Emerging Trends in Neuroendocrine Tumor Management

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Objectives

- 1) Diagnostic dilemmas:
  - Understand the features distinguishing slow-growing tumors from the aggressive endocrine carcinomas
- 2) Therapeutic conundrums:
  - Can novel effective therapy be based on underlying pathogenetic/progression factors?

Aims:

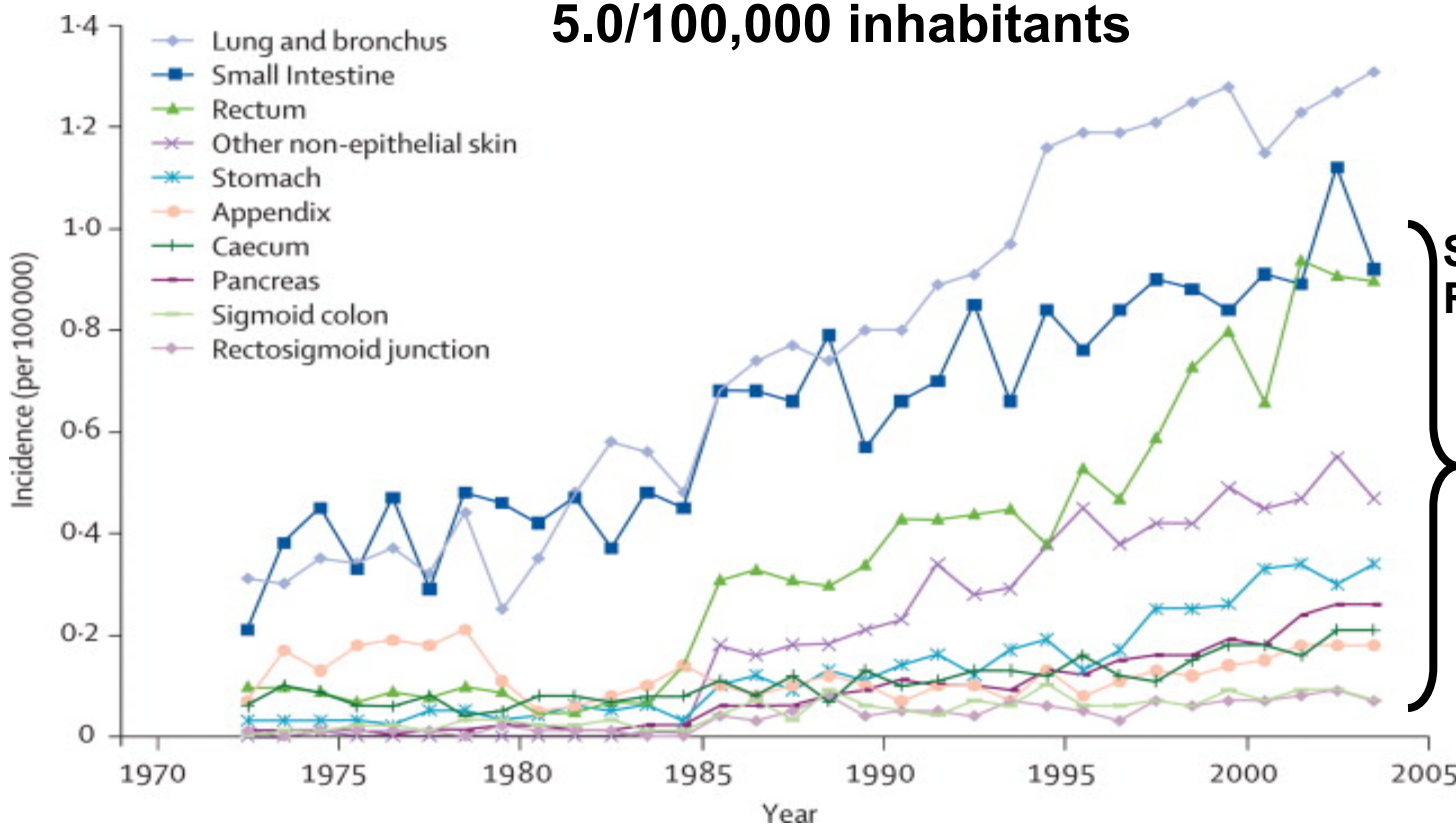
- Advances in classification of NETs
- Clinical Features
- Biomarkers
- Molecular imaging
- Today’s therapeutic landscape

Myth #1

- Neuroendocrine tumors (NETs) are extremely rare

Increasing Incidence of neuroendocrine tumors in the western world

5.0/100,000 inhabitants



Lung

Small intestine
Rectum

GEP-NET

~ 75%

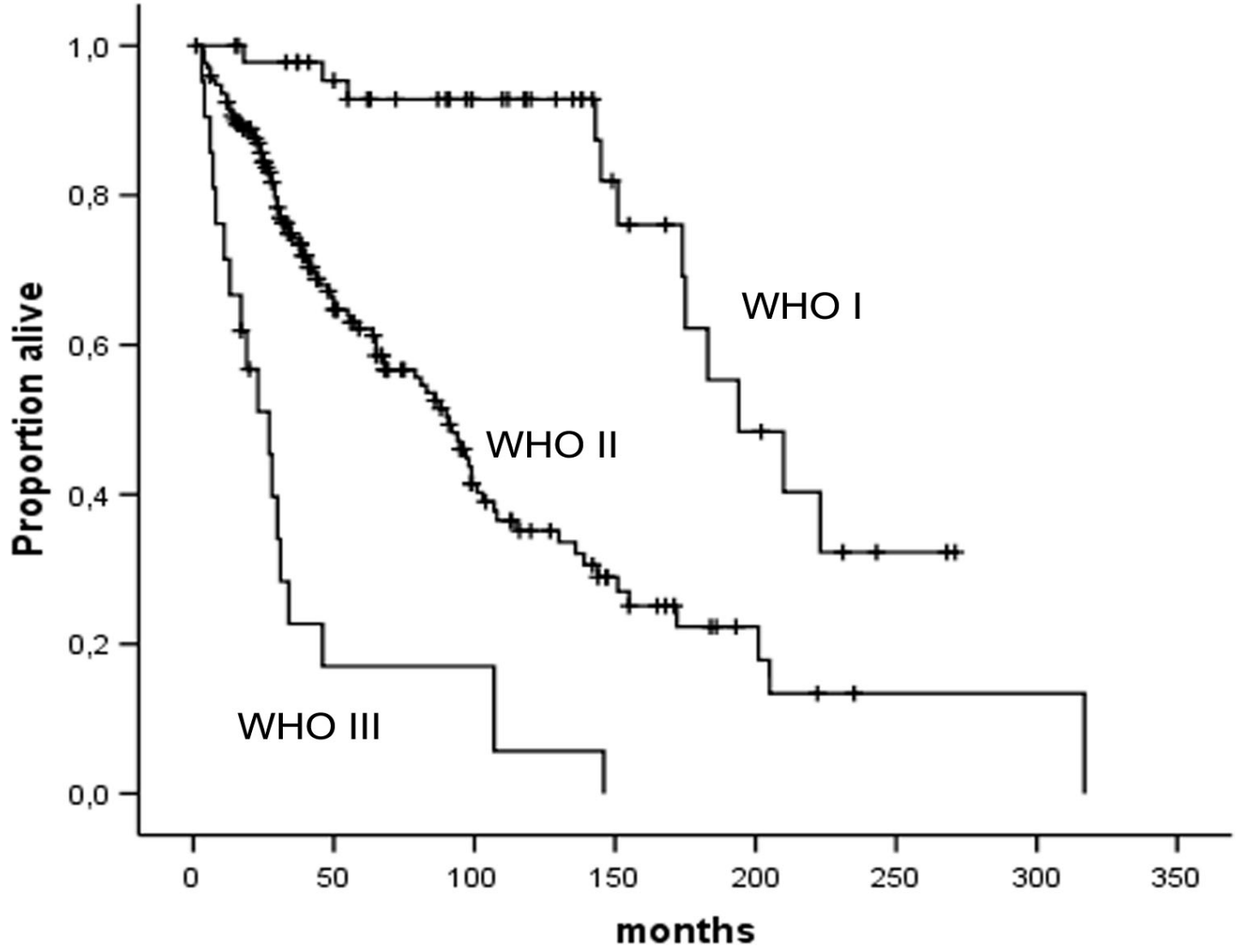
Surveillance, Epidemiology and End Results (SEER), US population 1974-2005

Modlin et al., Lancet Oncol. 2008

Myth #2

- Neuroendocrine tumors (NETs) are not really cancers

Survival in patients with pancreatic endocrine tumors 2004 WHO grading



Ekeblad et al

Myth #3:

- Neuroendocrine tumors are gut tumors resulting largely in flushing and diarrhea

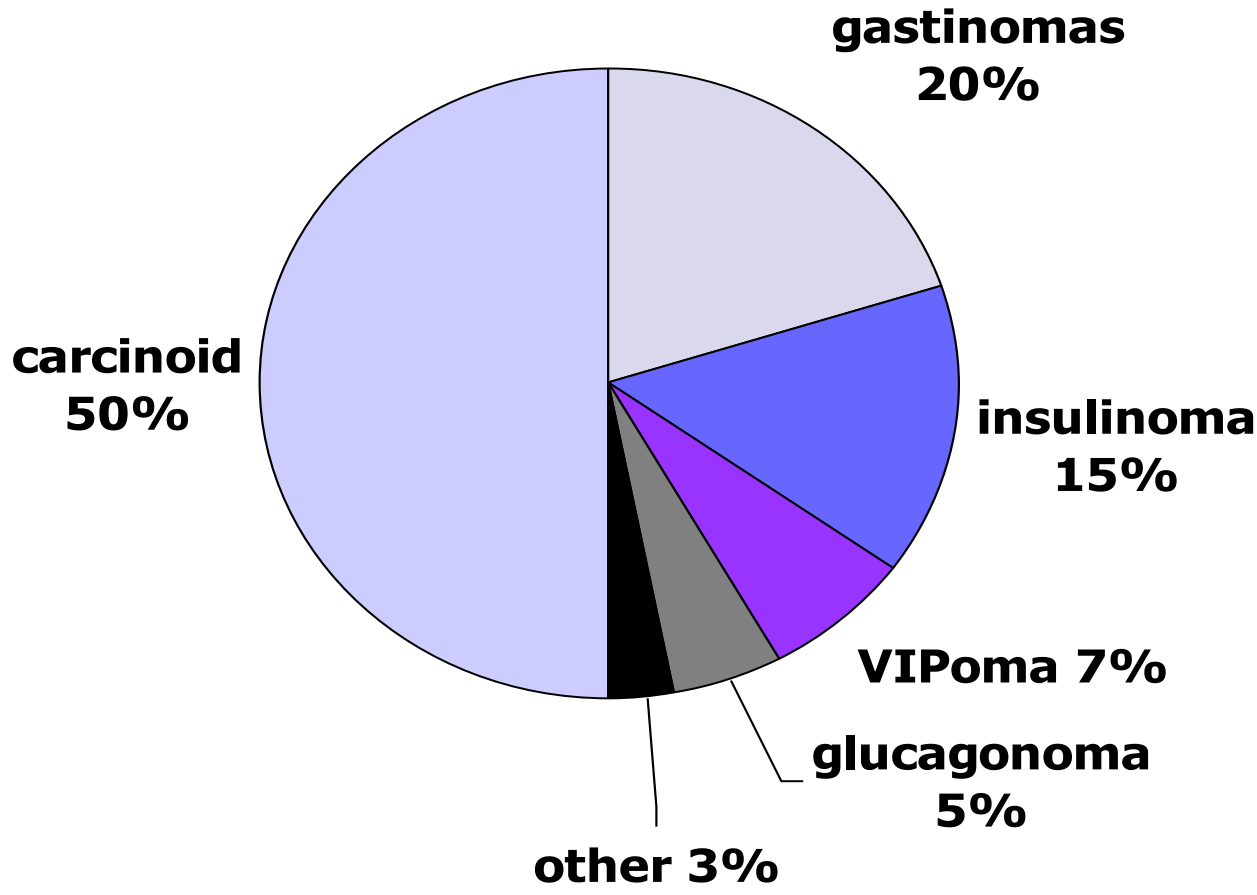
Cellular Classification of GEP Endocrine Tumors

