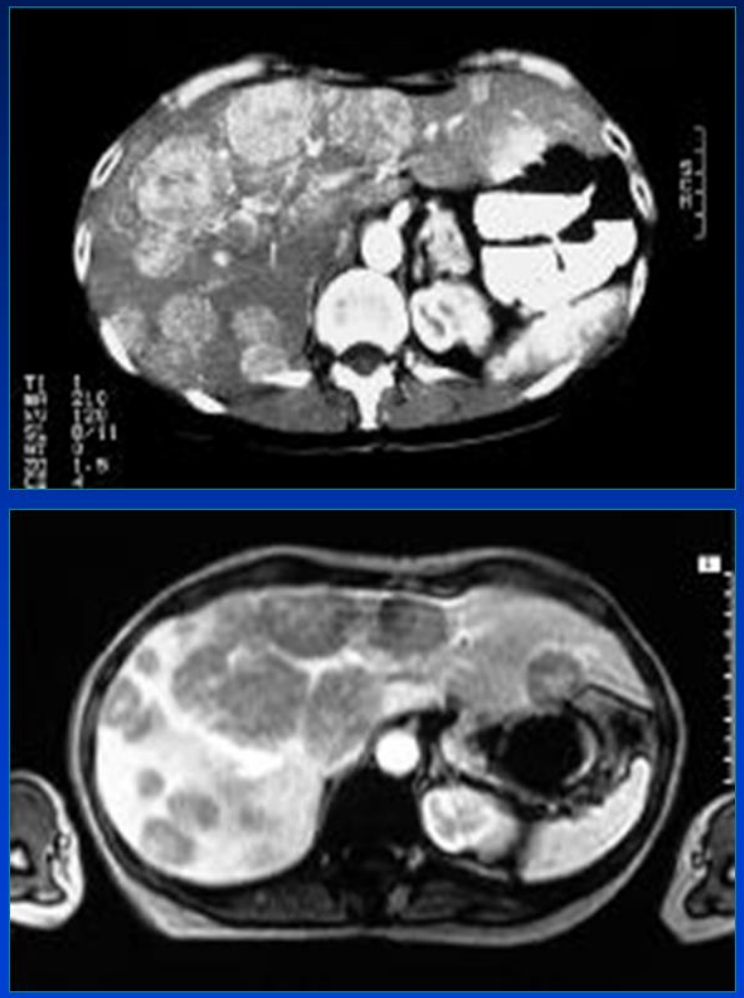
3. Early diagnosis of GEP NETS by blood PCR of the signature of 51 genes in 3 micro array data sets. Far more sensitive and specific than chromogranin A.

Commercially Available.

