Why the Zebra?

"When you hear hoofbeats, think horses, not zebras."
This phrase is told to medical students throughout their training.

In medicine, the term "zebra" is used in reference to a rare disease or condition. Doctors are taught to assume that the simplest explanation is usually the best, so as not to go around diagnosing patients with all sorts of exotic illnesses that are highly unlikely. Common diseases are what doctors should expect to encounter.

But many doctors seem to forget that “zebras” exist, and so getting a diagnosis and getting treatment can be more difficult for sufferers of rare diseases.

MONDAY TEACHING

SCOPE TODAYS SESSION

- Case 1:
  - Basic Questions
- Case 2
  - Basic Questions

- Basic Theory Stuff:
  - AJCC TNM + Stage Group for Carcinoid of the Appendix
  - Management of Carcinoid of the Appendix (NCCN)

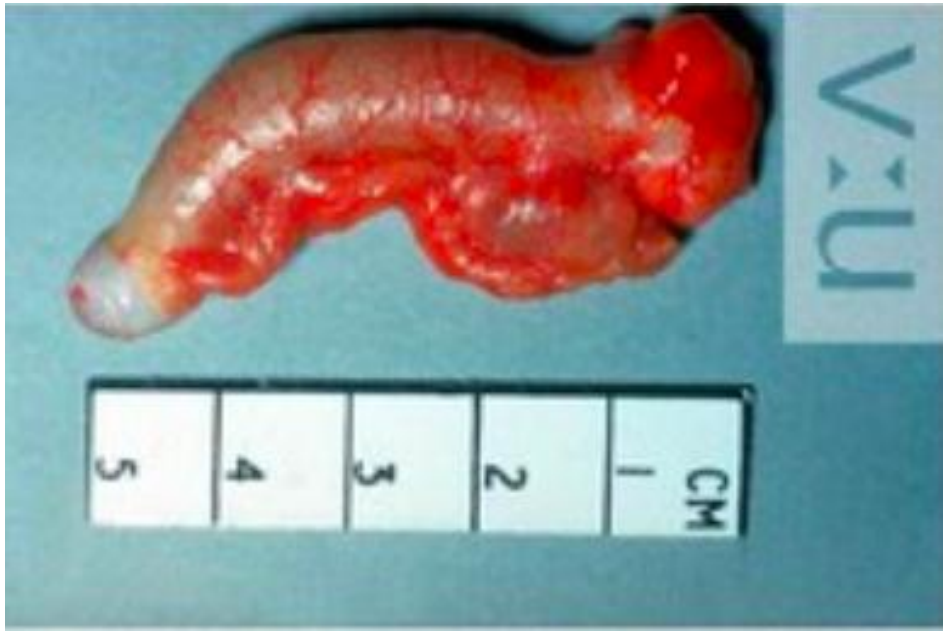
- Heavy Stuff
  - Neuroendocrine Tumours
    - Carcinoid Tumours

Case 1

- 19yo male
- HPI:
  - 24Hr central abdominal pain
  - Radiates RIF
  - Nausea, 1 x vomit
  - Anorexia
- PMH
  - Well, no allergies, no meds, vaccinated
- No significant family Hx
- Examination
  - RR21
  - Temp 38.1
  - HR 91
  - Tender RIF
  - Guarded RIF
  - Scrotum normal
- Bloods:
  - WCC 14

Case 1

- What is the Diagnosis?
- Does this patient have SIRS?
- Do you image this patient? If so how?
- At surgery you find this:
- Describe..



- How can carcinoid of the appendix present?

Basic Questions

- What is the incidence of incidental carcinoid at appendicectomy?
- Which histologic type should we be most concerned about, and what is special about their recommended treatment?
- We will discuss management later…