Hormone	Cell	Syndrome
Gastrin	G	ZE syndrome
Glucagon/GLP	A/L	DM/rash
Insulin	ß	hypoglycemia
Secretin	S	WDHA
Serotonin	ED	“carcinoid”
Somatostatin	D	DM/gallstone
VIP	?	VM syndrome

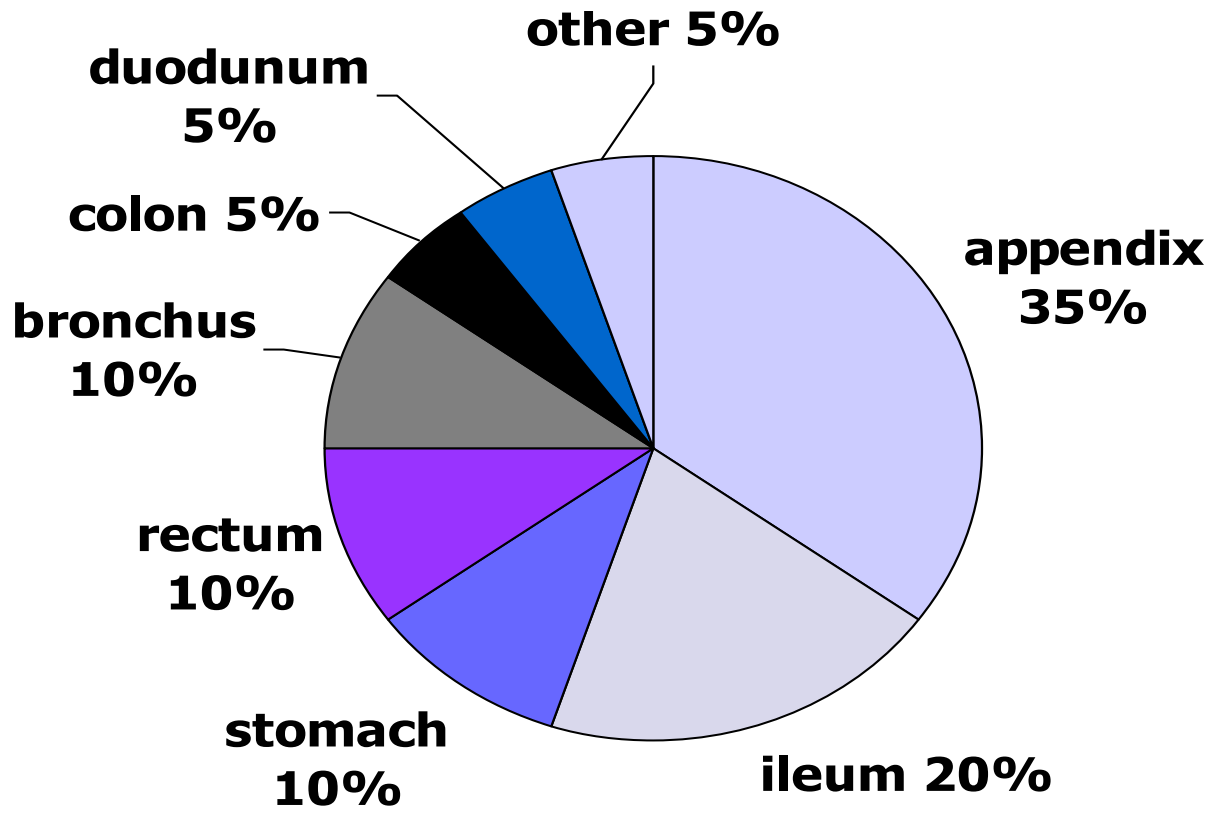
Classification of GEP Endocrine Tumor Cells

Hormone	Cell	Syndrome
–		
Cholecystokinin	I	?
Pancreatic polypeptide	PP	?

GEP-Neuroendocrine tumours



Anatomic Distribution of GEP tumours



“Carcinoid” or “Endocrine Carcinoma”

- ? well differentiated neuroendocrine tumors
- ? clinical “carcinoid syndrome”
- ? prognosis

Histologic Diagnosis of Endocrine Carcinoma

- Difficulties:
  - primary not obvious
  - malignancy not obvious

Immunohistochemical Diagnosis of Neuro-Endocrine Carcinomas

- General:
  - Neuron specific enolase (NSE)
  - Synaptophysin
  - Chromogranin
  - Thyroid transcription factor (TTF1)
    - Am J Surg Pathol 2001;25:815-19

Immunohistochemical Diagnosis of Neuro-Endocrine Carcinomas

- Specific:
  - Hormones
    - Eutopic
      - gastrin, insulin, glucagon, VIP, etc
    - Ectopic
      - GHRH, CRH, etc.

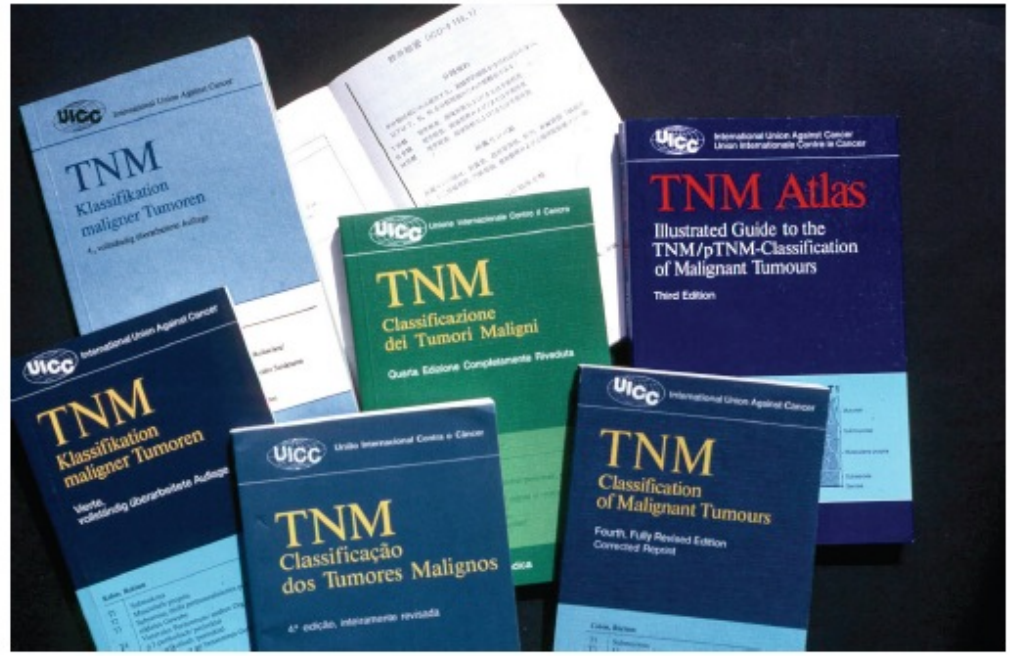
Criteria of Malignancy in GEP Tumors

- Cytologic features
- DNA Ploidy
- Proliferation markers:
  - *Ki 67 or MiB1 labeling index
- Invasion
  - capsular, adjacent tissues, perineural, vascular

WHO 2004 Grading of Well-Differentiated Neuroendocrine Tumors

Behavior	BENIGN	UNCERTAIN	LOW GRADE CARCINOMA
Extra-pancreatic extension	no	no	grossly visible (and/or)
Metastasis	no	no	yes (and/or)
Angioinvasion	no	yes	yes
Perineural invasion	no	yes	±
Size	<2 cm	>/= 2cm	any
Mitosis/10HPF	</= 2	>2	2-9
Mib1 (Ki-67)	</= 2%	> 2%	2-10%
Hormones	non-functioning or insulin	gastrin, insulin, VIP, glucagon, somatostatin or ectopic ACTH, GH or PTHrP or non-functioning	gastrin, insulin, VIP, glucagon, somatostatin or ectopic ACTH, GH or PTHrP, or non-functioning tumors.

Translations of 7th edition planned



Carcinoids and Neuroendocrine tumours

Staging

GI tract:

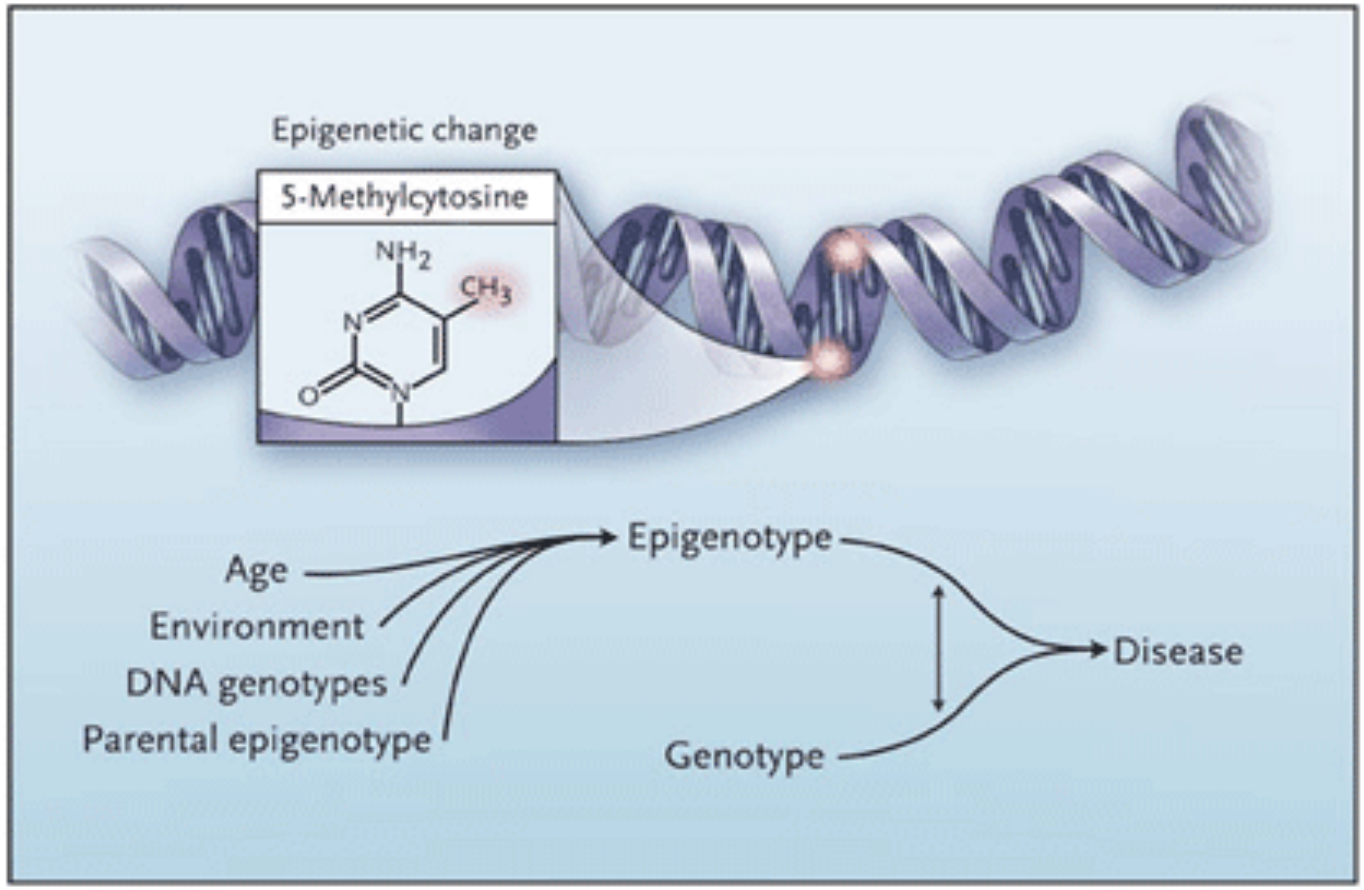
- Carcinoid : separate staging by site
- Small cell/large cell: stage as carcinoma

