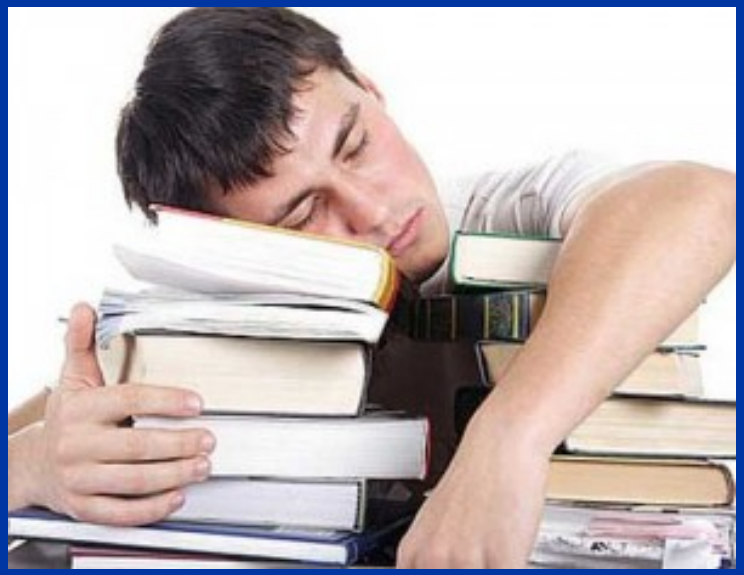
A, B …Zs of Neuroendocrine Tumours (NETs)



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Objectives

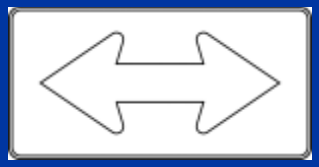
- What is the neuroendocrine system
- Where can neuroendocrine cancers start
- General statistics
- Diagnosis:
  - Pathology, Biomarker tests, Imaging
- Classification

Disclosures

- Thanks to Dr. Celia Marginean, Dr. Maroun and others use of slides

What is the Neuroendocrine System?

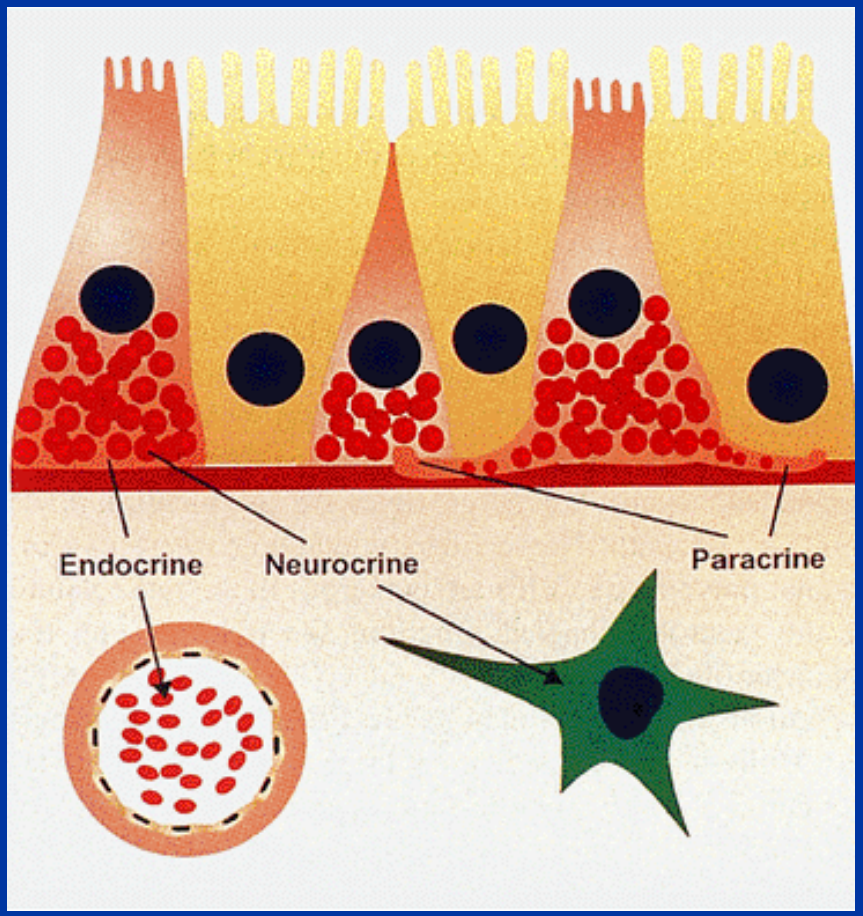
NERVOUS SYSTEM



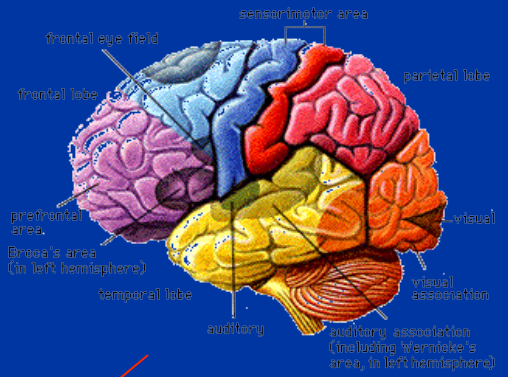
ENDOCRINE SYSTEM

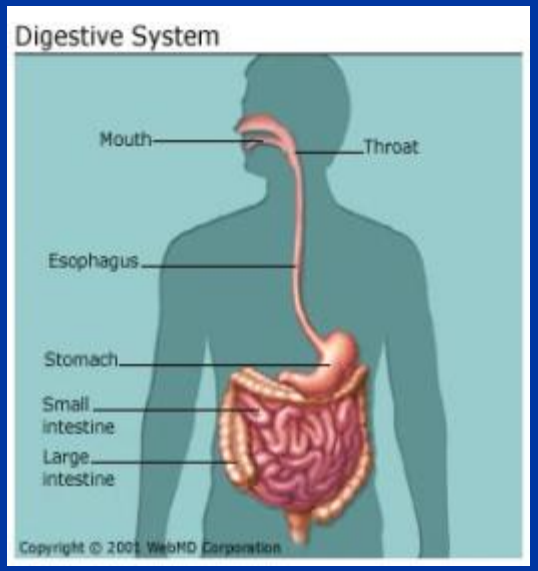
Neuroendocrine cells

- Neuroendocrine system made up of neuroendocrine cells
- Special group of nerve cells that can also produce hormones that influence body functioning



Examples of Neuroendocrine system

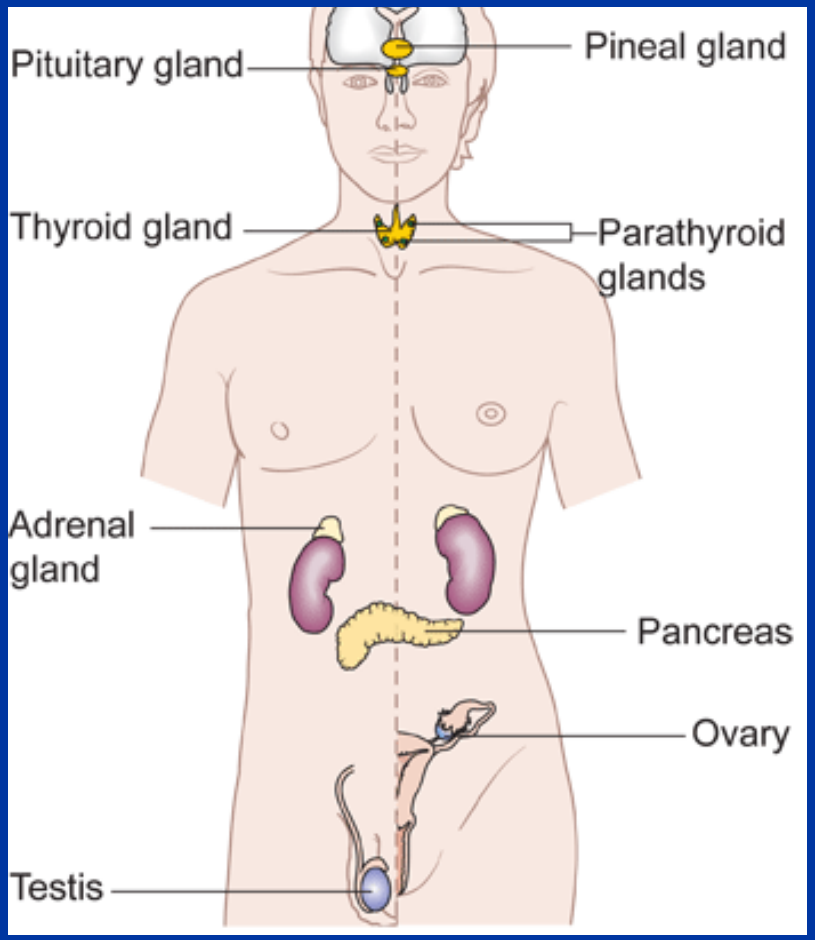




Where can neuroendocrine tumours start?