Case 2

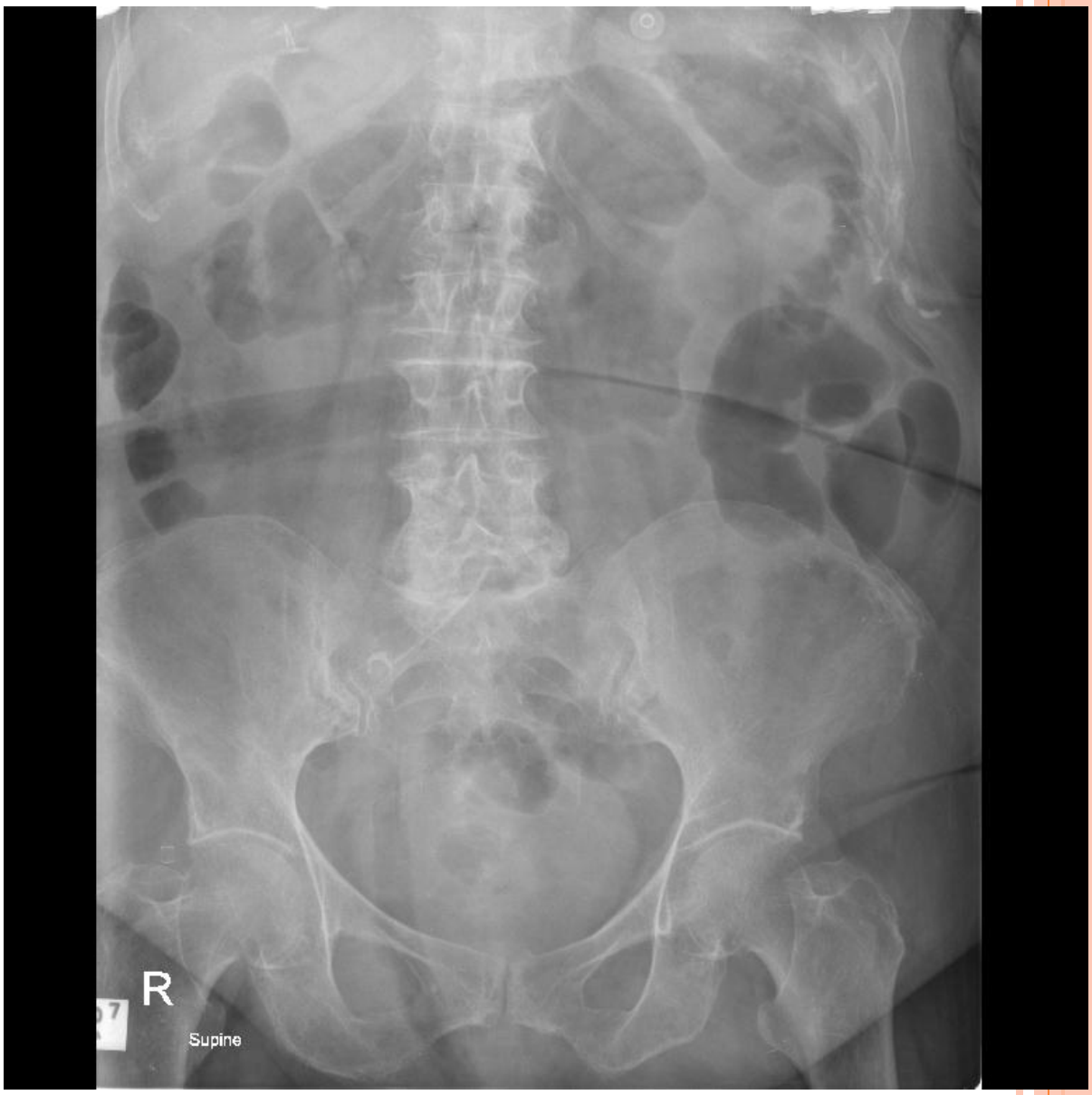
- HPI:
  - Worse pain(10/10), D+V for 3 days
  - Nil fevers or chills, nil infectious contact
  - Flushing of face recently
- PMH:
  - Colonscopy 12 months ago ? Normal
  - Cramping RIF pain /12
  - Diarrhoea
  - AF, IHD, T2DM
- Examination:
  - Afebrile
  - HR 100 irregular
- Dry mucous membranes
- Flushed cheeks
- Abdomen:
  - soft,
  - tender epigastrium and RIF,
  - nil rebound tenderness or guarding
- Pigmented lower legs
- Bloods;
  - WCC: 18.5, CRP: 109