Pancreas: stage as carcinoma

Lung: stage as carcinoma

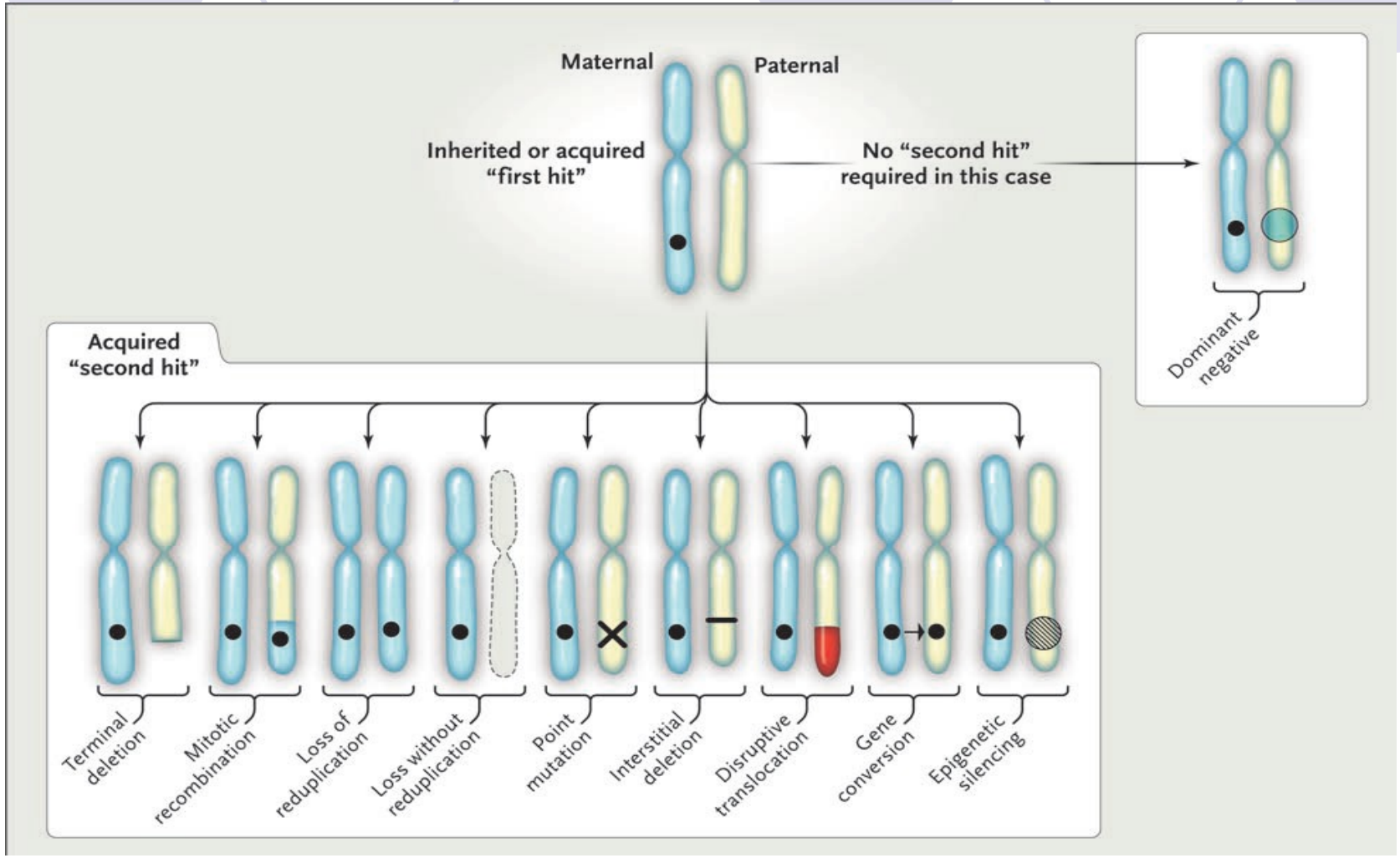
Skin: separate classification for Merkel cell carcinoma

Is it all in the genetic information?