Variety of the spice of Life

Where can neuroendocrine tumours start?



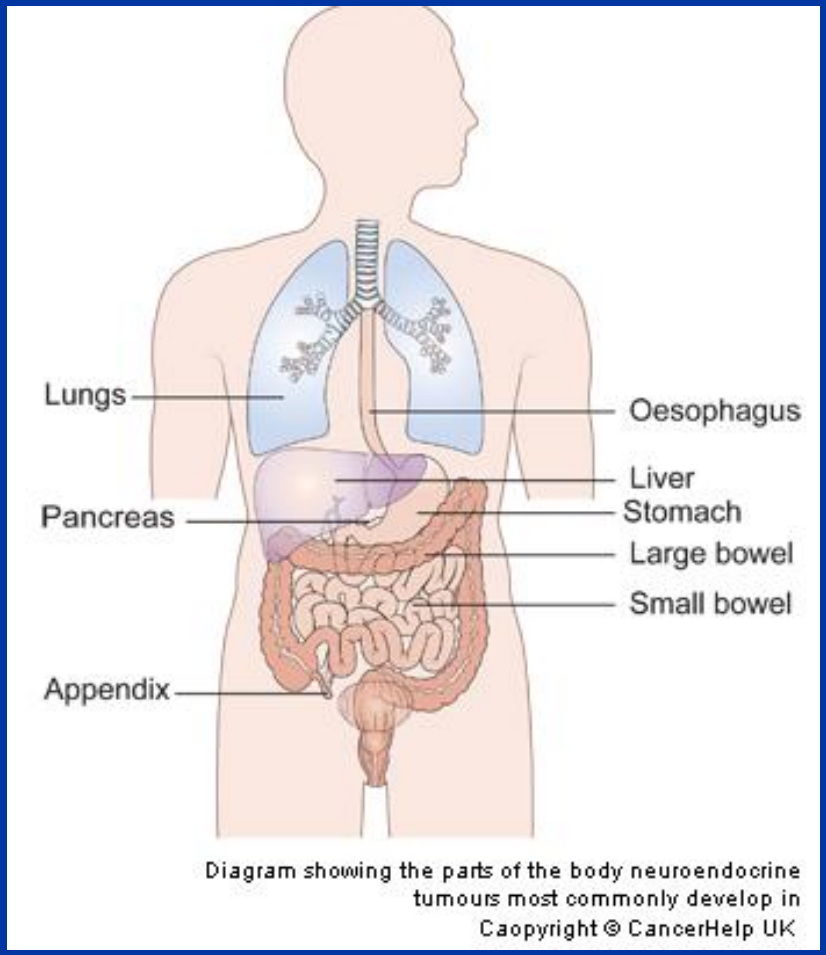


Diagram showing the parts of the body neuroendocrine tumours most commonly develop in

General Organization of the NE Gastrointestinal System

- NE cells are widely distributed throughout the epithelia of the stomach, intestines, distal esophagus, and anus

- At least 14 types of NE cells populate the GI mucosa

Cell type	Localisation	Products	Factors that regulate secretion
D	Gastrointestinal tract	Somatostatin	Hormones, neural factors, and acid
Enterochromaffin (Kulchitsky cells)	Gastrointestinal tract (and lung)	Serotonin, substance P, guanylin, and melatonin	Luminal factors, hormones, and neural factors
Enterochromaffin-like	Stomach	Histamine	Hormones, gastrin, and neural factors
G	Stomach and duodenum	Gastrin	Amino acids, neural factors, and acid
Gr	Gastrointestinal tract	Ghrelin	Luminal factors and hormones
I	Duodenum	Cholecystokinin, gastrin, etc	Lipids and neural factors
K	Duodenum and jejunum	Gastric inhibitory polypeptide	Nutrients and hormones
L	Small intestine	Glucagon-like peptide, peptide YY, and neuropeptide Y	Glucose and hormones
Motilin	Duodenum	Motilin	Neural factors and luminal factors
N	Small intestine	Neurotensin	Lipids
S	Duodenum	Secretin	Acid
VIP	Gastrointestinal tract	Vasoactive intestinal peptide	Neural
X	Stomach	Amylin	Not defined

Statistics

Statistics

- 0.5% of all cancers
  - Breast cancer 25% all cancer
- 2.5 to 5 cases per 100,000
  - Breast cancer 100 per 100,000
- Ottawa (1.5 million)= 75 new cases/year
- Toronto (3 million) = 150 new cases/year

QUESTION

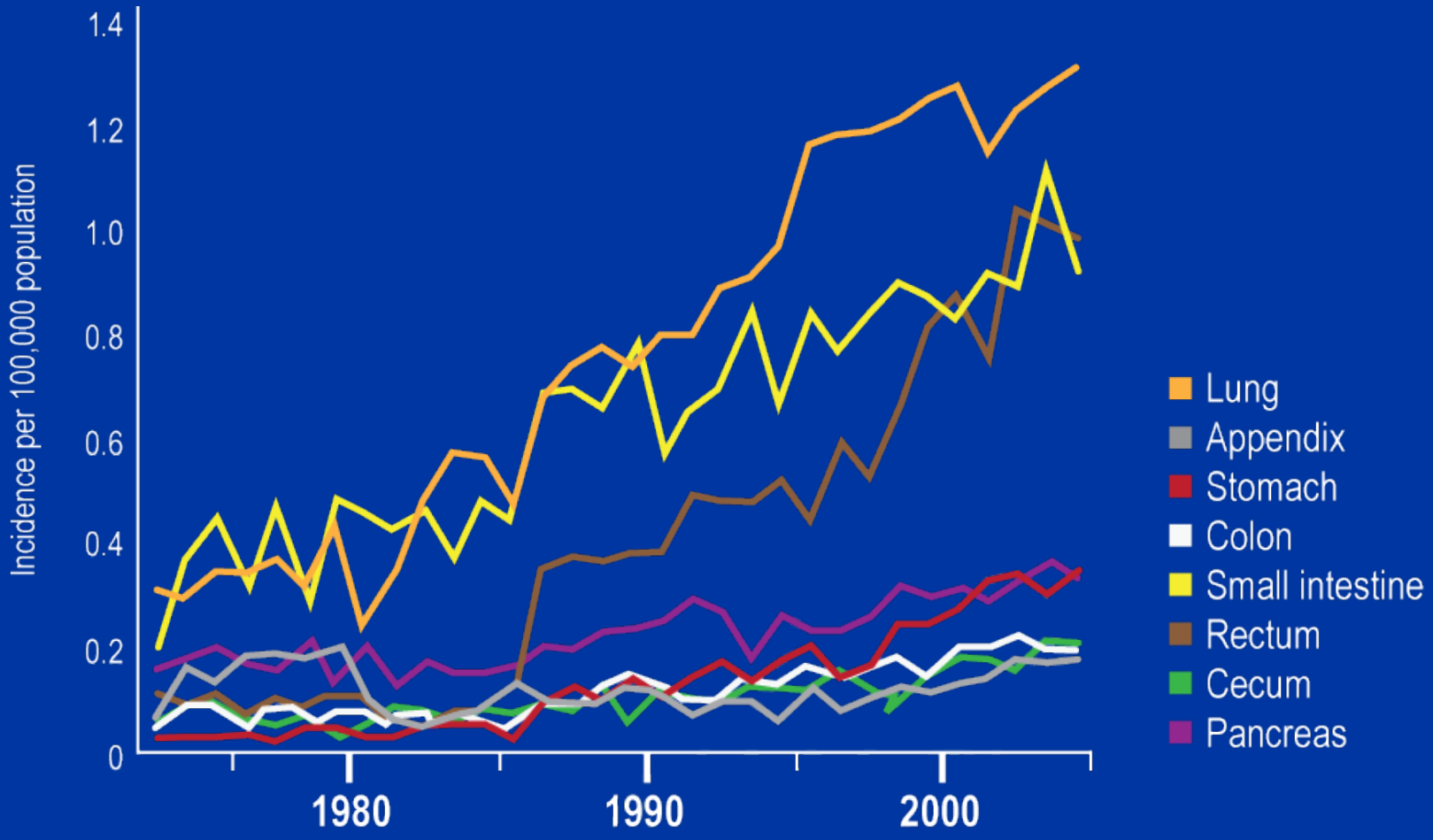
- The number of new neuroendocrine tumour are currently….
  - Rising
  - Decreasing
  - Stable