Case 2

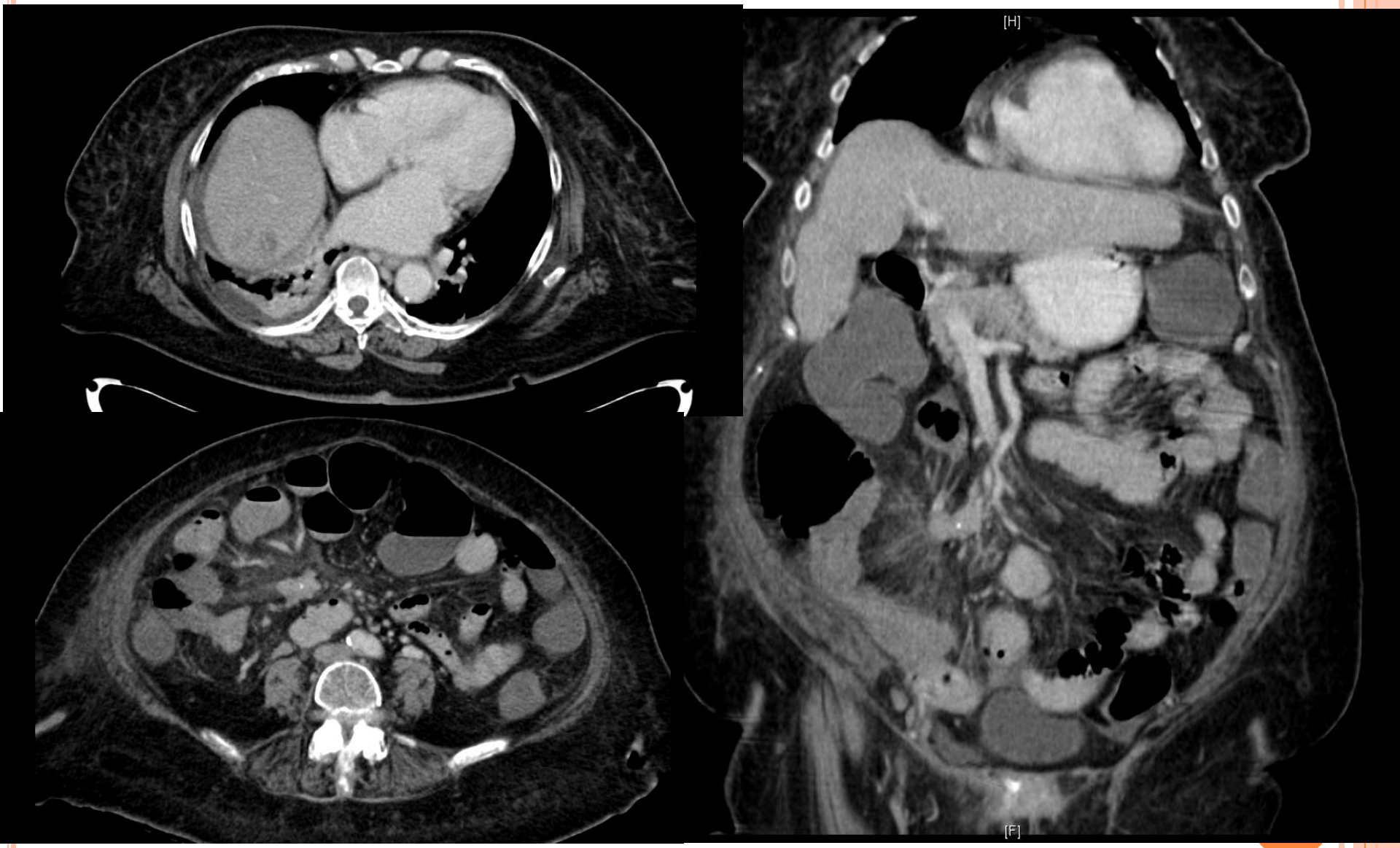
- Basic Questions:
  - What is the possible diagnosis?
  - Do you want imaging?
  - Do you want any other tests?

Abdominal x-ray

- Describe this image?