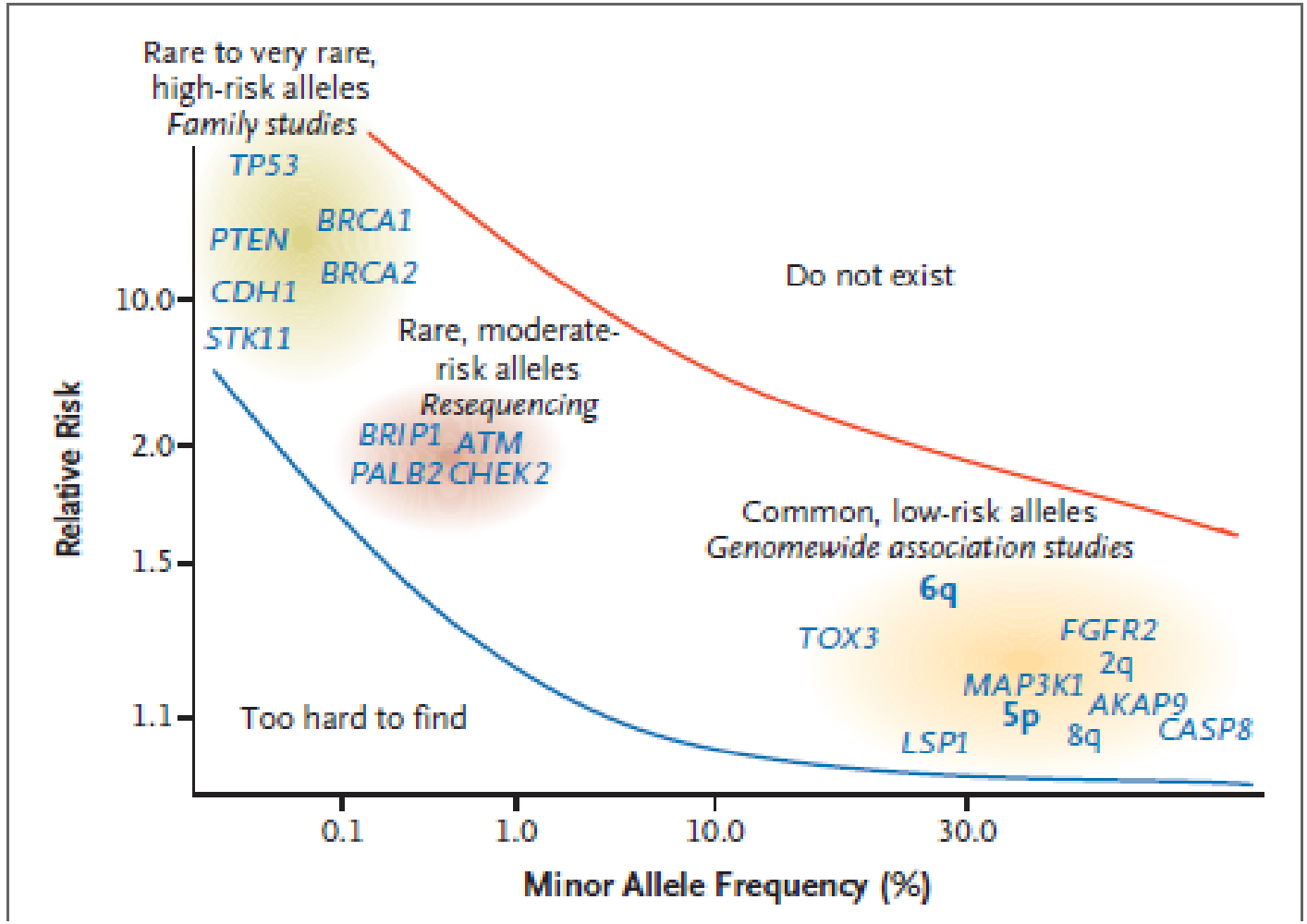


N Engl J Med. 2007;356:731-3

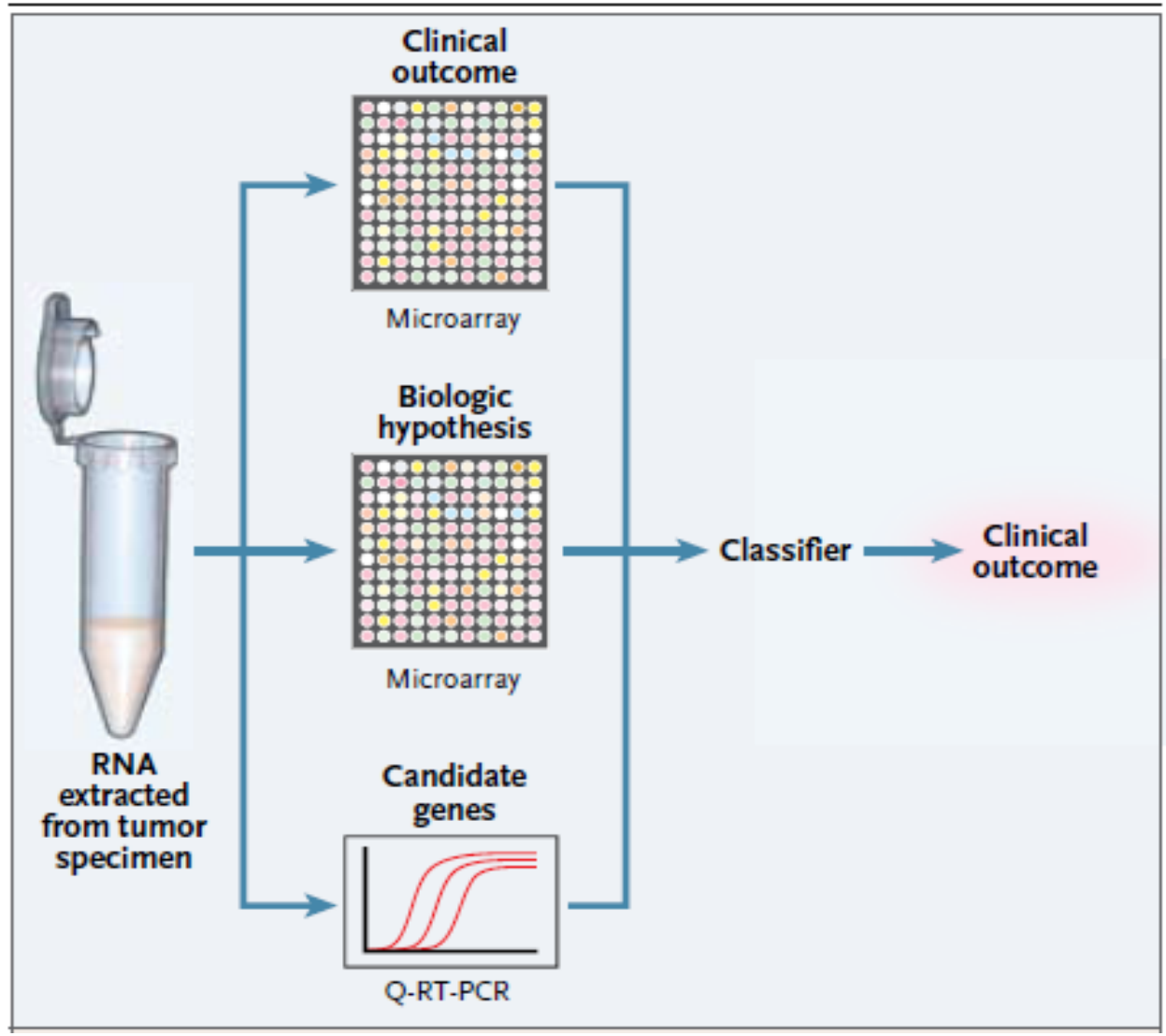
Gain or loss of genetic information



Cancer Susceptibility Genes

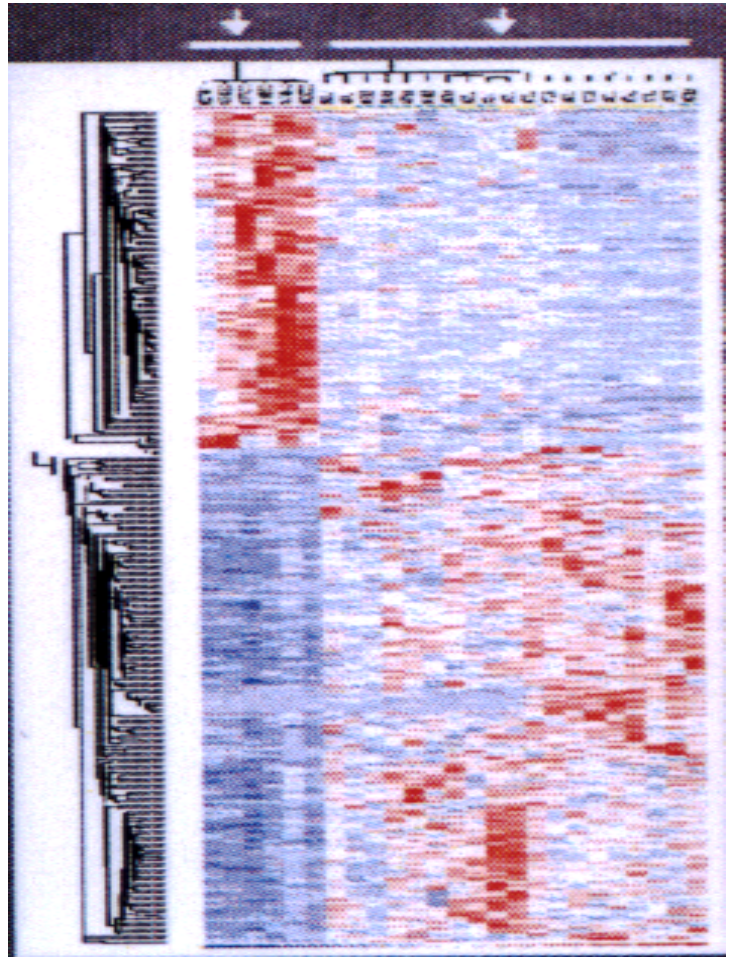


Identifying Genetic Signatures in Cancers



DNA Microarray Analysis:GI Carcinoids and PNETs Cluster independently

GI Carcinoid PNET



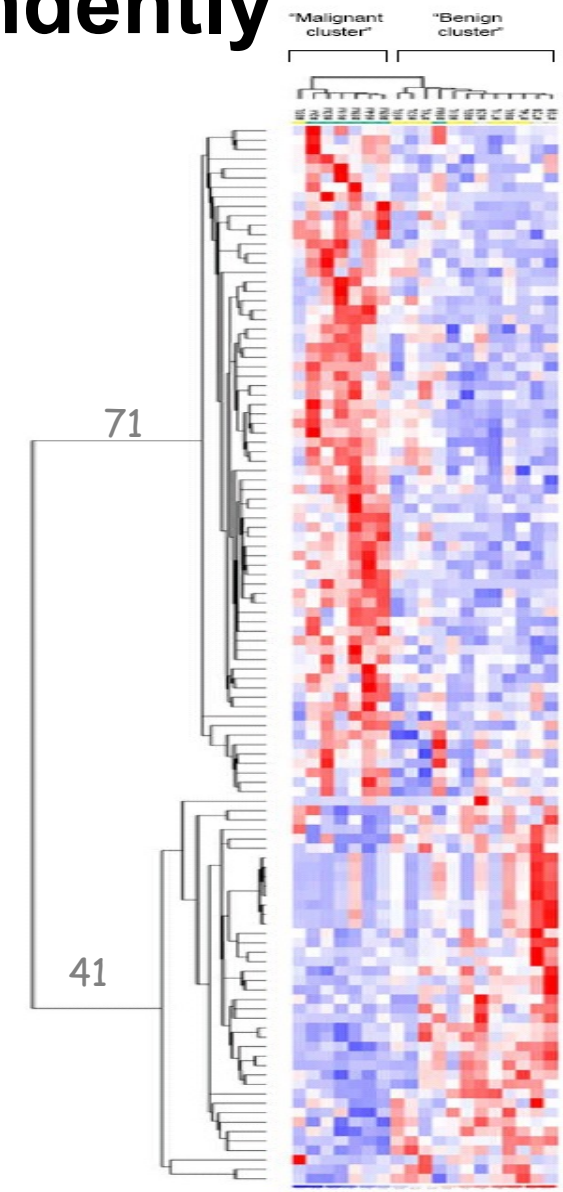
Duerr et al. Endocr Rel Cancer. 2008

Benign and malignant PNETs cluster independently

- 112 genes differentially expressed with P < 0.05

- "benign" cluster
  - 3/3 WDETs – benign
  - 8/9 WDETs – LGM
  - 1/7 WDEC

- "malignant" cluster
  - 6/7 WDECs
  - 1/9 WDETs - LGM



Duerr, et al. Endo Rel Cancer, 2008

Distinction between pNET and PDAC

Different Genes for Different Pancreatic Tumors

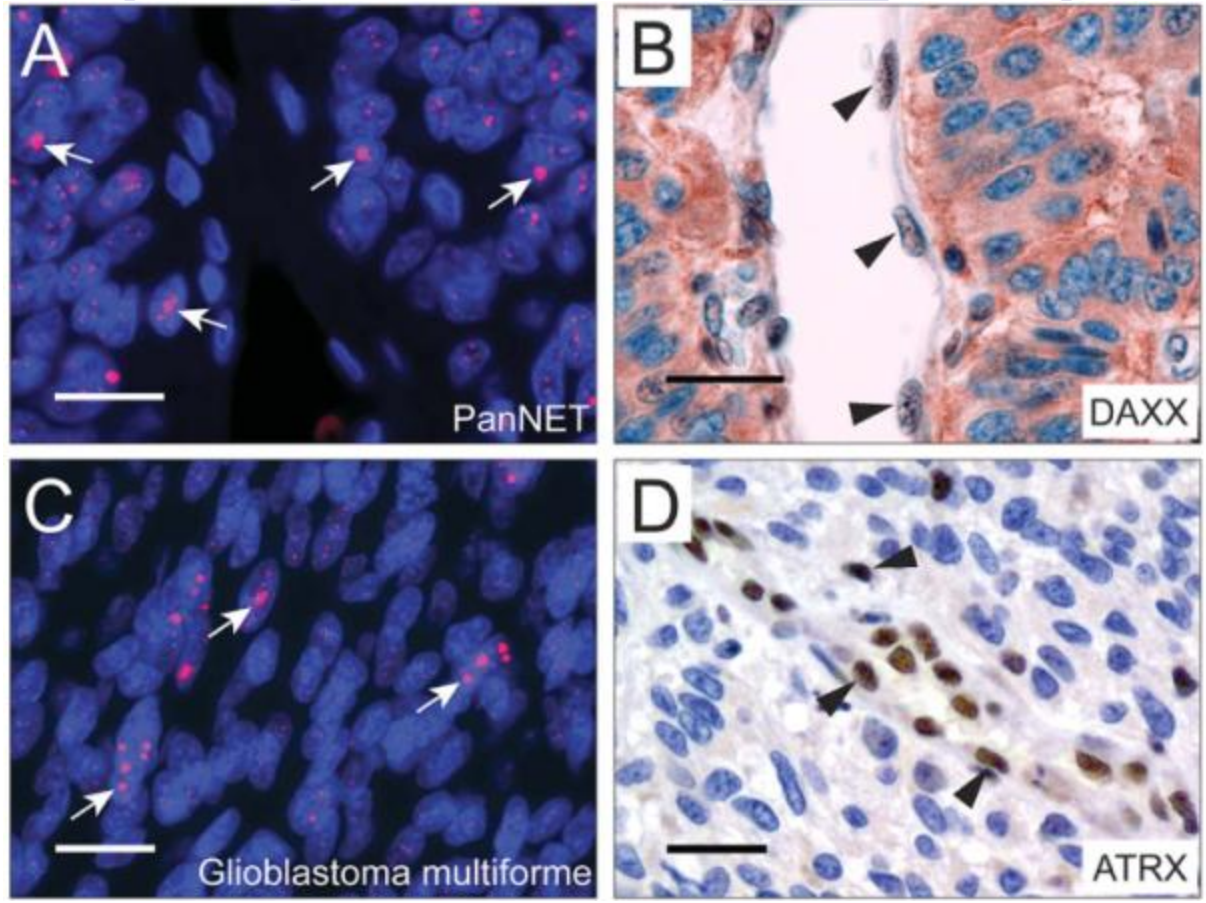
Table 1

Comparison of commonly mutated genes in PanNETs and PDAC[c]

Genes[a]	PanNET	PDAC[b]
MEN1	44%	0%
DAXX, ATRX	43%	0%
Genes in mTOR pathway	15%	0.80%
TP53	3%	85%
KRAS	0%	100%
CDKN2A	0%	25%
TGFBR1, SMAD3, SMAD4	0%	38%

[a]Includes point mutations and indels.
[b]Data from Jones*et al*., *Science* **321**, 1801 (2008).
[c]Based on 68 PanNETs and 114 PDACs.