QUESTION

- The number of new neuroendocrine tumour are currently….
  - Rising
  - Decreasing
  - Stable

NET Incidence Is Increasing

US SEER data show a 5-fold increase in the past 30 years

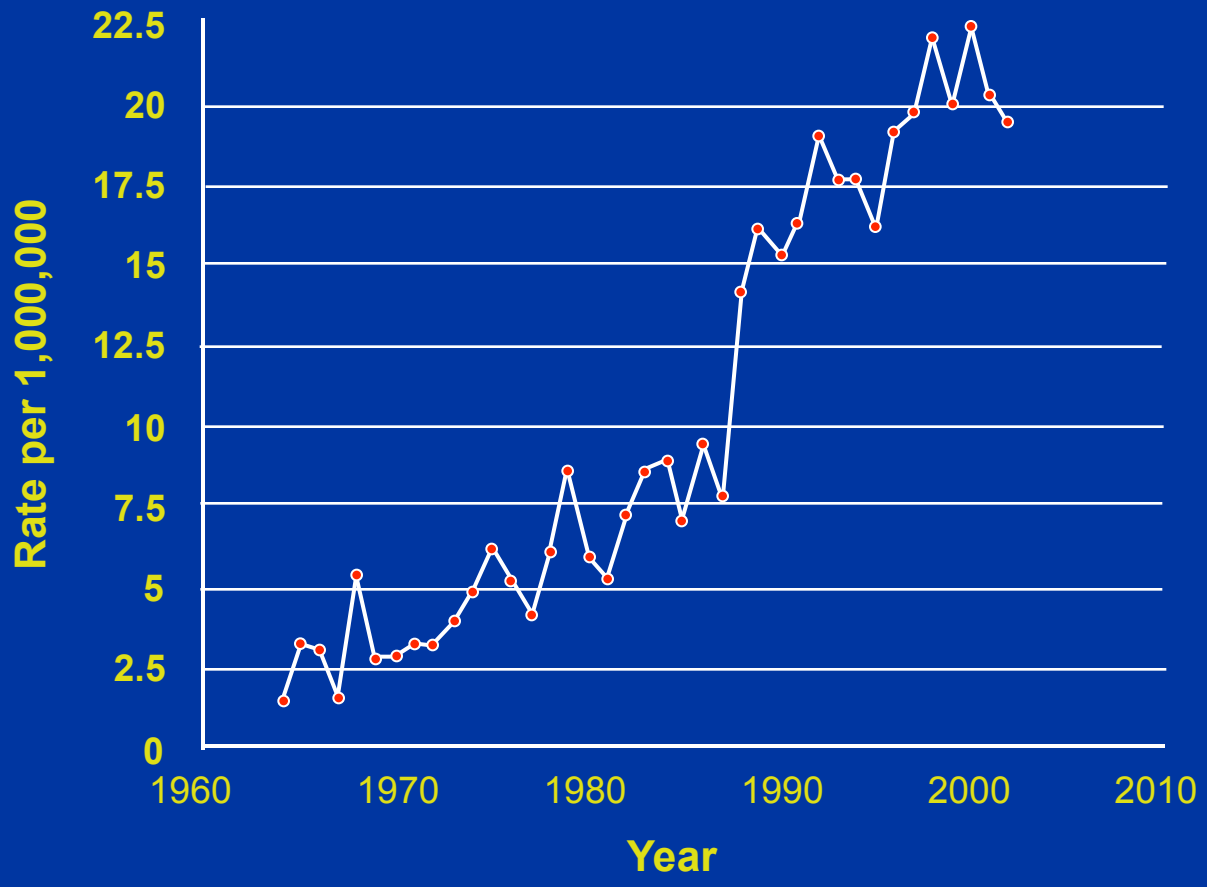


SEER = Surveillance, Epidemiology and End Results.

Adapted with permission from Yao JC, Hassan M, Phan A, et al. *J Clin Oncol*. 2008;26(18):3063-3072.

Increasing Incidence of NETs: Ontario

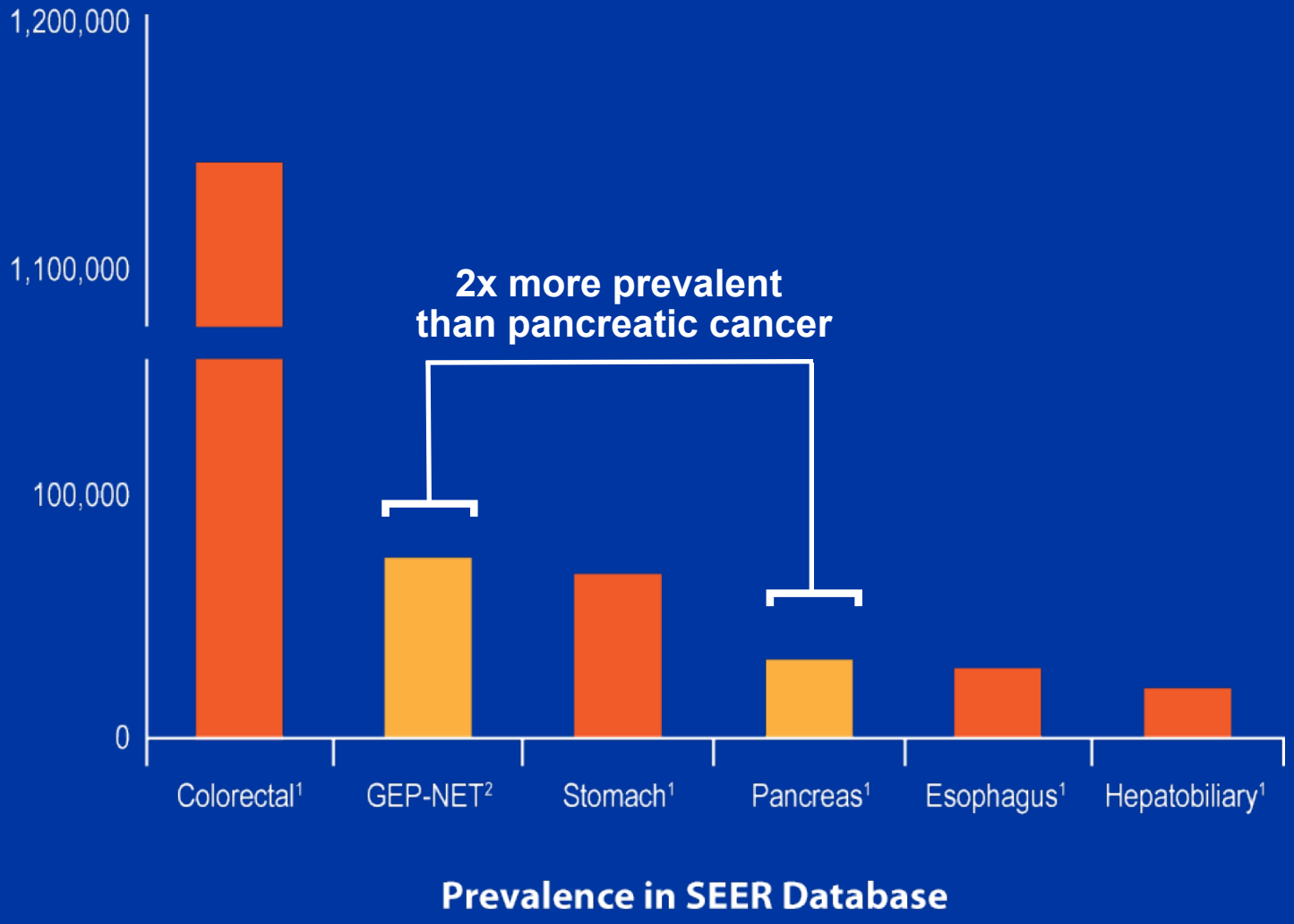
Incidence of carcinoid tumours in Ontario, 1964-2002