Further Imaging

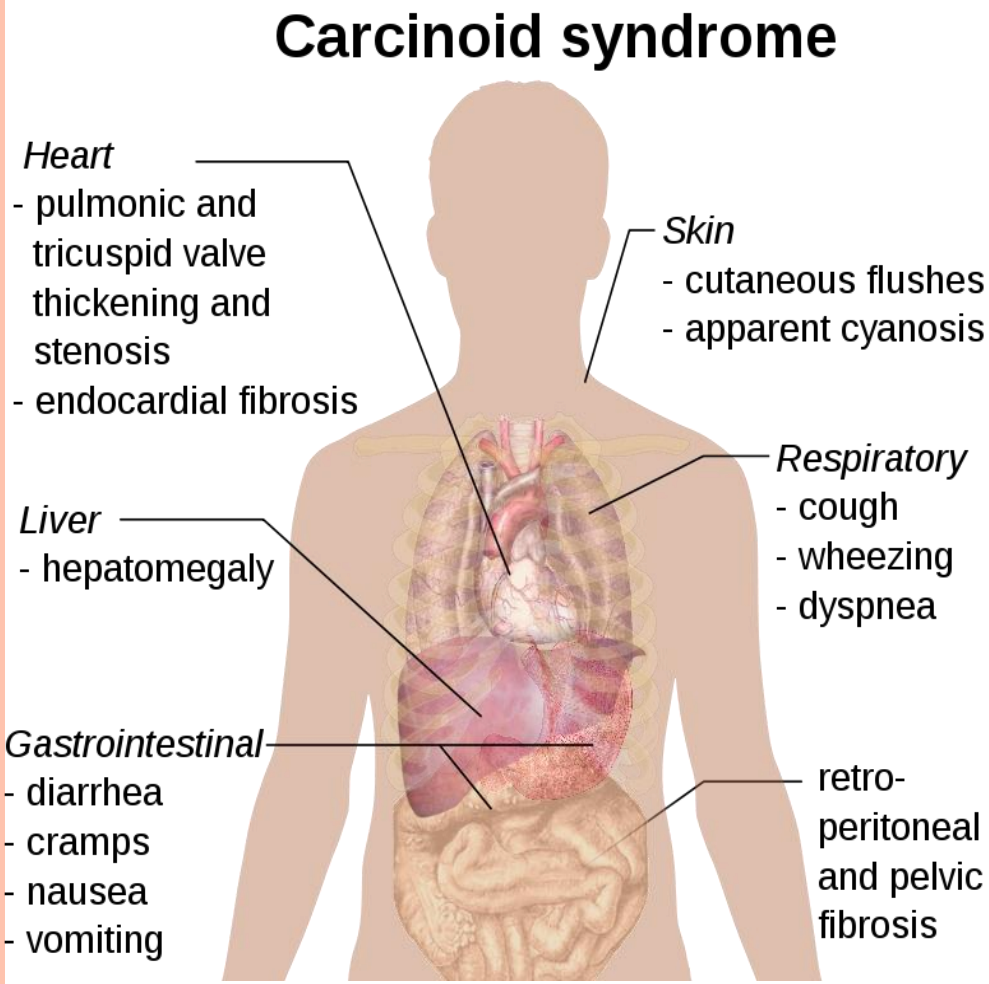


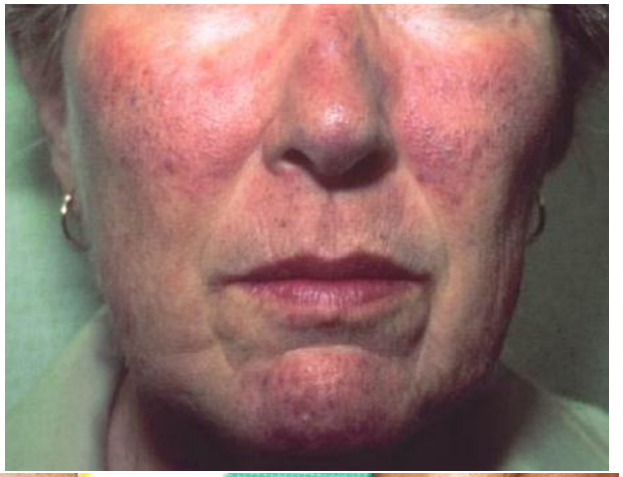
Describe these images?

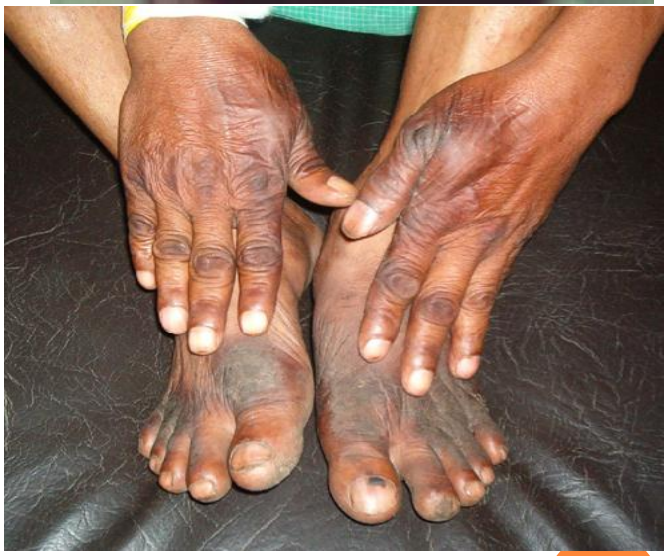
The Typical CT Description carcinoid tumour:

- mass with *soft-tissue attenuation*
- *spiculated borders* and radiating surrounding strands.
- *Calcification* may be noted in the tumor.
- *Linear strands within the mesenteric fat* probably are thickened and retracted vascular bundles and represent *peritumoral desmoplastic* reaction.
- Lymphadenopathy and *liver metastases* may be visualized on CT scans

Why does this patient have the additional findings?







pellagra

Basic Theory Stuff – Appendiceal Carcinoid

- Most common tumour of the appendix
- Found in 0.5%- 1% of appendicectomy specimens
- Accounts for 85% of all appendiceal tumours
- Usually an incidental finding found during appendicectomy

- Appencideal Location:
  - 75% occur at the tip,
  - 15% in the middle and
  - 10% at the base of the appendix

- Size: 80% < 1 cm, 5% >2 cm in diameter

AJCC 7th Ed Appendiceal Carcinoid

- Appendix Classification New to 7th Edition
  - Carcinomas (i.e. adenocarcinoma)
  - Carcinoid (this is separate to SB and NET)
    - Although neuroendocrine in nature they are seperately classified because of greater frequency, variety of subtypes and behavioural differences to other gastrointestinal NET