Altered Telomers in DAXX/ATRX + pNETs

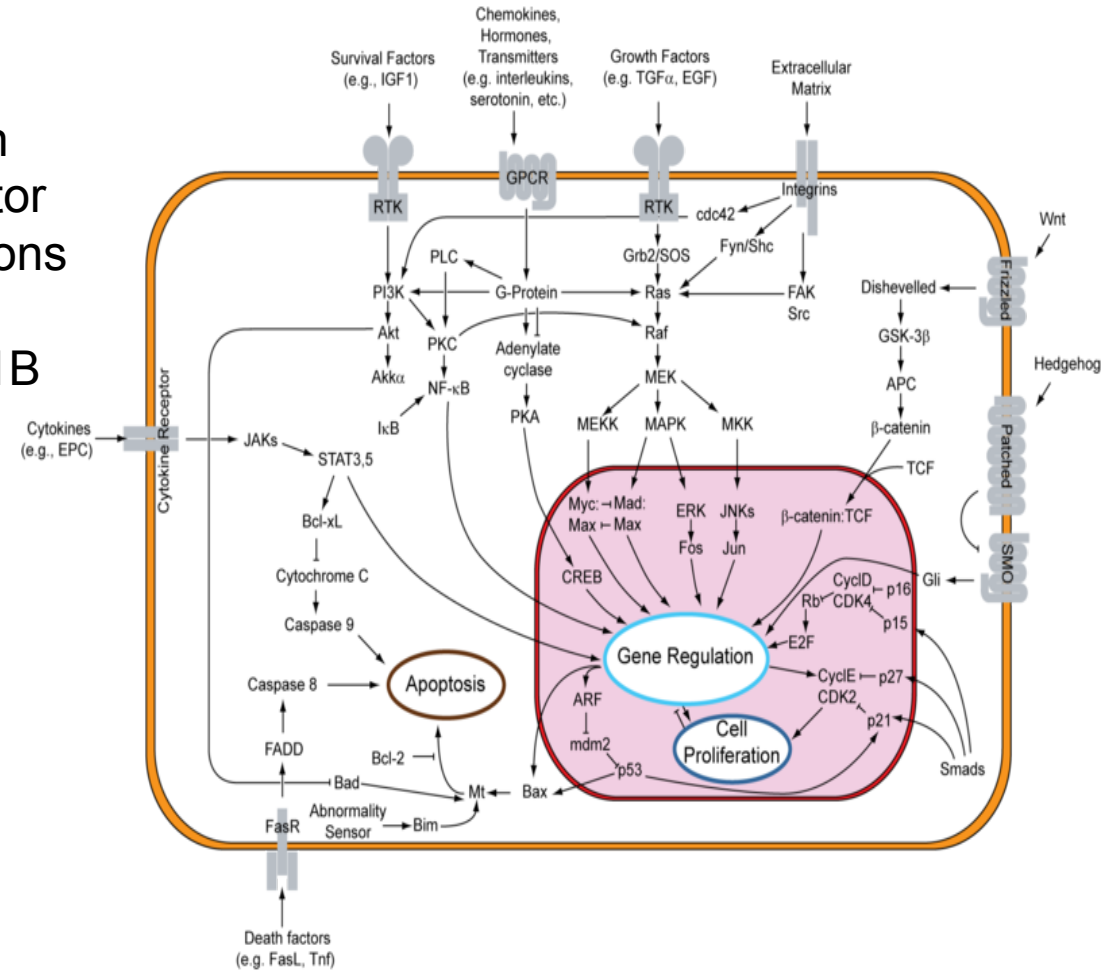


- Science. 2011 Jul 22;333(6041):425

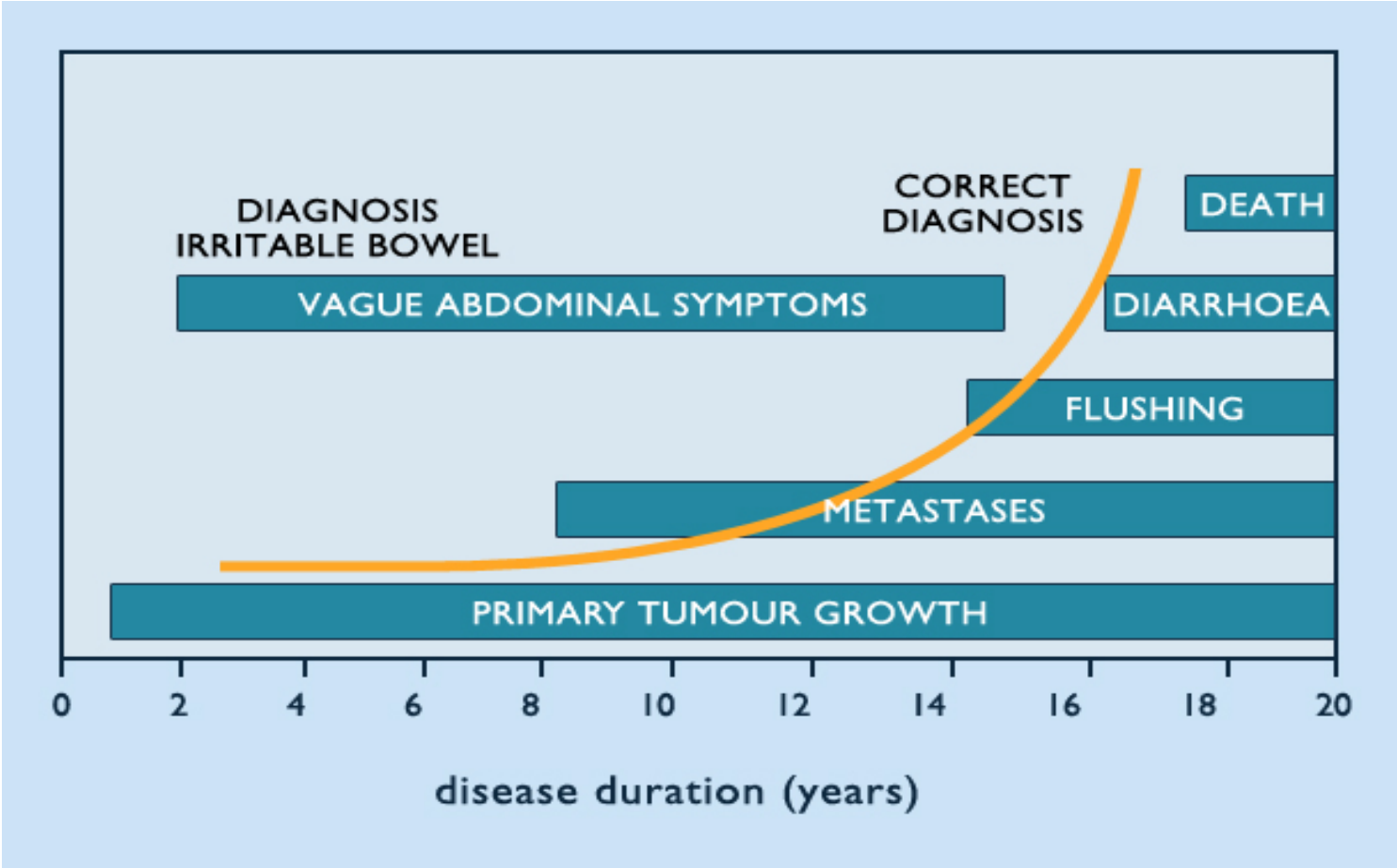
The Elusive Small Bowel NET Gene

Recurrent somatic mutations and deletions in CDKN1B, the cyclin-dependent kinase inhibitor gene, which encodes p27. Frameshift mutations of CDKN1B in 14 of 180 SI-NETs, and hemizygous deletions encompassing CDKN1B in 7 out of 50 SI-NETs: nominating p27 as a tumor suppressor and implicating cell cycle dysregulation in the etiology of SI-NETs.

Nature Genetics; 2013:45,1483–1486.



Progression and survival in classical “carcinoid syndrome”



Vinik A, et al. *Dig Dis Sci*. 1989; 34: 14S–27S.

Carcinoid syndrome

- <10% of carcinoid tumours
- Features
  - Diarrhea 83%
  - Flushing 49%
  - Dyspnea 20%
  - Bronchospasm 6%
  - Valvular heart disease
- ↑ serotonin levels
  - 96% with carcinoid syndrome
  - 25% without carcinoid syndrome