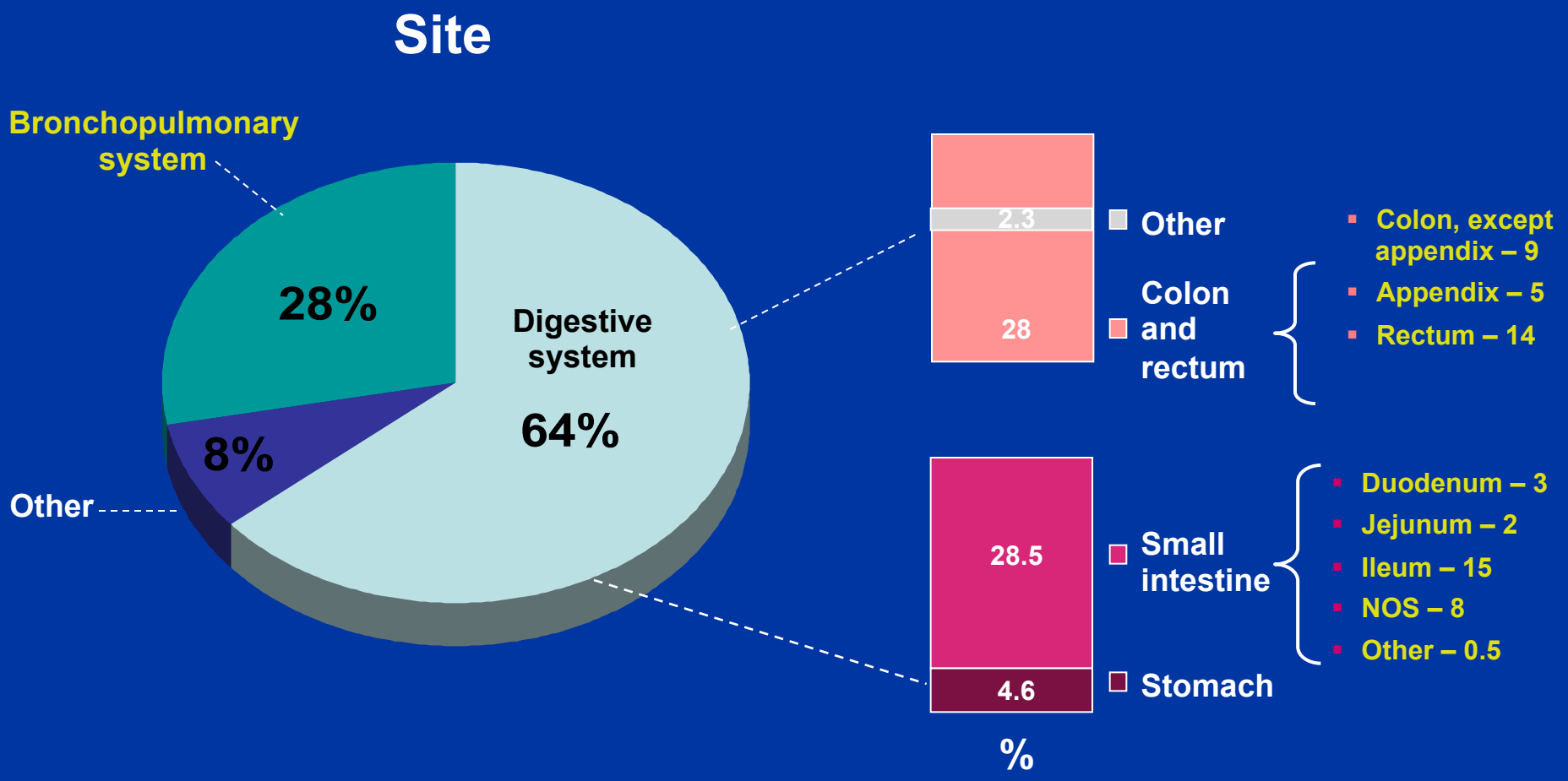
Age-adjusted rates standardized to 1991 in rate per 1 million population by year of diagnosis.

Ontario Cancer Registry, 2004.

NETs Are the Second Most Prevalent Type of GI Malignancy



Neuroendocrine tumours: Origin



Cause of neuroendocrine tumours?

- Exact cause or risk factors are unknown
- Rare genetic conditions
- MEN1
  - Parathyroid
  - Pituitary
  - Adrenal

Diagnosis

Clinical Symptoms

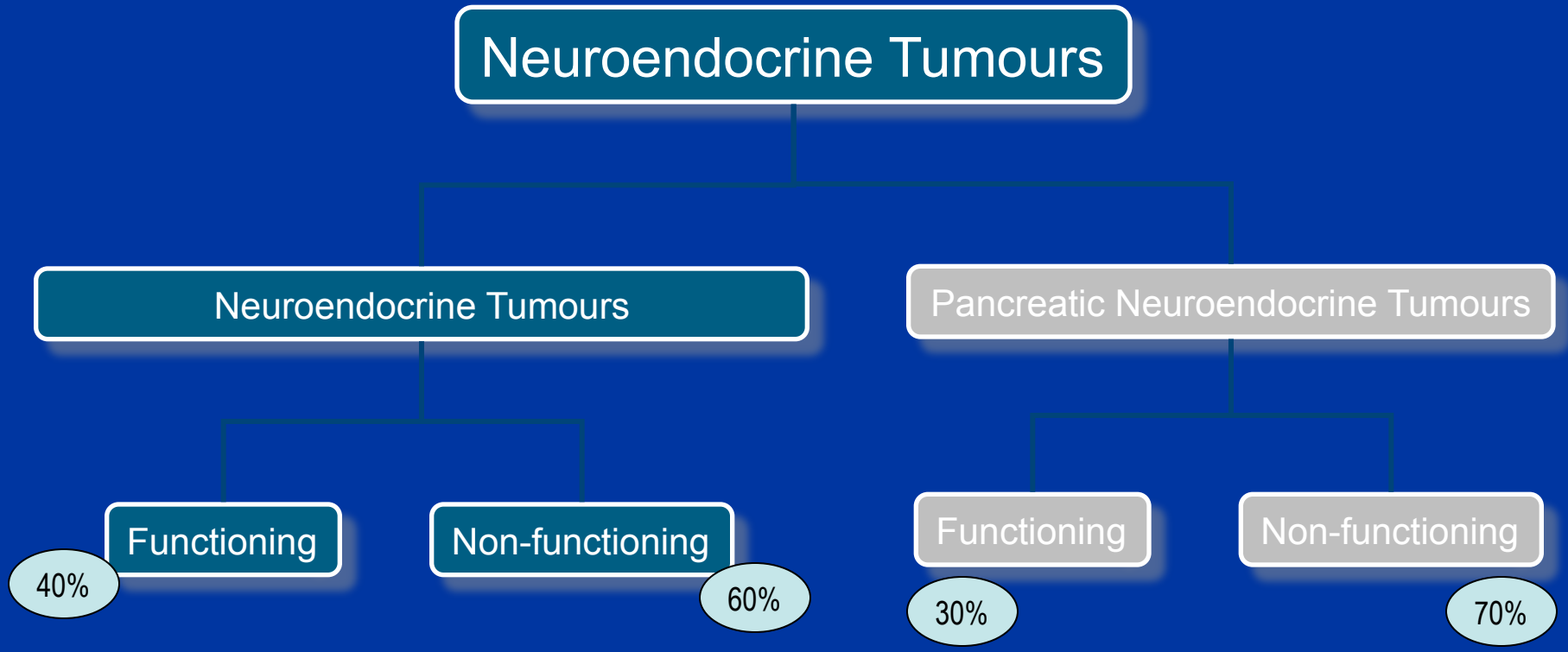
Functioning:

- Tumour produces hormones and/or "proteins/peptides" that cause symptoms

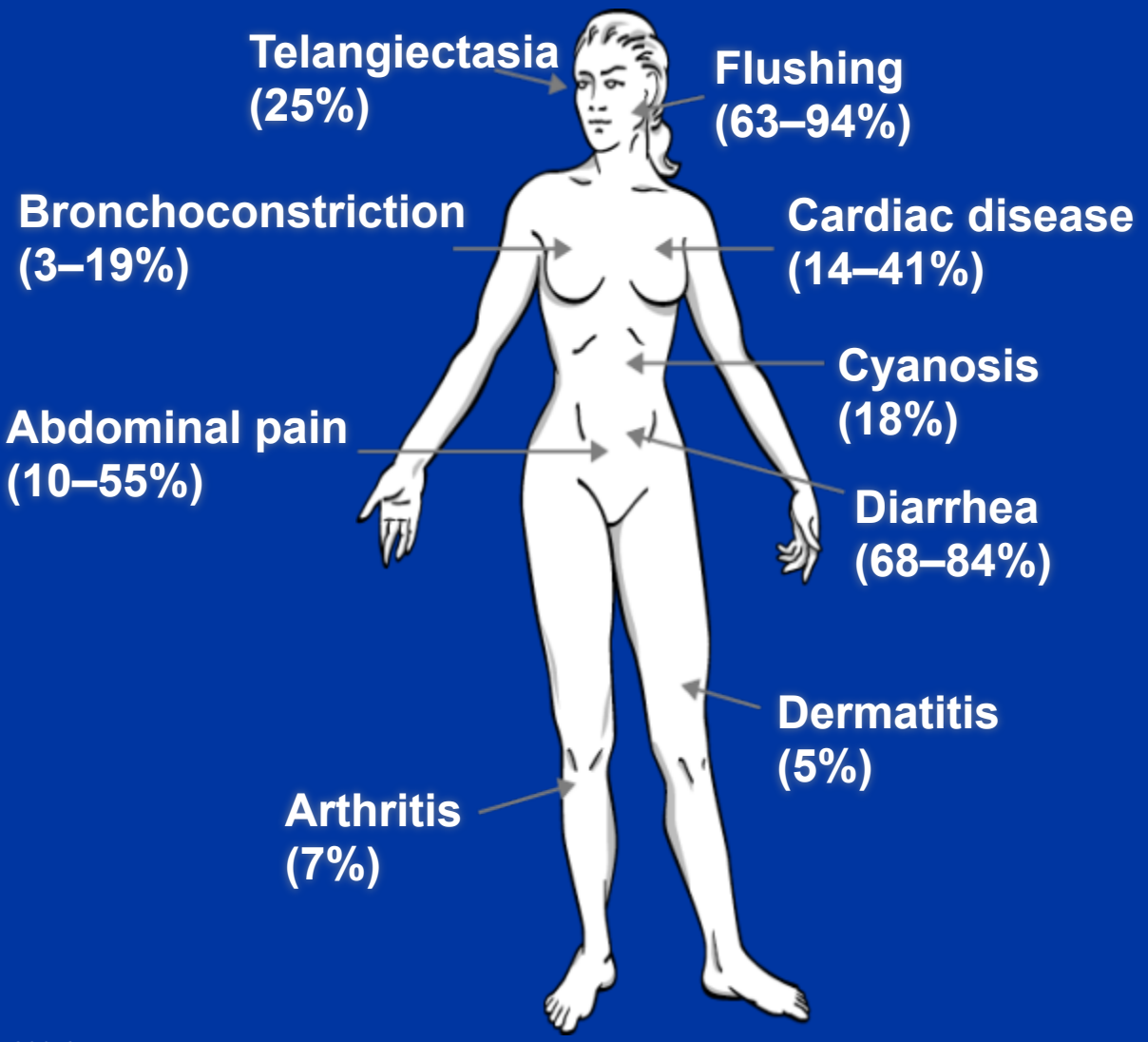
Non-functioning tumour:

- Tumours in general do not produce hormones
- Tumour may produce hormones, but patient has no symptoms

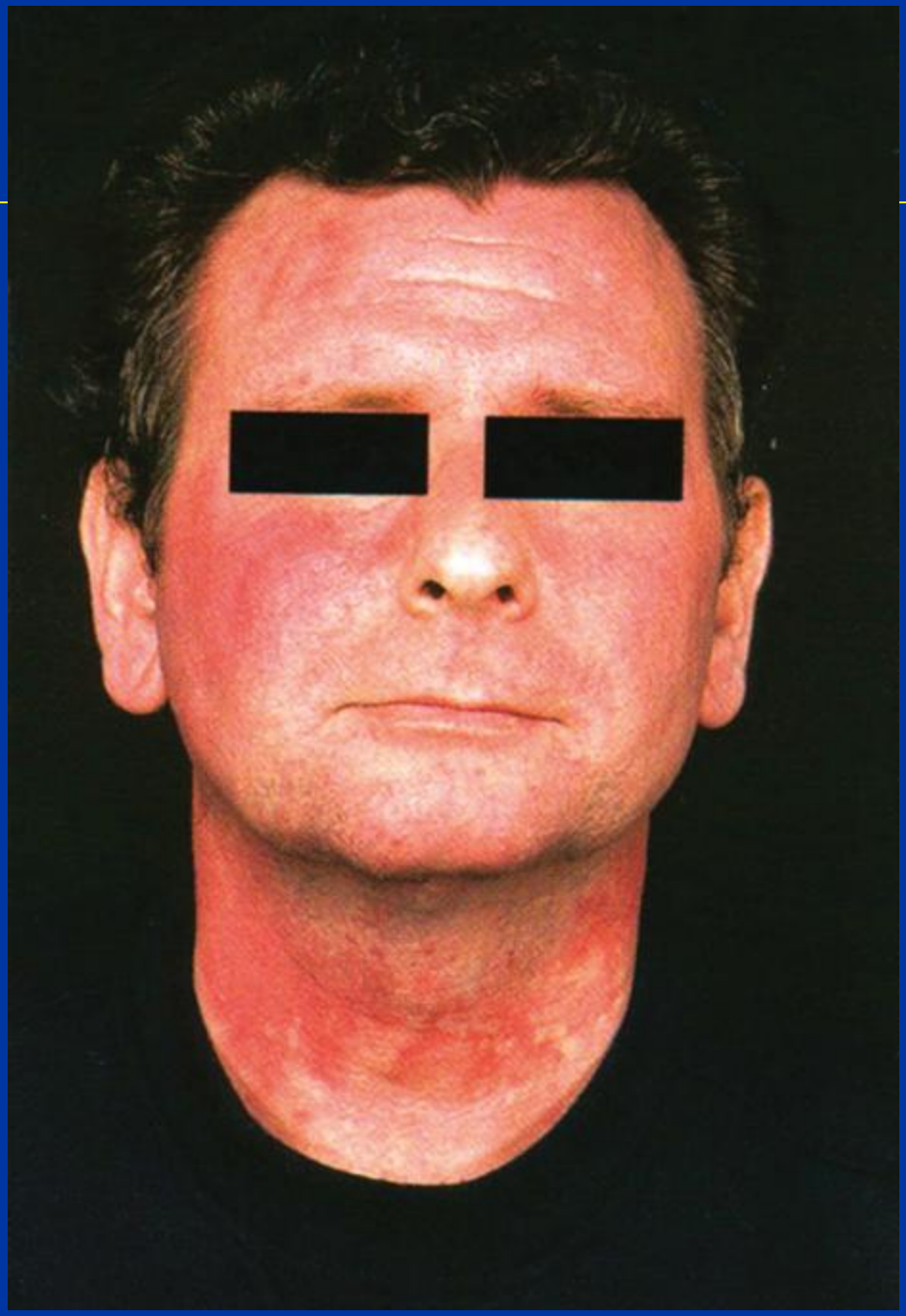
Neuroendocrine Tumour Classification: Functioning



Carcinoid Syndrome: Clinical Presentation



Öberg K, et al. *Acta Oncol*. 2004b.



clevelandclinicmeded.com

Previously used to describe “slow-growing” Neuroendocrine tumour

Does not adequately describe what we know about these tumours today

Presentations of PNET

Tumor	Symptoms	Cell type	% of Mets	location
Insulinoma	Hypoglycemia	*B* cell	<15%	pancreas
Glucagonoma	Rash, (necrotizing migratory erythemia), cachexia	Alpha cell	Majority	pancreas
VIPoma	Profound secretory diarrhea,	Non-B cell	Majority	Usually pancreas
Gastinoma ZES	PUD, “ulcers” acid hypersecretion	Non-B cell	<50%	duodenum
somatostatinoma	Mass effect	Theta cell	Marjority	pancreas