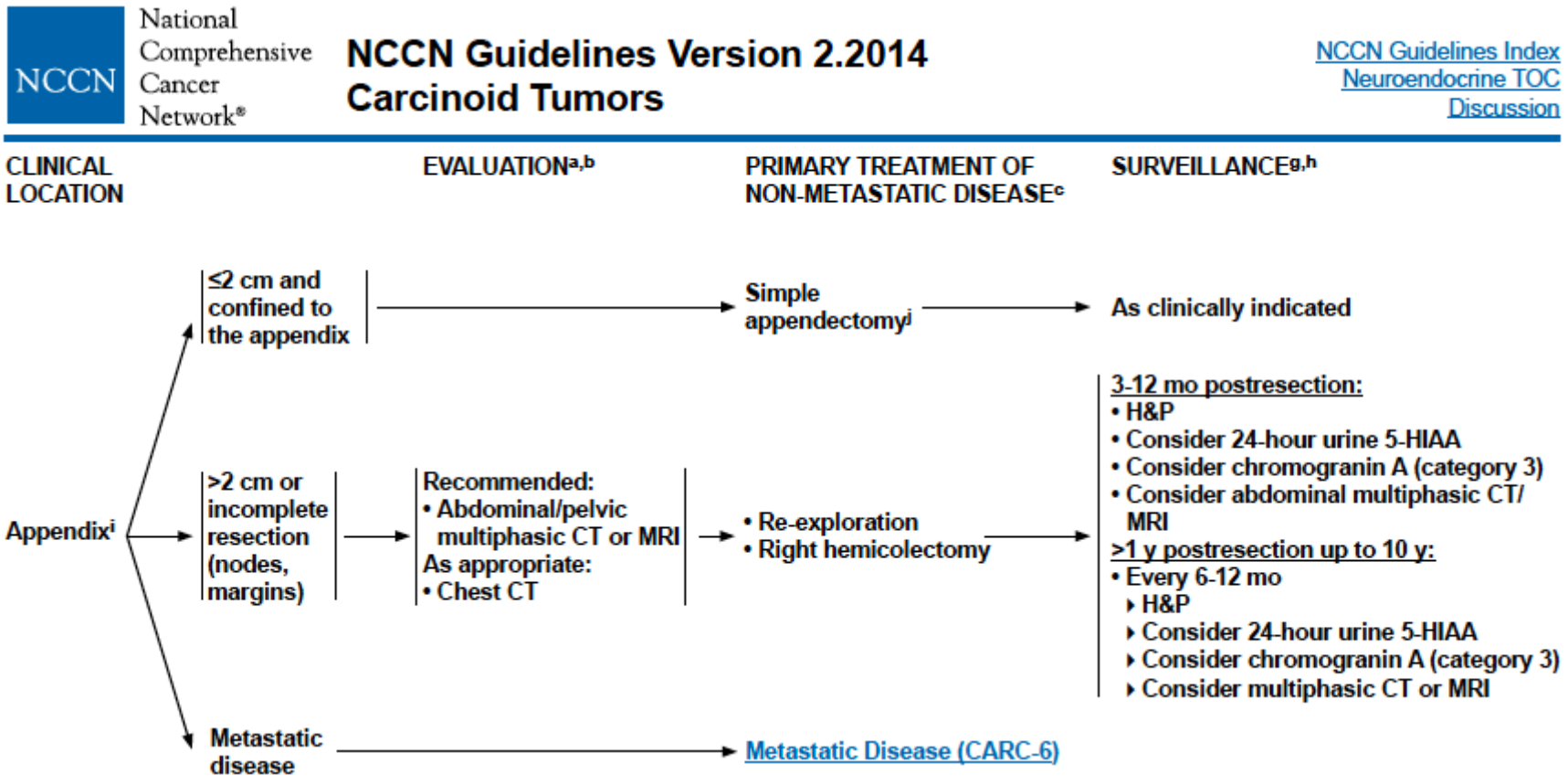
- **T:**
  - T0
  - T1 <2cm
  - T2 2-4cm or extends caecum
  - T3 >2cm or extends ileum
  - T4 invades other organs

- **N:**
  - N0
  - N1 = regional nodes
- **M**
  - M0
  - M1 other organ

- **Stages:**
  - I-II = T1-3
  - III = N1
  - IV = M1

- Note: Goblet cell carcinoid staged as carcinoma

Management Appendiceal Carcinoid (NCCN)



[a] See Principles of Pathology for Diagnosis and Reporting of Neuroendocrine Tumors (NE-A).
[b] See Serum Hormone Evaluation Potentially Indicated in the Workup of Neuroendocrine Tumors (NE-B).
[c] See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).

[g] Earlier, if symptoms.
[h] Somatostatin scintigraphy and PET scan are not recommended for routine surveillance.
[i] Some appendiceal carcinoids will have mixed histology, including elements of adenocarcinoma. Such tumors should be managed according to colon cancer guidelines. See NCCN Guidelines for Colon Cancer.
[j] Some institutions will consider more aggressive treatments for 1- to 2-cm tumors with poor prognostic features. See Discussion for details.