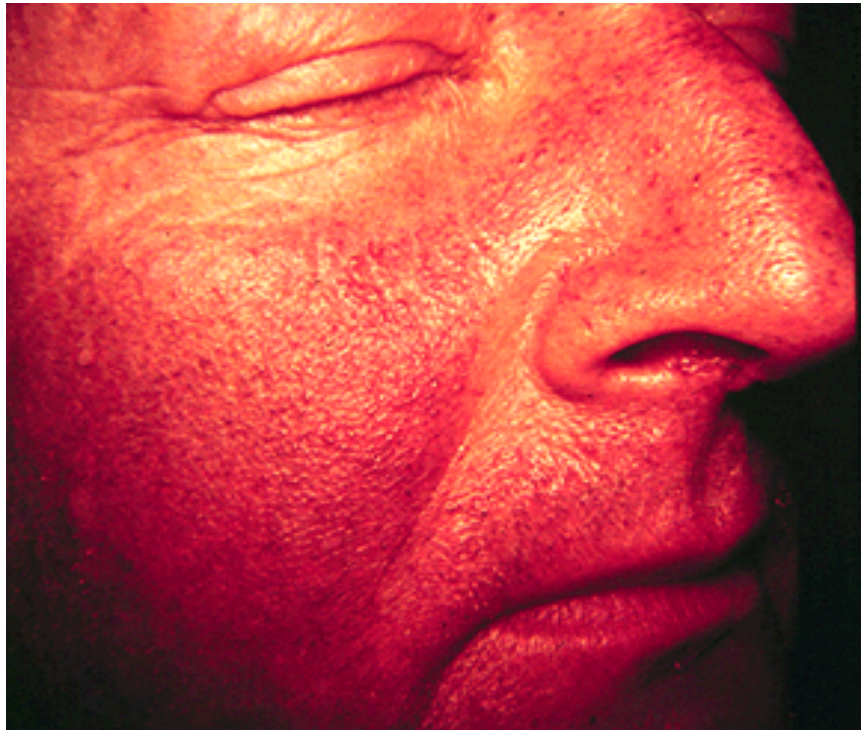
Diarrhea

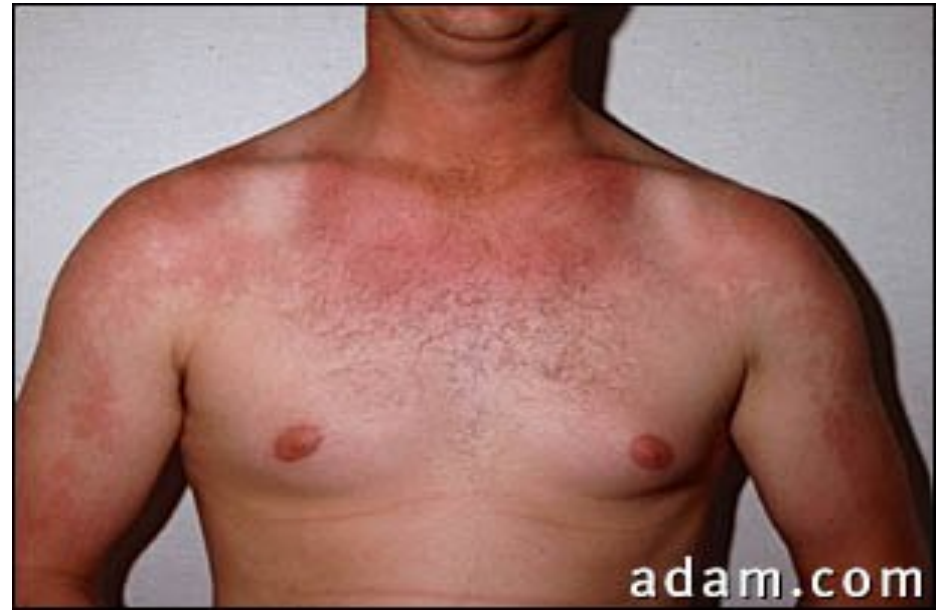
- Secretory diarrhea
  - Large volume (>500cc/d)
  - Persists with fasting
- Hypermotility
- Partial mechanical obstruction
- Mesenteric vascular insufficiency

Diarrhea

- Differential diagnosis
  - Medullary cancer of the thyroid
  - VIPoma (WDHHA)
  - Gastrinoma (Zollinger-Ellison syndrome)
  - Rectal villous adenoma
  - Laxative ingestion

Flushing





Flushing

- Dry – not associated with sweating
- Foregut tumours
  - Intense, protracted duration
  - Purplish
  - Followed by telangiectasia
  - Upper trunk + limbs
  - Acrocyanotic
  - Skin thickens

Flushing

- Midgut tumours
  - Faint pink – red
  - Face and upper truck (to nipple line)
  - Provoked by EtOH, tyramine containing foods (blue cheese, chocolate, sausage, red wine)
  - Last few minutes
  - No permanent discolouration

Flushing

- Differential diagnosis
  - Physiologic
    - Menopause, hot drinks, emotional
  - Drugs
    - EtOH ± chlorpropramide/disulfiram, niacin, diltiazem, bromocriptine, levodopa
  - Tumours
    - MTC, mastocytosis, renal cell carcinoma, VIPoma, diencephalic seizures

Carcinoid heart disease

- Valvular disease
  - Dyspnea
  - Fatigue
  - Ascites
  - Anorexia
  - edema

Laboratory investigations

- Urinary 5-HIAA
- Serotonin
- Chromogranin A (CgA)
- Others
  - Bradykinin
  - Kallikrein
  - Neuropeptide K
  - Substance P
  - Pancreatic Polypeptide
  - Vasoactive intestinal Peptide

Biomarkers

- General marker: Chromogranin A
- Pancreatic Polypeptide
- HCG-subunits

- Specific markers: Gastrin
- Urinary 5 HIAA
- Insulin
  - Glucagon
  - Vasoactive intestinal Peptide

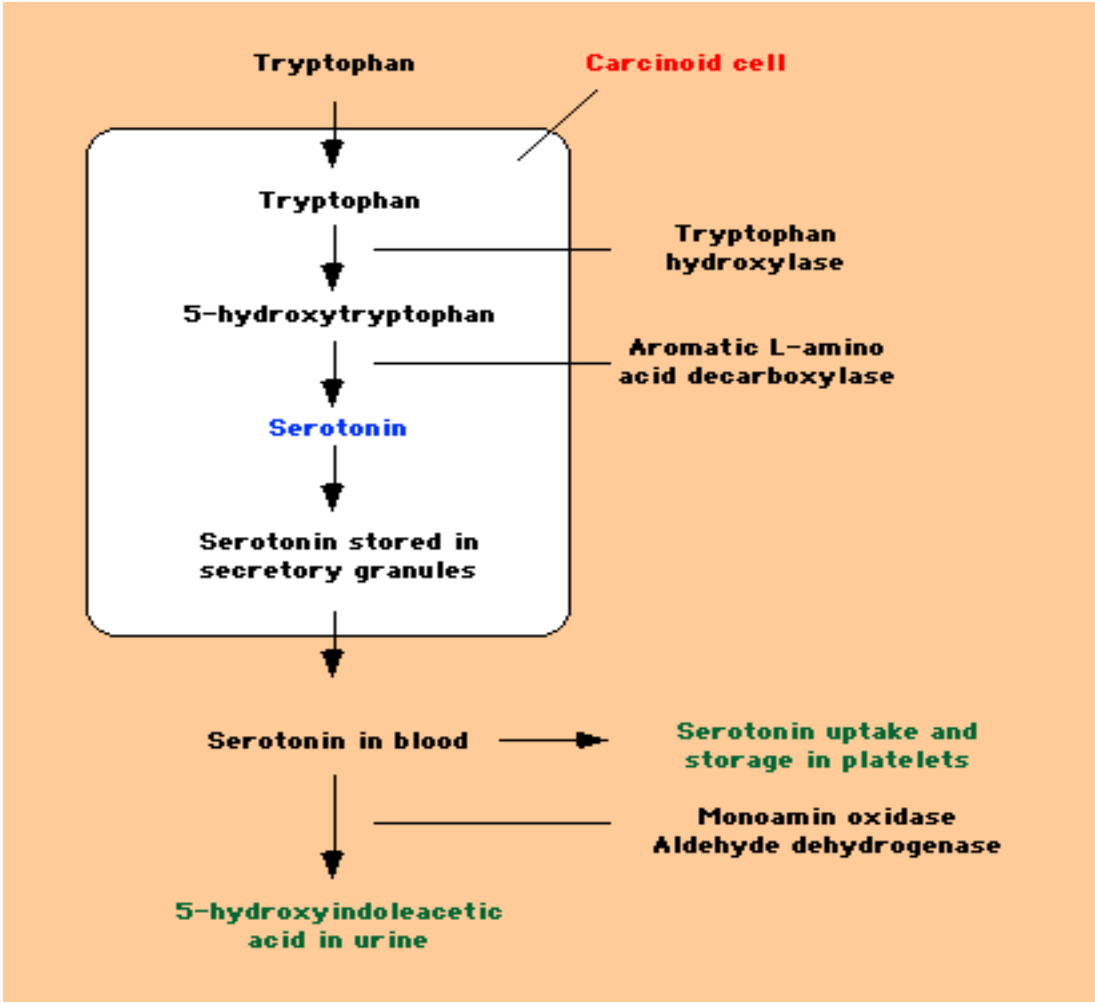
Urinary 5-HIAA

- 24 hour urine collection (HPLC)

Condition	**μmol/d**
Normal	10-42
Malabsorption	Up to 157
Carcinoid syndrome	>523
Metastatic carcinoid w/o carcinoid syndrome	262-1360