Presentation of NET tumors

Tumor	Symptom
Lung	Cough, hemoptysis, Cushing syndrome
Esophageal/Gastric	Swallowing trouble Bleeding, pain
Bowel	Pain Obstruction
Appendix	Usually incidentally found
Rectal	Bleeding, constipation

Diagnosis = Pathology

Biopsy

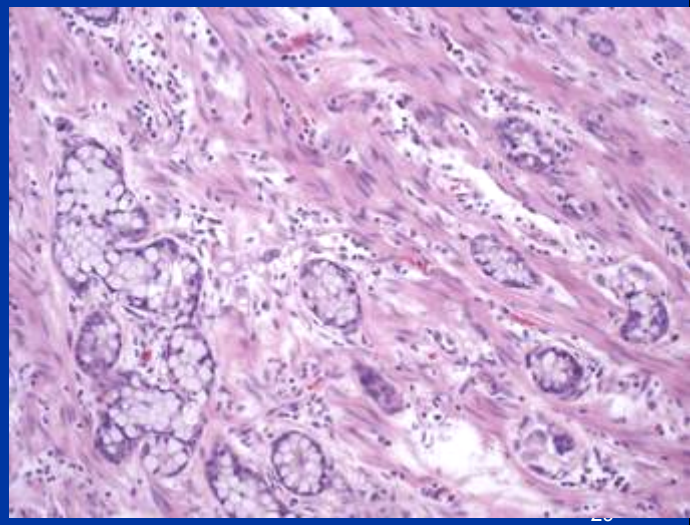
- Tumour site
- Neuroendocrine
- Special stains
  - Chromagranin
  - Synaptophysin
- Differentiation
- Grade
  - Ki-67
  - Mitotic rate

Surgery

- Lymph nodes
- Margins
- Size
- Lymphovascular invasion
- Perineural invasion

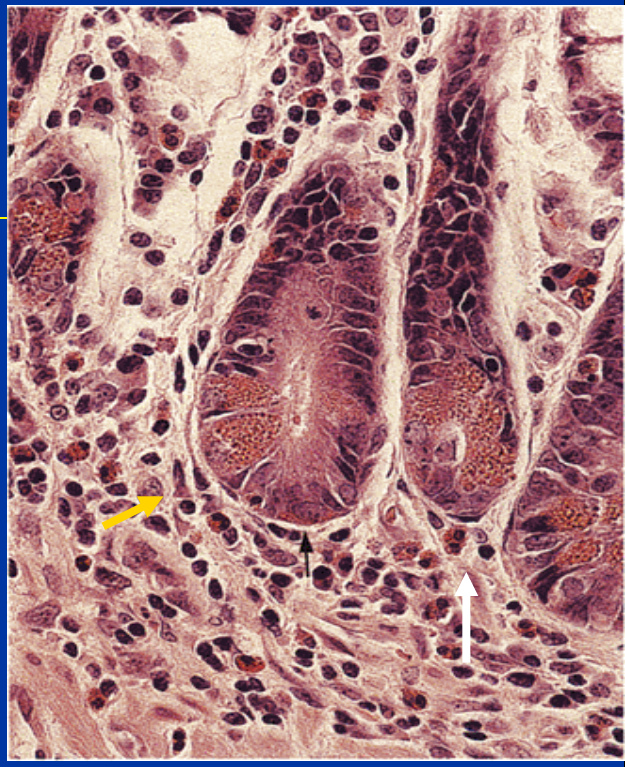
Example

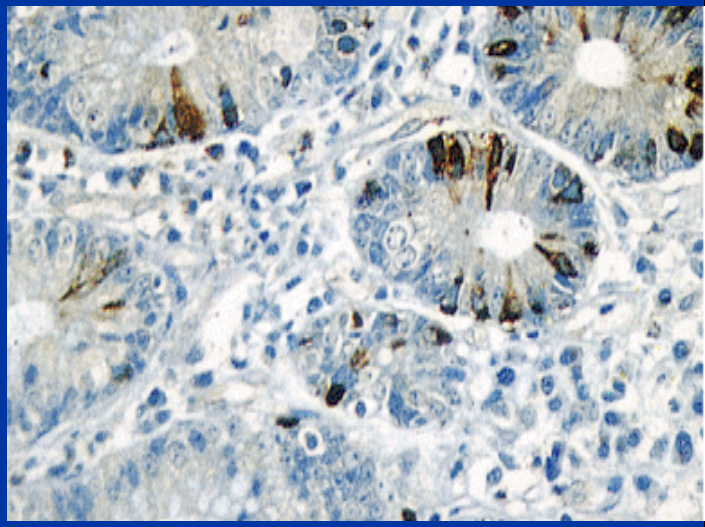
- Post right hemi-colectomy for appendix NET
- PATH
  - 3 cm well differentiated neuroendocrine tumour (T2)
  - Mitosis 1/10 HPF
  - Ki-67<=2%
  - Extension into mesoappendix
  - Negative margins
  - No regional Lymph nodes (0/15)
  - +LVI, Indeterminant Perineural



Identification of Neuroendocrine Cells

- NE cells can be recognized
  - pyramidally shaped
  - Clear cells lying along the basement membrane.
- Special IHC stains: synaptophysin, chromogranin, CD56, CD57, CDX2 and SSR2A (somatostatin receptor type 2A)
- IHC for specific hormones: insulin, glucagon, somatostatin, gastrin etc





chromogranin

Proliferation activity of NET

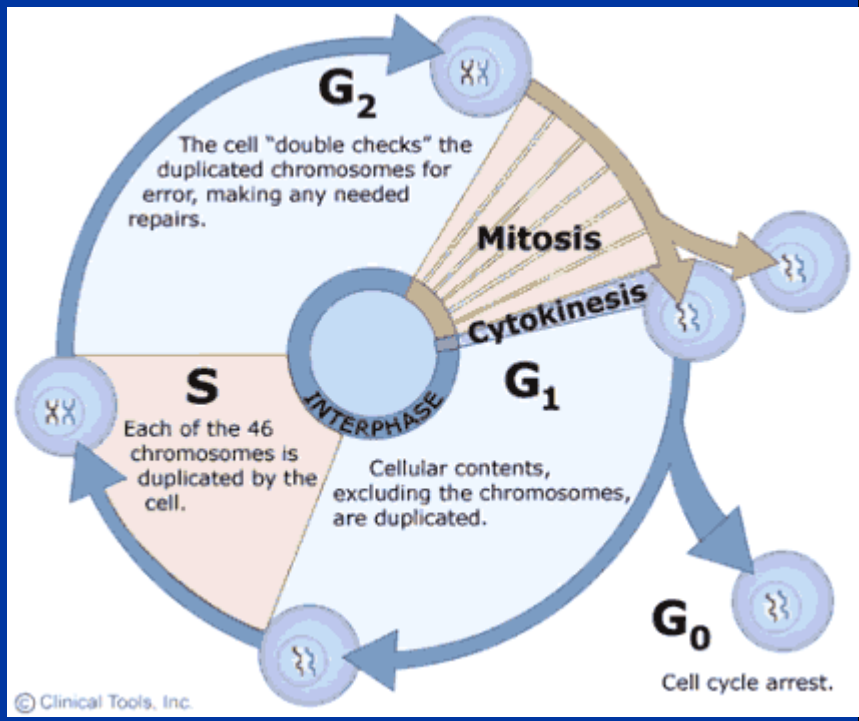
1. Ki-67 protein

- Positive in dividing cells
- Correlate with faster growing tumour
- Ex Ki67 2% vs 90%