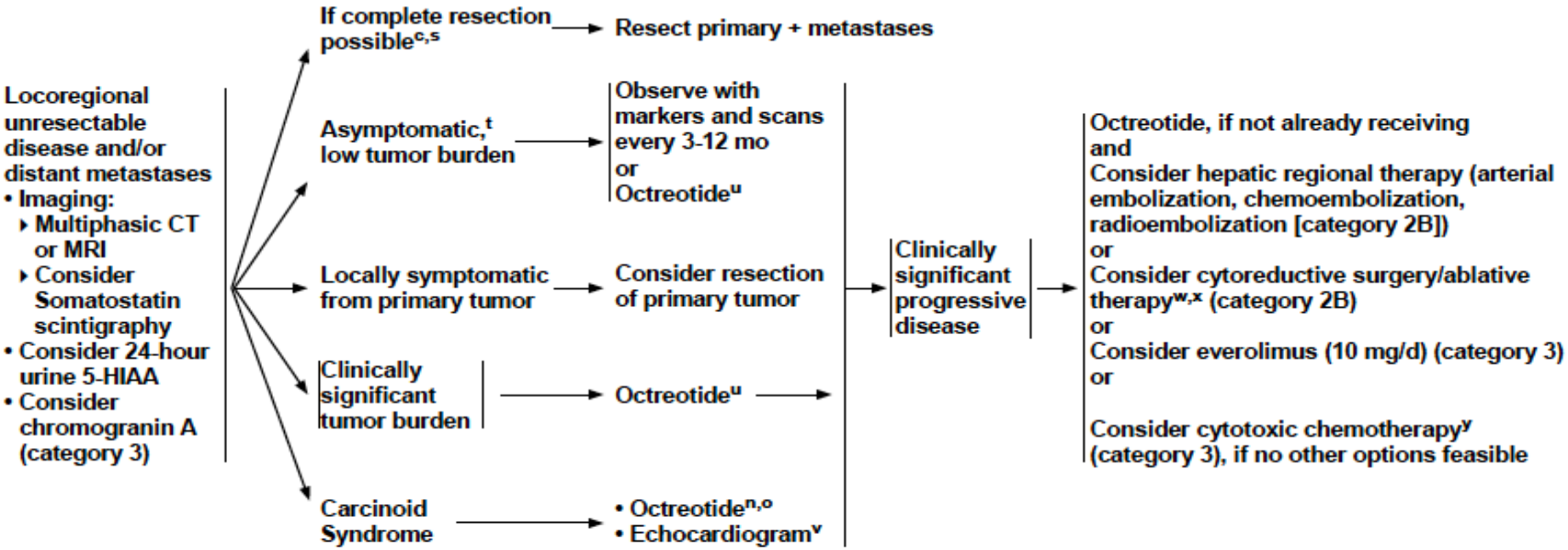
Metastatic Disease

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2014
Carcinoid Tumors

NCCN Guidelines Index
Neuroendocrine TOC
Discussion

MANAGEMENT OF LOCOREGIONAL UNRESECTABLE DISEASE AND/OR DISTANT METASTASES[c]



[c] See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).

[n] For symptom control, octreotide 150-250 mcg SC TID or octreotide LAR 20-30 mg IM every 4 weeks. Dose and frequency may be further increased for symptom control as needed. Therapeutic levels of octreotide would not be expected to be reached for 10-14 d after LAR injection. Short-acting octreotide can be added to octreotide LAR for rapid relief of symptoms or for breakthrough symptoms.

[o] Lanreotide is approved for symptom control in Europe. Lanreotide has a similar mechanism of action as octreotide and may be preferable in patients who have difficulty tolerating an IM versus SC injection.

[s] Noncurative debulking surgery might be considered in select cases.

[t] Resection of a small asymptomatic (relatively stable) primary in the presence of unresectable metastatic disease is not indicated.

[u] For tumor control, the PROMID study (J Clin Oncol 2009;27:4656-4663) used octreotide LAR 30 mg IM every 4 weeks.

[v] If signs and symptoms of heart disease or planning major surgery.

[w] Includes ablative techniques such as radiofrequency, microwave, and cryotherapy. There are no randomized clinical trials and prospective data for these interventions are limited. However, data on the use of these interventions are emerging.

[x] Only if near complete resection can be achieved.

[y] Anticancer agents such as capecitabine, dacarbazine, 5-FU, interferon, oxaliplatin, and temozolomide can be used in patients with progressive metastases for whom there are no other treatment options. See Discussion for details.