- Sensitivity 75%
- Specificity 90%

Serotonin metabolism



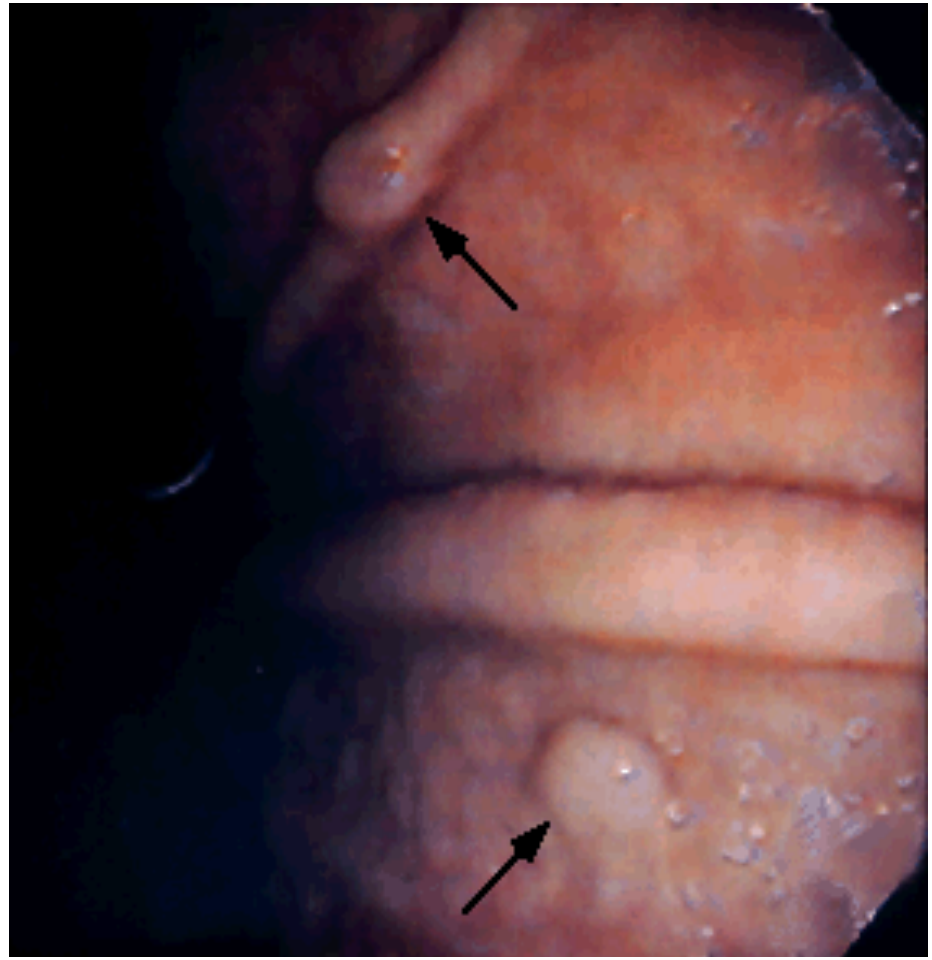
Blood serotonin

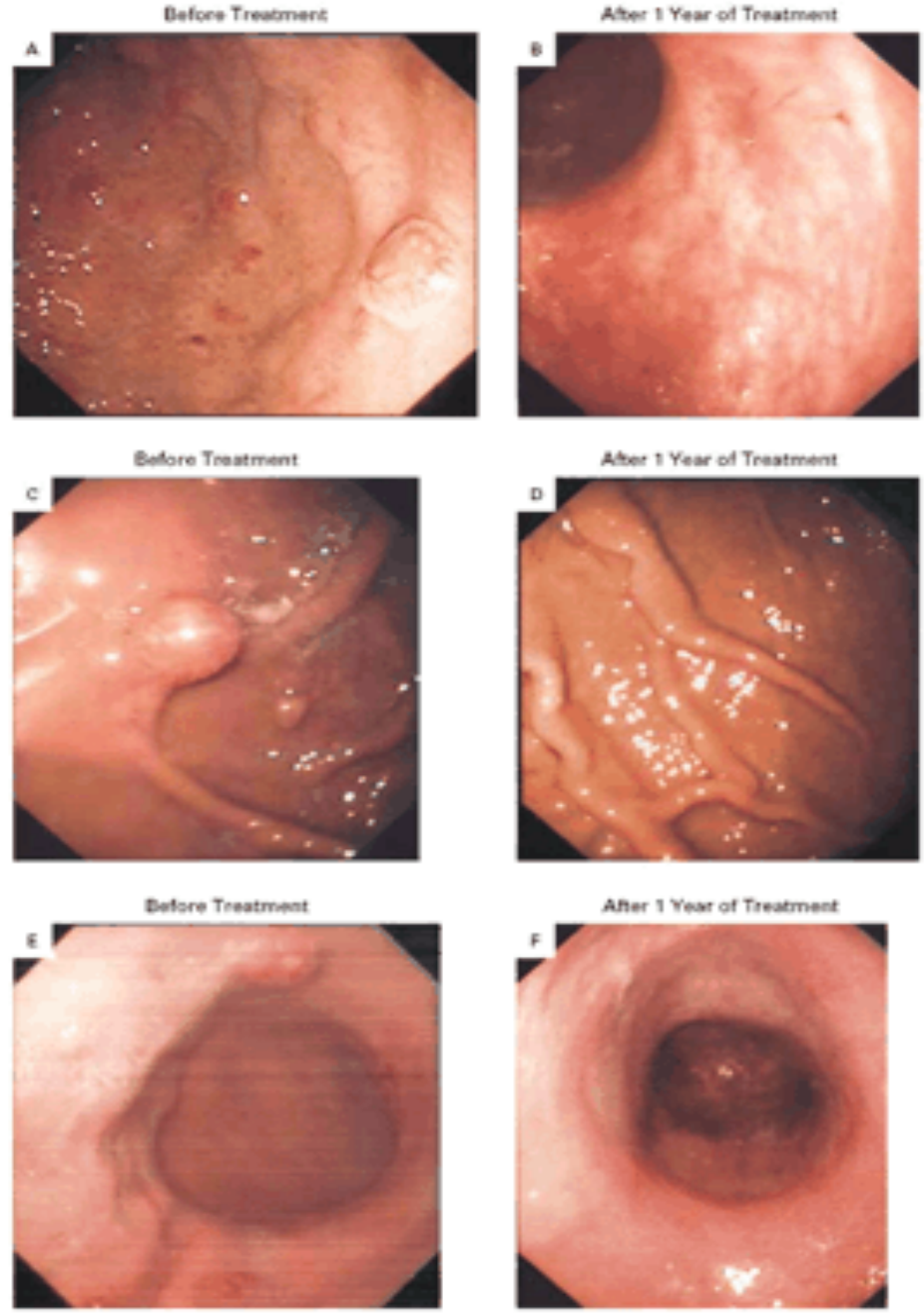
- If 5-HIAA testing equivocal
- Normal fasting level 0.4-1.8 μmol/L
- Elevated in carcinoid syndrome (4.5-25.5 μmol/L)

Localization

- Endoscopy/wireless capsule
- CXR
- CT
- MRI
- Angiography
- Octreoscan
- PET

Endoscopy

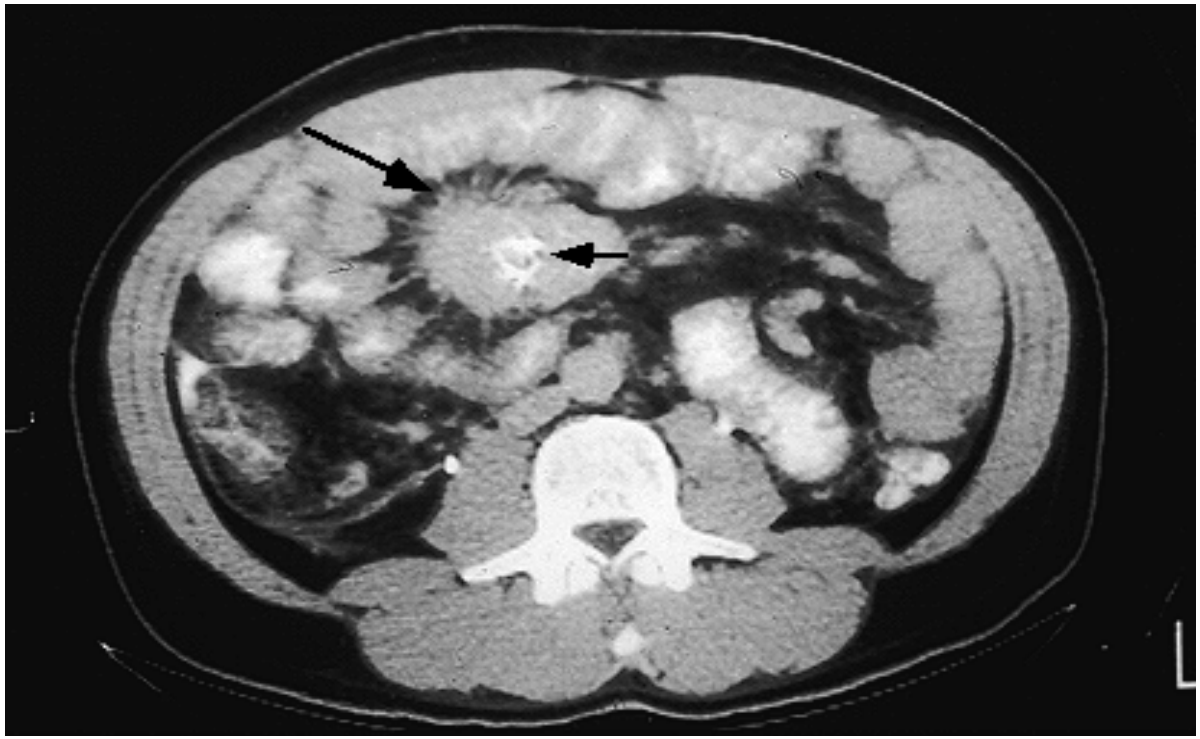



Before Treatment
A
After 1 Year of Treatment
B
Before Treatment
C
After 1 Year of Treatment
D
Before Treatment
E
After 1 Year of Treatment
F

Abdominal CT

- 87% sensitive for detecting ≥ 1 of:
  - Liver metastases
  - Mesenteric stranding
  - Lymph node enlargement
  - Primary tumour
    - rarely due to submucosal location

Abdominal CT



- Soft tissue mass
- Central calcification
- Desmoplastic response
- Spiculation of adjacent mesenteric fat

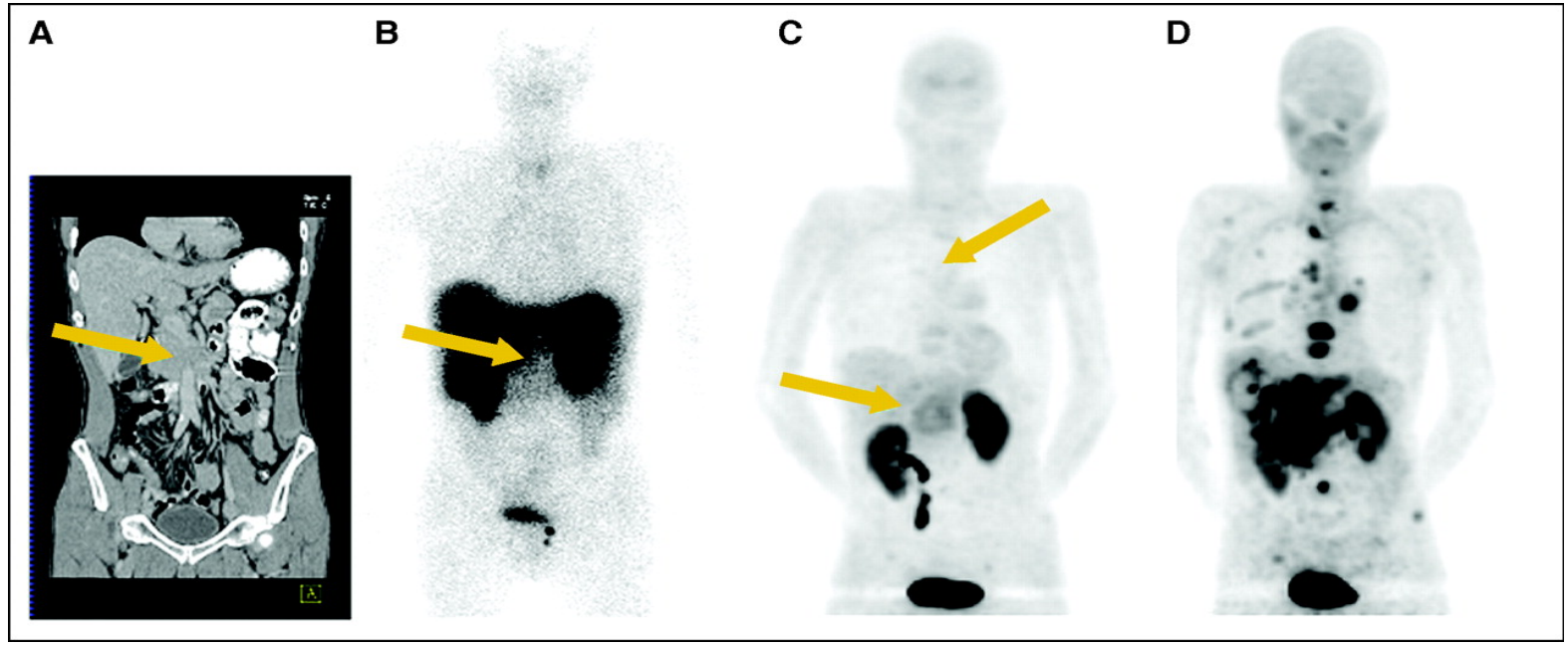
Molecular Imaging
Functional techniques

- Octreoscan (somatostatin receptor scintigraphy)
- MIBG-scintigraphy (metaiodobenzylguanidine)
- PET (positron emission tomography) (^{11}C-5-HTP, ^{18}F-DOPA, ^{68}Ga-Dota-octreotide ^{99}Tc EDDA-HYNIC-TOC)

Specific isotopes for NETs

- ^{11}C-5HTP (hydroxytryptophan)
- ^{11}C-Dopamine
- ^{18}F-Dopamine
- ^{68}Ga-Dota Octreotide
- ^{99}Tc EDDA-HYNIC-octreotide
- [Lys40(Ahx-DTPA-^{111}In)NH2]-Exendin-4 (GLP-1)

(A) Computed tomography (CT) scan, (B) somatostatin receptor scintigraphy (SRS), (C) 18F-dihydroxy-phenyl-alanine (18F-DOPA) positron emission tomography (PET), and (D) 11C-5-hydroxy-tryptophan (11C-5-HTP) PET of a 54-year-old male patient with metastatic islet cell tumor