Standard Imaging Techniques

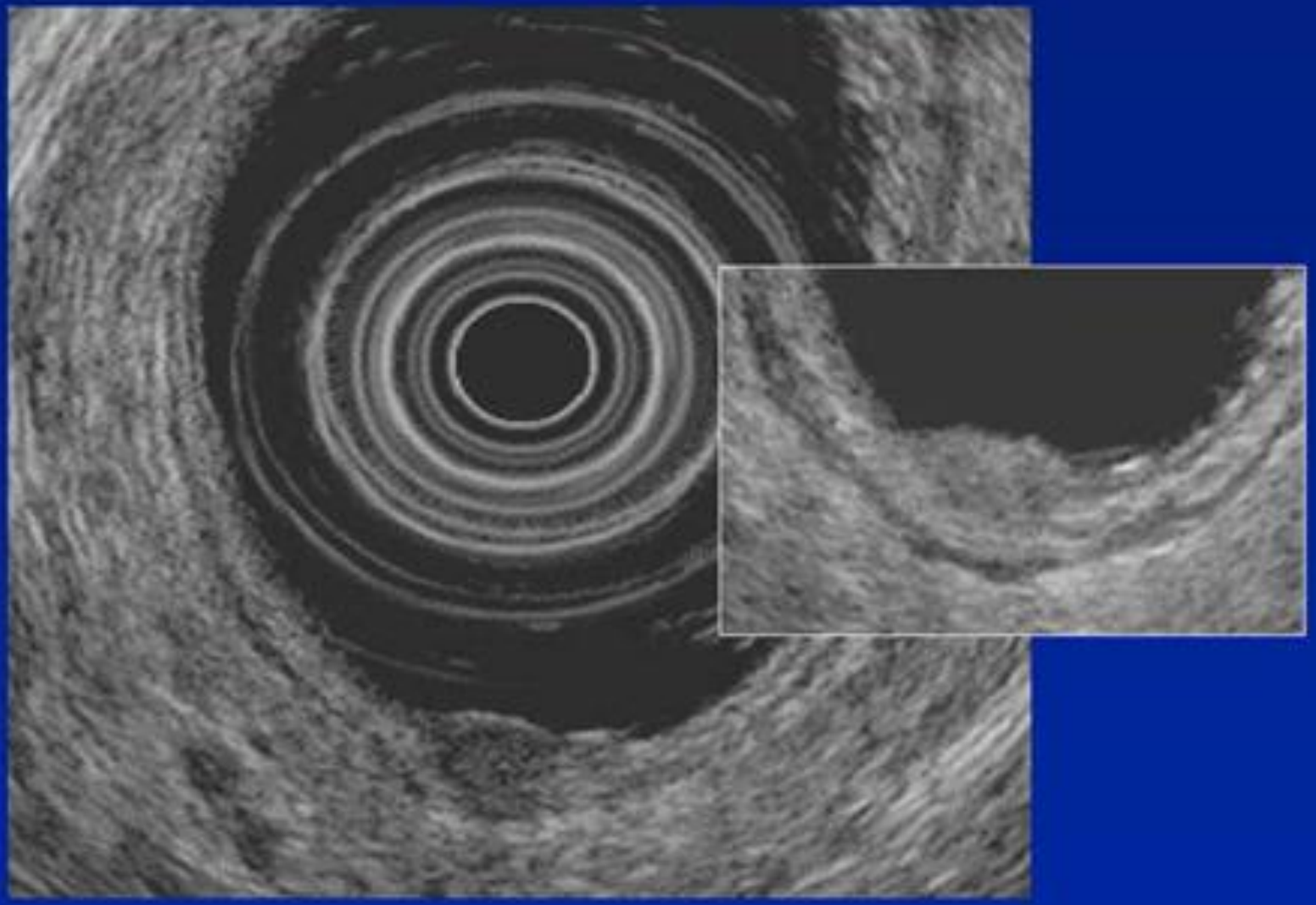
- X-Ray
- CT-scan
- MRI- scan
- Ultrasound scan (sonography) (EUS)
- Isotope bone scan
- *OctreoScan® (SRS) NET specific
- FDG PET scan
- OctreoScan® (PET) / CT Fusion scan
- MIBG scan