2. Mitotic rate

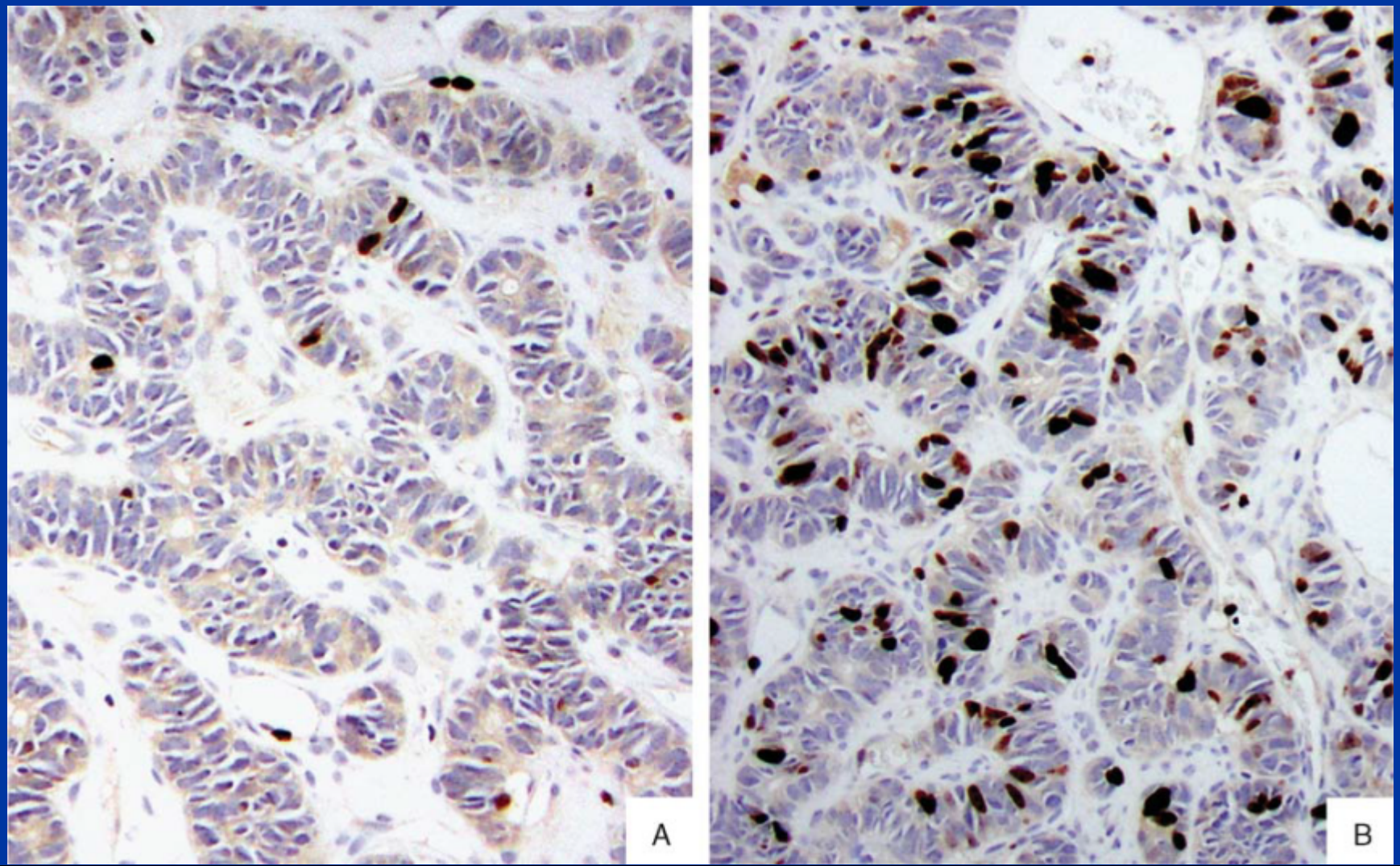
- Count the number of dividing cells
- Ex. Mitosis = 1/10HPF

Cell cycle:

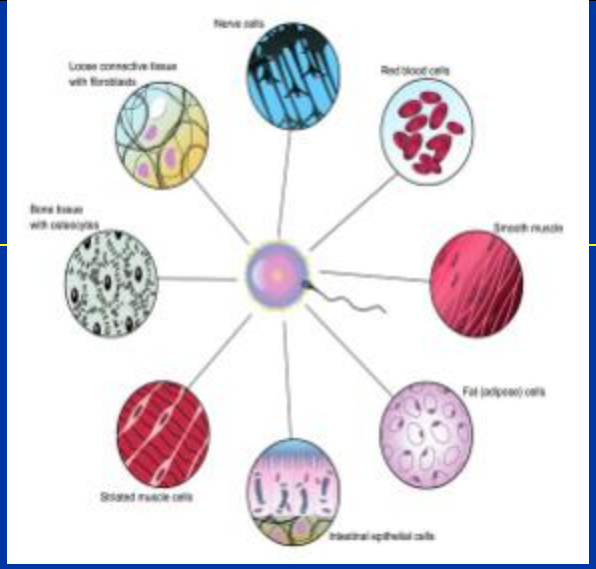


Tumor heterogeneity KI67

count 2000 cells in “hot spots”



Pathology report

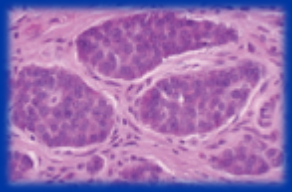
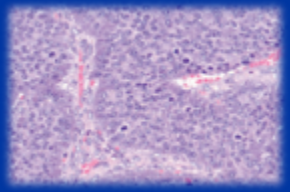
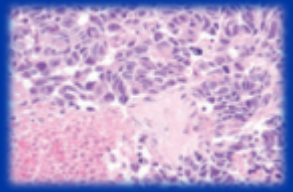


- Differentiation
- Normal cells
  - How a less specialized cell becomes more specialized
- Cancer
  - How closely the cancer cell looks like the parent cell
  - More poorly differentiated more often cancer will spread and will be faster growing
  - Linked with grade of the cancer

WHO Classification Groups NETs by Diagnostic Factors

Prognosis of Patients With NETs

Good → Poor

Differentiation	Well-differentiated neuroendocrine tumor	Well-differentiated neuroendocrine tumor	Poorly differentiated neuroendocrine carcinoma
Grade	G1 Low	G2 Intermediate	G3 High
Mitotic count	<2 per 10 HPF	2-20 per 10 HPF	>20 per 10 HPF
Ki-67 index (%)	<3%	3-20%	>20%

Counted in 10 high power fields . 10 HPF=2mm^2, at least 40 fields (400x magnification) in areas of highest density

Ki-67 assessed by MIBI antibody stain; percent positive after count of 2000 cells in area of highest nuclear labelling

Bosman et al. WHO Classification of Neuroendocrine tumours of the Digestive System, Lyon France IARC Press, 2010, endorsed by ENETS

Other tests

Staging Workup

Biomarker

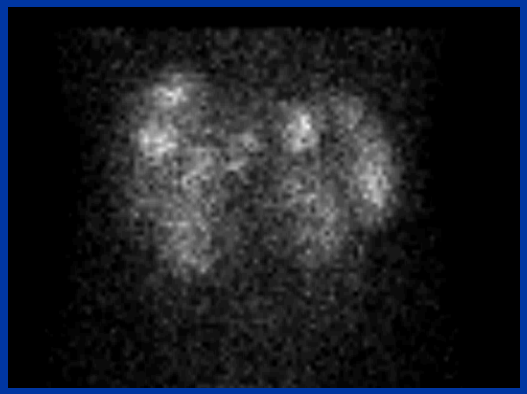
- Definition:
  - Something measurable that indicates a disease state

Caution of Bio-marker tests

- Patient needs to follow test directions
- There are many factors that can cause “false positive” test
  - Diet
  - Medications
  - Other illnesses
- There can be “false negative test”
- Often there is a normal amount in body: Cut-off?