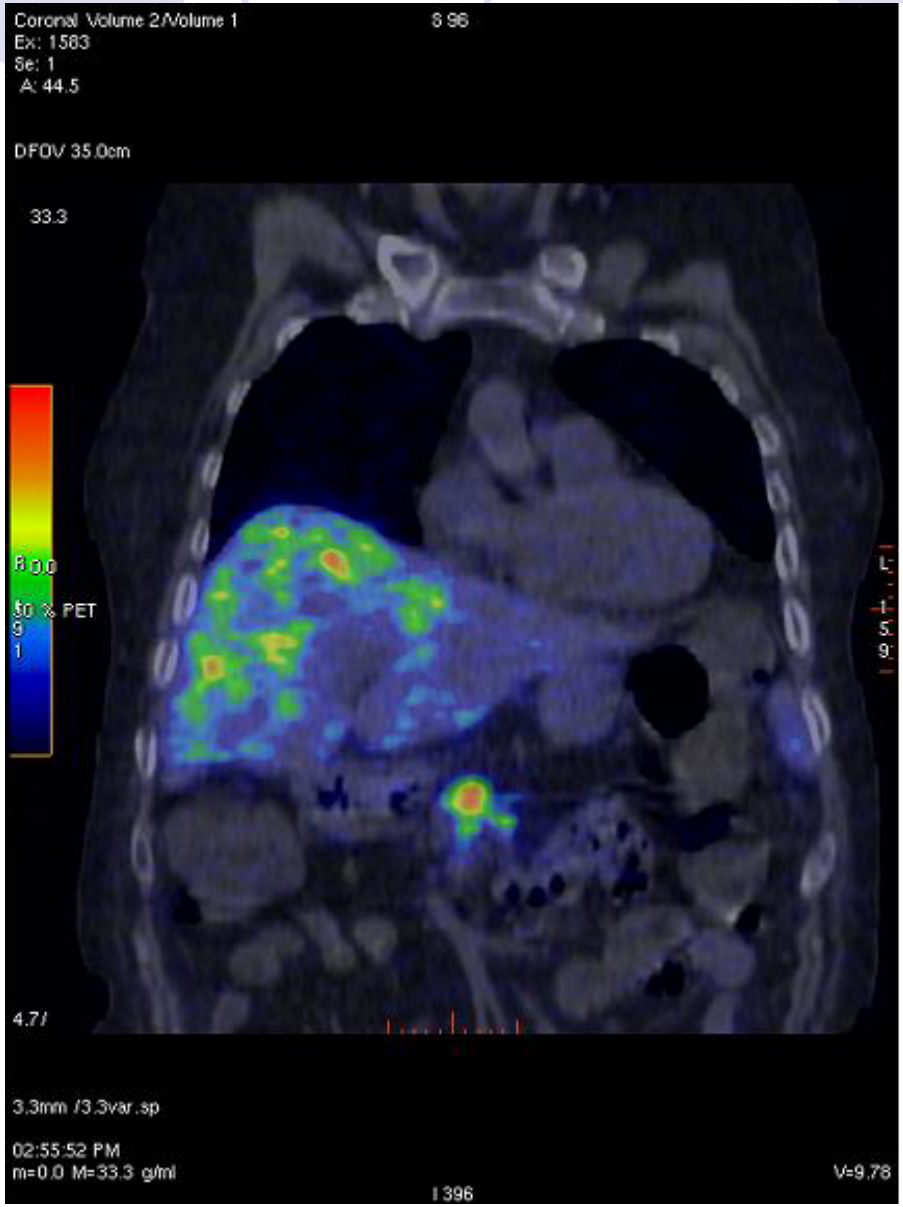


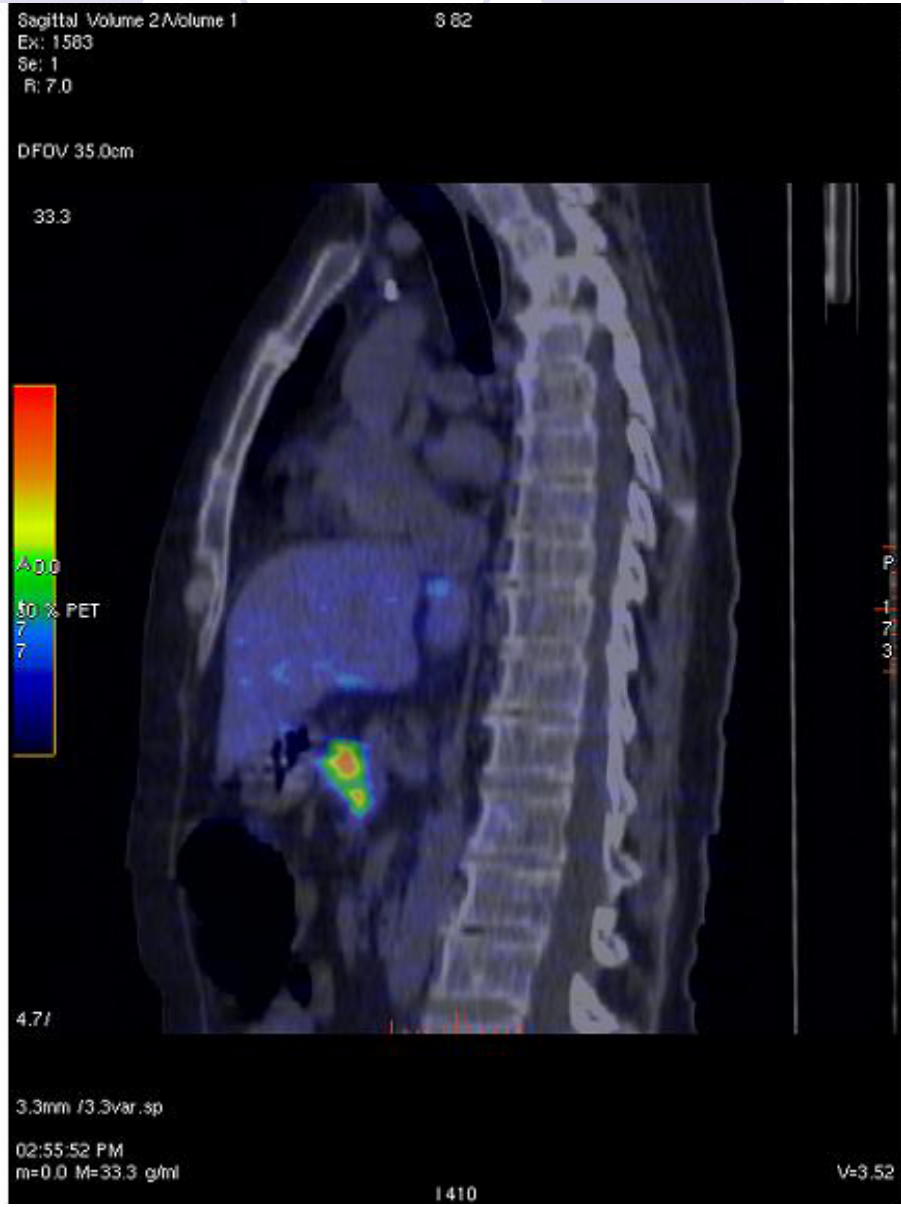
Koopmans, K. P. et al. J Clin Oncol; 26:1489-1495 2008

PET with ^{68}Ga-DOTA-octreotide

- Advantages:
- no cyclotron required
- more sensitive than Octreoscan
- possible to use for radioactive or tumor-targeted treatment
- may be possible to quantify somatostatin receptors - tumor-targeted therapy

PET/CT with ^{68}Ga-DOTA-octreotide





Therapeutic Options NETs

Surgery Curative (rarely)
Ablative (very often)

Debulking Radiofrequency ablation (RFA)
Embolization/chemoembolization/
radioembolization

Irradiation External (bone, brain-mets)
Tumor targeted
Radioactive therapy (MIBG, Y^{90}-DOTATOC,
Lu^{177} -DOTATATE)

Medical therapy Chemotherapy
Biological treatment:

- Somatostatin analogs
- α-interferon
- m-TOR inhibitors
- VEGF R inhibitors
- Other TKI:s

Factors influencing the therapeutic decision

- Type of NET-tumor
- TNM stage and grade
- Extent of liver involvement
- Functioning v.s. non-functioning tumor
- Patients performance status
- Availability of different therapeutic modalities
- ***NB!*** The treatment of most patients is a combination of surgery, PRRT and medical treatment

Conclusions

- Endocrine carcinomas of the GEP system vary widely in terms of:
  - pathogenetic mechanisms
  - morphologic appearance
  - biologic behavior

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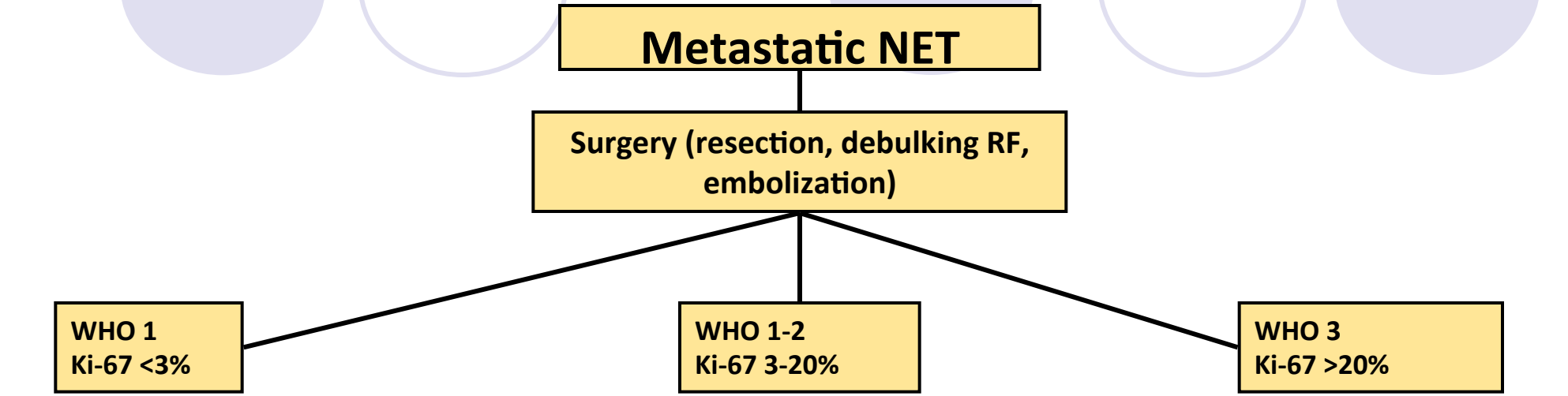
C. Moulton

Radiation Oncology

J. Brierley
R. Tsang
R. Wong

Management Approaches



Biotherapy
-Somatostatin analogue (SMS)
-α-IFN
-Combination
-SMS + α-IFN
-SMS + Everolimus
-SMS + bevacizumab

Chemotherapy
- STZ+5FU/Dox
- STZ + RAD001
- Temozolomide + capecitabine

SMS for symptom control

Chemotherapy:
Cispl + Etoposide
Temozolomide
+ capecitabine
+ bevacizumab

SMS for symptom control

Targeted Radiotherapy
Lu^{177} DOTA-octreotate, Y^{90} DOTATOC

Experimental Protocols