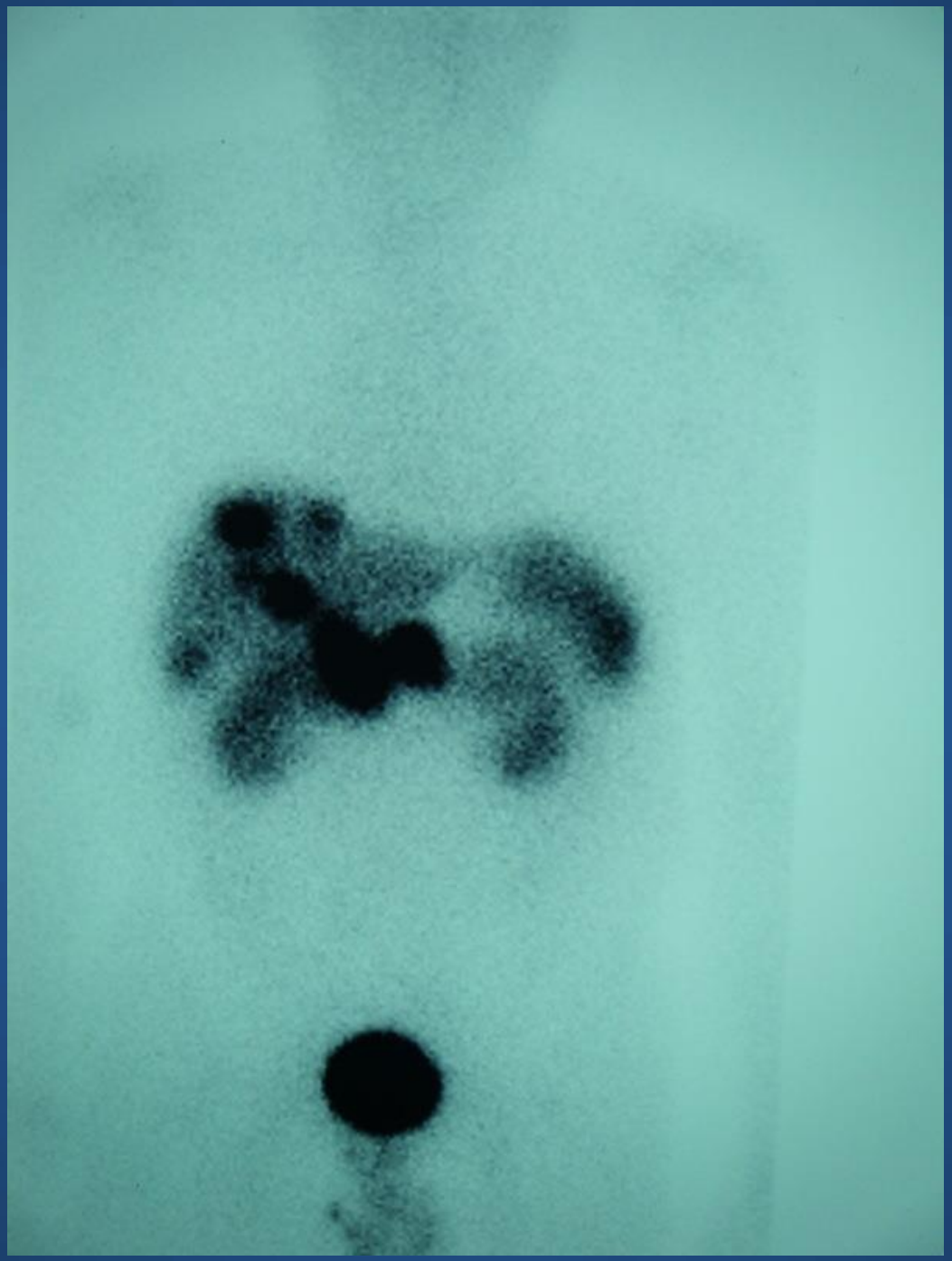
Diagnosis: CT/MRI

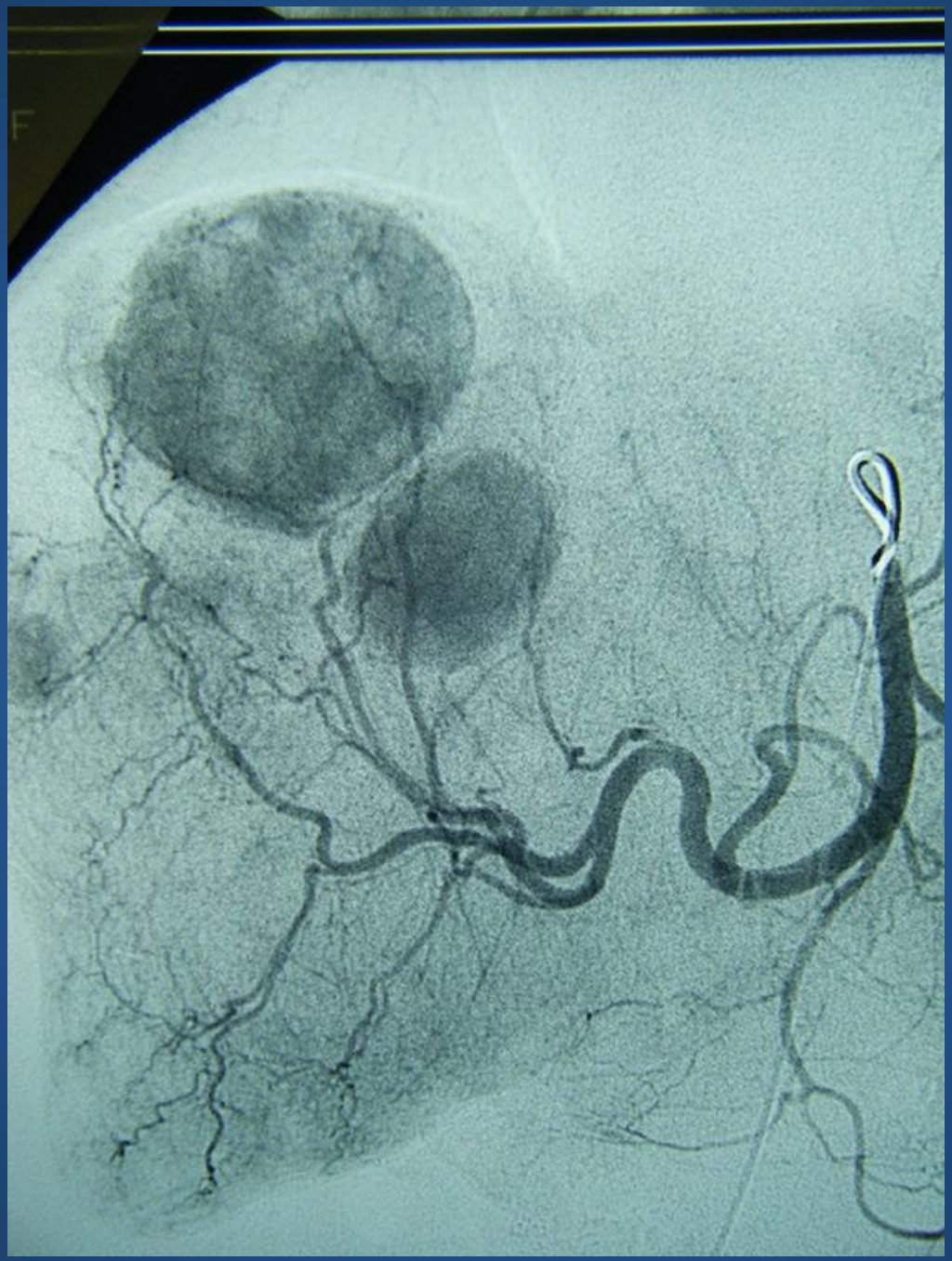


Contrast-enhanced CT scan (top) and MRI (bottom) of patient with metastatic small bowel carcinoid

Rectal carcinoid







Bulges

- Stretched mucosa
  - White appearance of stretched and thinned mucosa attests to submucosal process
- Lobulated mucosa
  - Not a single, smooth bulge of an adjacent bowel loop

Minimum Pathology Data Set

- Depends on tissue source
- Common requirements:
  - Site of tumor/metastasis
  - Grade
  - Mitotic index
  - Proliferation index (Ki-67 or MIB-1)
  - Diagnosis
- Immunohistochemical staining
  - Chromogranin
  - Synaptophysin
- TNM staging

TMN, tumor, lymph node, metastasis.

1. Klimstra DS *et al.* The pathological classification of neuroendocrine tumors. *Pancreas* 2010;39:707–712.

KI-67 Helps Predict Survival

PNETS		
Grade	KI-67%	5 Yr. Survival
G1	≤ 2/5	80-90%
G2	> 2/5 ≤ 20	40-80%

Intestinal NETS		
Grade	KI-67%	5 Yr. Survival
G1	≤ 2	79-95%
G2	> 2 ≤ 10	65-85%
G3	> 20	0-50%

KI-67

A good predictor of tumor recurrence after radical surgery.

Treatment of Carcinoid Tumors and Syndrome

- Supportive
- Surgery
- Antiproliferative

“Wait and See” For NETS is Out!

- Surgery is more cost-effective than periodic surveillance
- Exceptions are small PNETS (Lee-Mayo Clinic)

Boudreaux's Data – PNETS With Liver METS