Heavy Duty Stuff – The History

- Characterized in 1907 by Siegfried Oberndorfer, a German pathologist.
- *karzinoide*, or "carcinoma-like", to describe the unique feature of behaving like a benign tumor despite having a malignant appearance microscopically.
- Endocrine-related properties were later described by Gosset and Masson in 1914, and these tumors are now known to arise from the enterochromaffin (EC) and enterochromaffin-like (ECL) cells of the gut.

- In 2000, the World Health Organization redefined "carcinoid", but this new definition has not been accepted by all practitioners.

- The 2000 WHO definition states:[5]
  - Neuroendocrine tumors: Neuroendocrine tumors are growths that look benign but that might possibly be able to spread to other parts of the body.
  - Neuroendocrine cancers Neuroendocrine cancers are abnormal growths of neuroendocrine cells which can spread to other parts of the body.

NETs

- Classfication / Nomenclature Battlefield:
  - NANETS
  - ENETS
  - WHO
  - AJCC

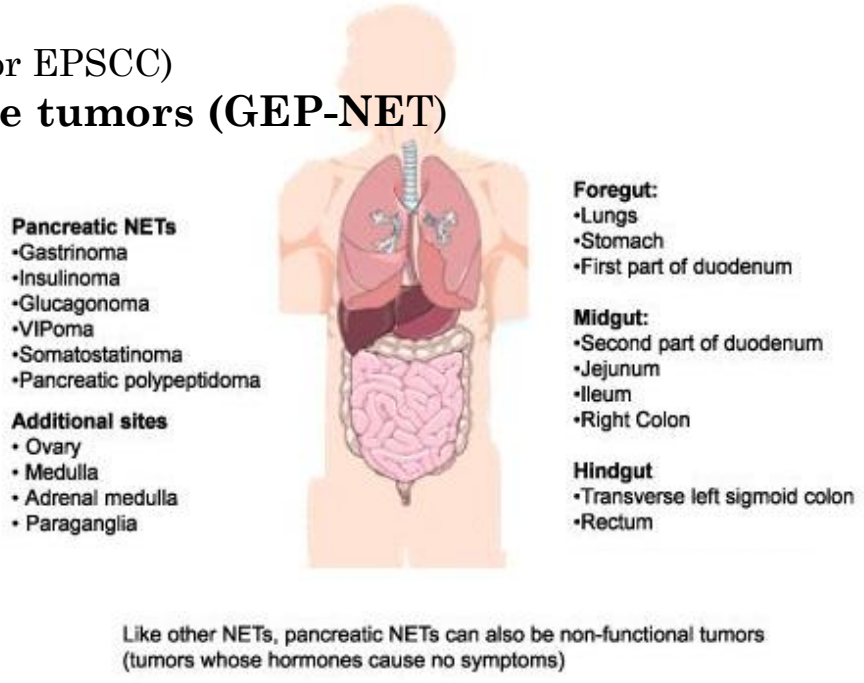
- ***But:***
- Neuroendocrine Tumours are neoplasms of neuroendocrine cells. They can occur in the lungs, GIT system, ovaries, adrenals, kidneys etc. They are divided into functional (forming a clinical syndrome) and non-functional. Commonly arise in Kulchitsky cells or similar enterochromaffin-like cells.

NET Genetic associations

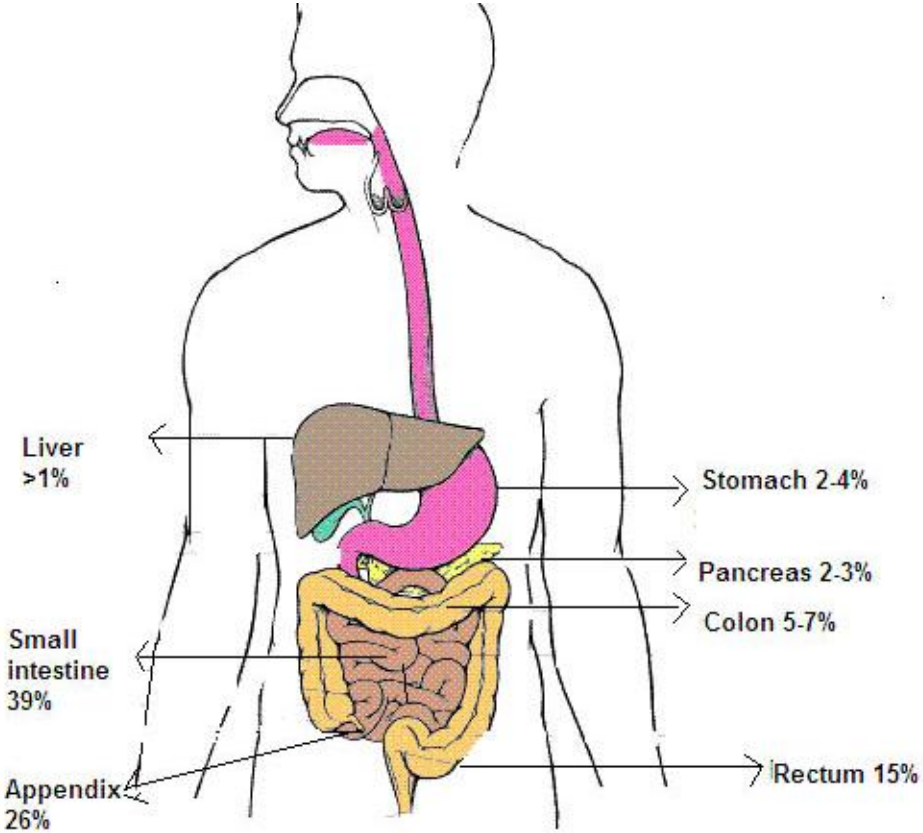
- multiple endocrine neoplasia type 1 (MEN1)
- multiple endocrine neoplasia type 2 (MEN2)
- von Hippel-Lindau (VHL) disease
- neurofibromatosis type 1
- tuberous sclerosis
- Carney complex