Biomarkers

Look for rises



Correlate

Biomarkers

Blood

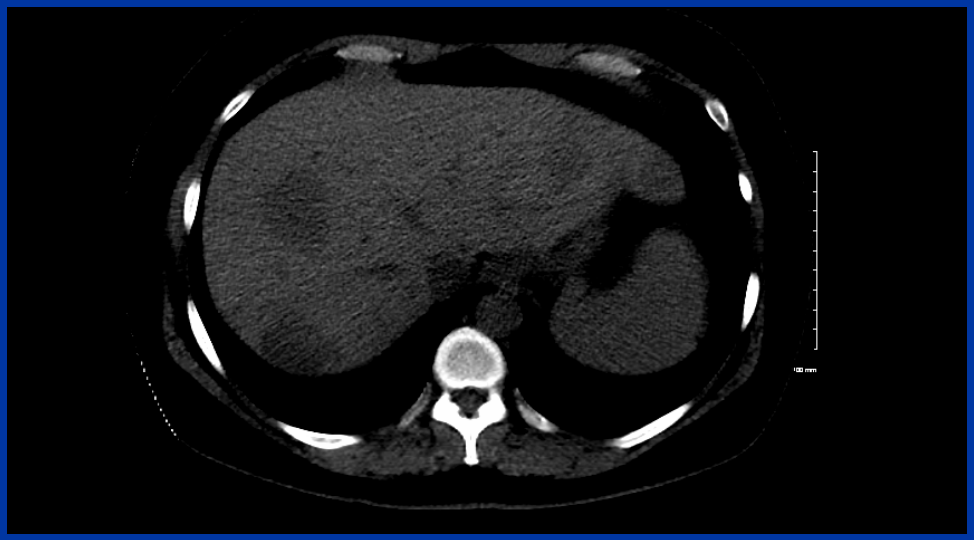
- Chromagranin

Urine

- 5HIAA
  - Serotonin
- Metanephrines
  - Pheochromocytoma
- Catecholamines
  - Pheochromocytoma

Staging Tests: Cancer that has travelled

- CT or MRI
  - Looking for a measurable cancer



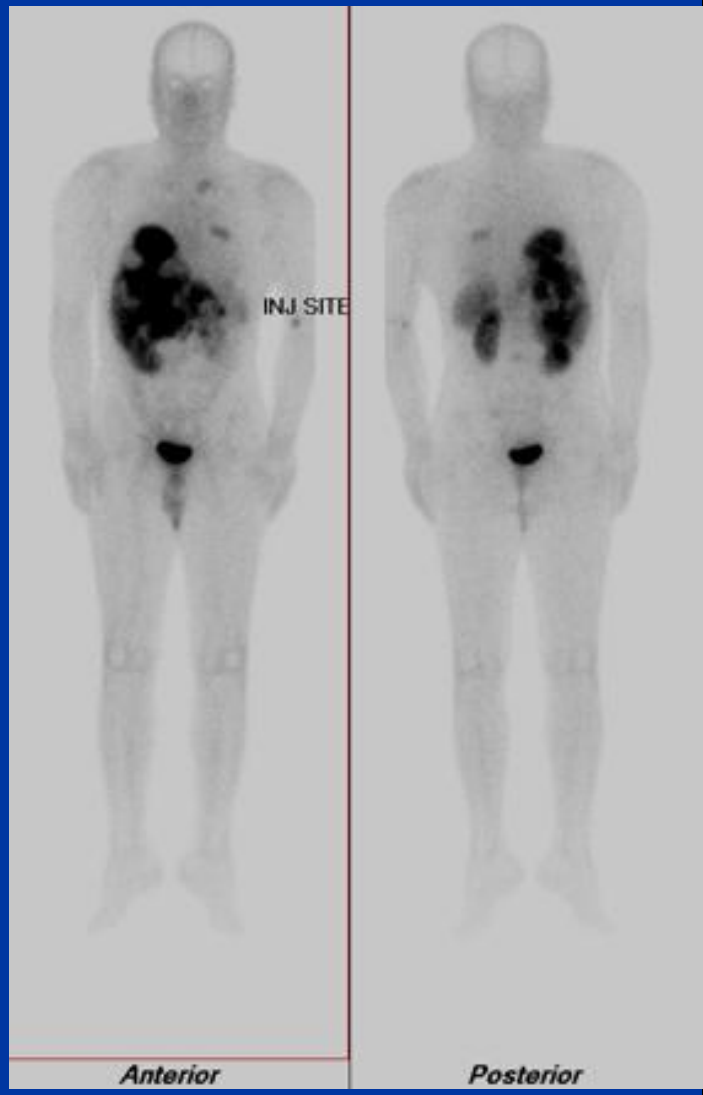
Nuclear Medicine scan: Functional

Octreotide Scan

- Octreotide, a drug similar to somatostatin, is radiolabelled with indium-111
  - injected into a vein and attaches to tumour cells that have receptors for somatostatin. A radiation-measuring device detects the radioactive octreotide

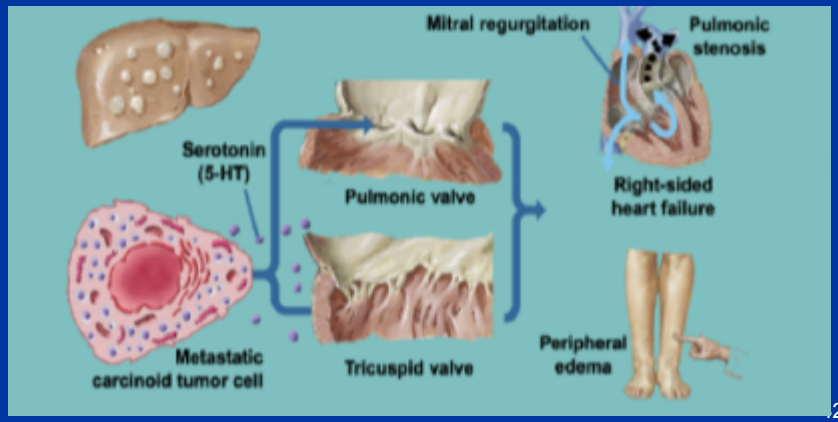
MIBG scan

- **metaiodobenzylguanidine** or **mIBG**, radiopharmaceutical similar to noradrenaline.



US of Heart

- Carcinoid heart disease
- Pathology:
  - Correlate with Urine 5HIAA
  - Thickening of right heart valves due to formation of fibrotic plaques
  - Affects valve function



Staging = Pathology + imaging

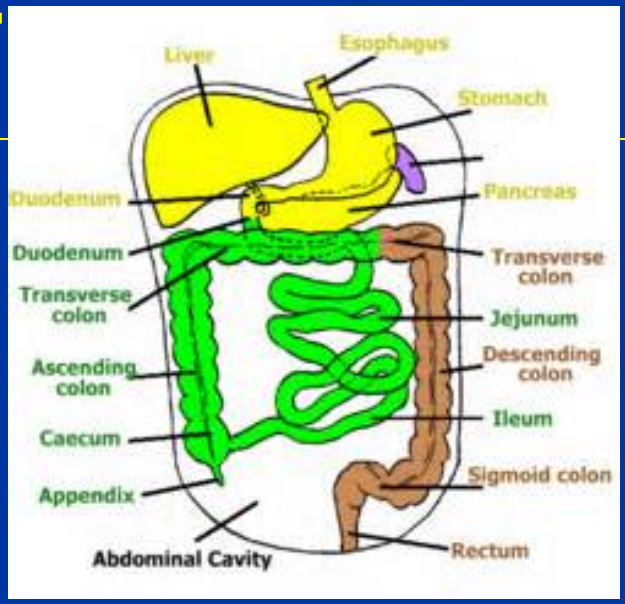
Primary tumor (T)*	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 2 cm or less in greatest dimension
T1a	Tumor 1 cm or less in greatest dimension
T1b	Tumor more than 1 cm but not more than 2 cm
T2	Tumor more than 2 cm but not more than 4 cm or with extension to the cecum
T3	Tumor more than 4 cm or with extension to the ileum
T4	Tumor directly invades other adjacent organs or structures, eg, abdominal wall and skeletal muscle•
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

pN0. Histological examination of a regional lymphadenectomy specimen will ordinarily include 12 or more lymph nodes. If the lymph nodes are negative, but the number or classify as pN0.

Anatomic stage/prognostic groups			
Stage I	T1	N0	M0
Stage II	T2, T3	N0	M0
Stage III	T4	N0	M0
	Any T	N1	M0
Stage IV	Any T	Any N	M1

AJCC Appendix Neuroendocrine

Other classification of NETS: Embryonic Origin



- Foregut
  - Lungs + bronchi
  - Stomach
- Midgut
  - Small intestine
  - Appendix, proximal large bowel
- Hindgut
  - Distal Colon
  - Rectum
  - Genitourinary origin
- Pancreatic
- Other

Conclusions

- NETs are rare, but increasing in number
- Some patients have functional tumours
- Staging based on Pathology (with grading/ differentiation) plus imaging
- Biomarkers need to be interpreted in context of other clinical factors
- NETs can be varied and have different clinical behaviour

What Does a Multi-Disciplinary Team Look Like ?

Thanks