5 & 10 year survival 19.5% and 7.1%.

With aggressive surgery, and multi-disciplinary care, 69% and 49%.

Radiomicrospheres

- Advantages -

- Outpatient application
- Minimum post embolization syndrome
- Gentler onset of effect and less hepatotoxicity than TACE
- Minimal hematologic toxicity
- Approximately equal beneficial response as TACE and ? longer duration

Advances in SIRT
(Liver Therapy via hepatic artery)

- Embolus injection: blood, chemo, Y90 particles (effectiveness varies – Y90 better in study by Y.U. Wu)
- Sure Fire Catheter
- Conjunction with systemic chemotherapy
- SP Y90 clinical trial

Significant New Clinical Trials in Progress

- Teletristat (Telestar) – Testing experimental tryptophan hydroxylase inhibitor, which inhibits serotonin synthesis
- 5HT3 Blockade with Ondonsetron improves carcinoid syndrome diarrhea unresponsive to Octreotide (1998, 2013)
- PRRT with LU-177 vs. Octreotide in treatment of carcinoid

Oncolytic Viruses

- 11 clinical trials
- For carcinoid-Seneca Valley virus (Picorno Virus)
- A genetically engineered adenovirus, selectively killing NET cells (intra-hepatic injection), reduced BON carcinoids in rats

Conclusion

Many diagnostic and treatment procedures are available for NETS to guide, supplement and often precede surgery.

Conclusion #2

CARCINOID/ NETS EXPERT DEBATE-? CONCLUSION