Neuroendocrine Tumours (NETs)

- NETS By Anatomical Site:
  - Pituitary gland: Neuroendocrine tumor of the anterior pituitary
  - Thyroid gland: - medullary carcinoma
  - Parathyroid tumors
  - Thymus and mediastinal carcinoid tumors
  - Pulmonary neuroendocrine tumors
    - Bronchus
    - Pulmonary carcinoid tumors
    - Small-cell lung cancer (SCLC)
    - LCNEC\
    - Extrapulmonary small cell carcinomas (ESCC or EPSCC)
  - **Gastroenteropancreatic neuroendocrine tumors (GEP-NET)**
    - **Carcinod:**
      - Foregut GEP-NET
      - Midgut GEP-NET
      - Hindgut GEP-NET
    - **Pancreatic endocrine tumors (pNET)**
  - Adrenal tumor:
    - Pheochromocytoma
    - Peripheral nervous system tumors, such as:
    - Schwannoma
    - paraganglioma
    - Neuroblastoma
  - Merkel cell carcinoma of skin



Carcinoid Tumours (GEP-NET) by Site



Location	%
Appendix	44
Rectum	15
Ileum	11
Lungs and Bronchus	10
Small intestine (non- specific)	5
Colon	5
Cecum	3
Stomach	2
Duodenum	2
Jejunum	1

Investigations for Carcinoid Tumours

- 24 hour urine collection 5HIAA
- Chromogranin A

- Imaging:
  - CT Chest/Abdomen/Pelvis
  - Octreotide scan
  - Dotatate PET scan
  - MIBG

- Scopes:
  - Bronchoscopy
  - Gastroscopy
  - Colonoscopy

Important Pathology charactoristics

- Mitosis
- Ki67 Index

Grade	**Criteria**
Low (G1)	<2 mitoses/10hpf + < 3% **Ki67** index
Intermediate (G2)	2-20 mitoses/10hpf / 3-20% **Ki67** index
High (G3)	>20 mitoses /10hpf/>20% **Ki 67** index

Carcinoid Syndrome

When the primary tumour is in the GIT the serotonin and kallikrein are inactivated in the liver; manifestations of carcinoid syndrome do not occur until there are mets to the liver or cirrhosis.

Carcinoid tumours arising in the bronchi may be associated with manifestations of carcinoid syndrome without liver metastases because their biologically active products reach the systemic circulation before passing through the liver and being metabolised.

Thank You

NANETS Consensus Guidelines

- Tumour differentiation refers to the extent of resemblance to the normal cellular counterpart.
- Tumour grade refers to the degree of biologic aggressiveness and is related to differentiation but different.
- Tumour stage refers to the extent of spread of the tumour.
- Consensus from US,Europe,North America 2010

- Grade Versus Differentiation in Neuroendocrine Tumors

Differentiation	Grade
• Well differentiated (WHO)	Low grade (ENETS G1)
	Intermediate grade (ENETS G2)
• Poorly differentiated (WHO)	High grade (ENETS G3)

Lowell et al. Pancreas 2010 39:6;767-774

Grade	Traditional	ENETS / WHO	Moran et al.
Low Grade	Carcinoid Tumour	NET Grade 1 (G1)	NEC Grade 1
Intermediate Grade	Carcinoid Tumour	NET Grade 2 (G2)	NEC Grade 2
High Grade	Small cell carcinoma	NE carcinoma Grade 3 (G3) small cell carcinoma	NEC Grade 3 small cell
	Large cell neuroendocrine carcinoma	NE carcinoma Grade 3 (G3) large cell neuroendocrine	NEC Grade 3 large cell

Prognostic Factors

- The general prognosis in carcinoid tumour is excellent compared with that of other visceral cancers.
- Based on a world literature of some 2,837 cases, the median 5-year survival rate for all cases is 82%