

# **Ga-68 DOTATOC Scan in Neuroendocrine Tumors**

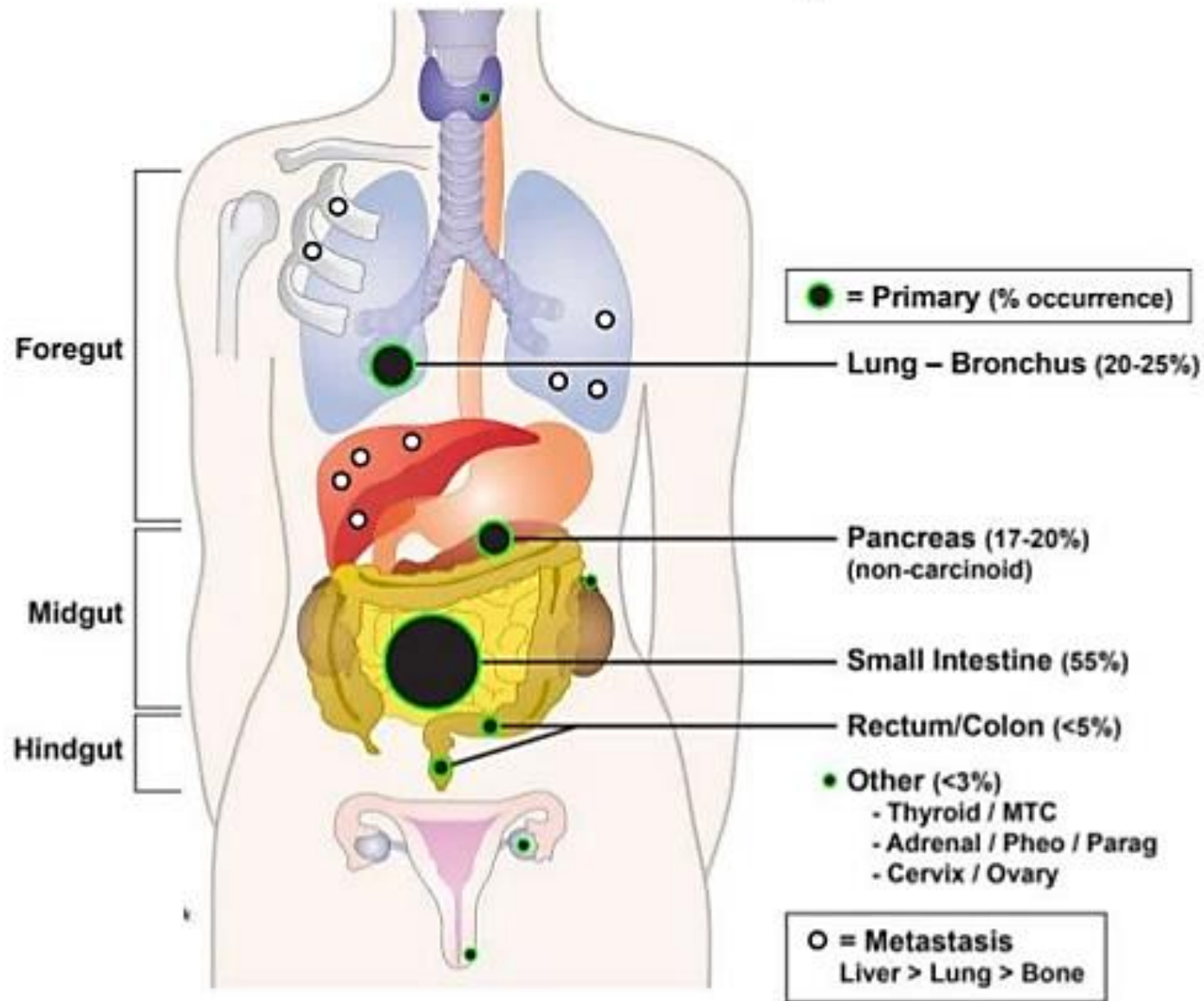
**Yu-Chen Chang, MD, PHD**

**Department of Nuclear Medicine and Molecular Imaging Center,  
Linkou Chang Gung Memorial Hospital and Chang Gung University**

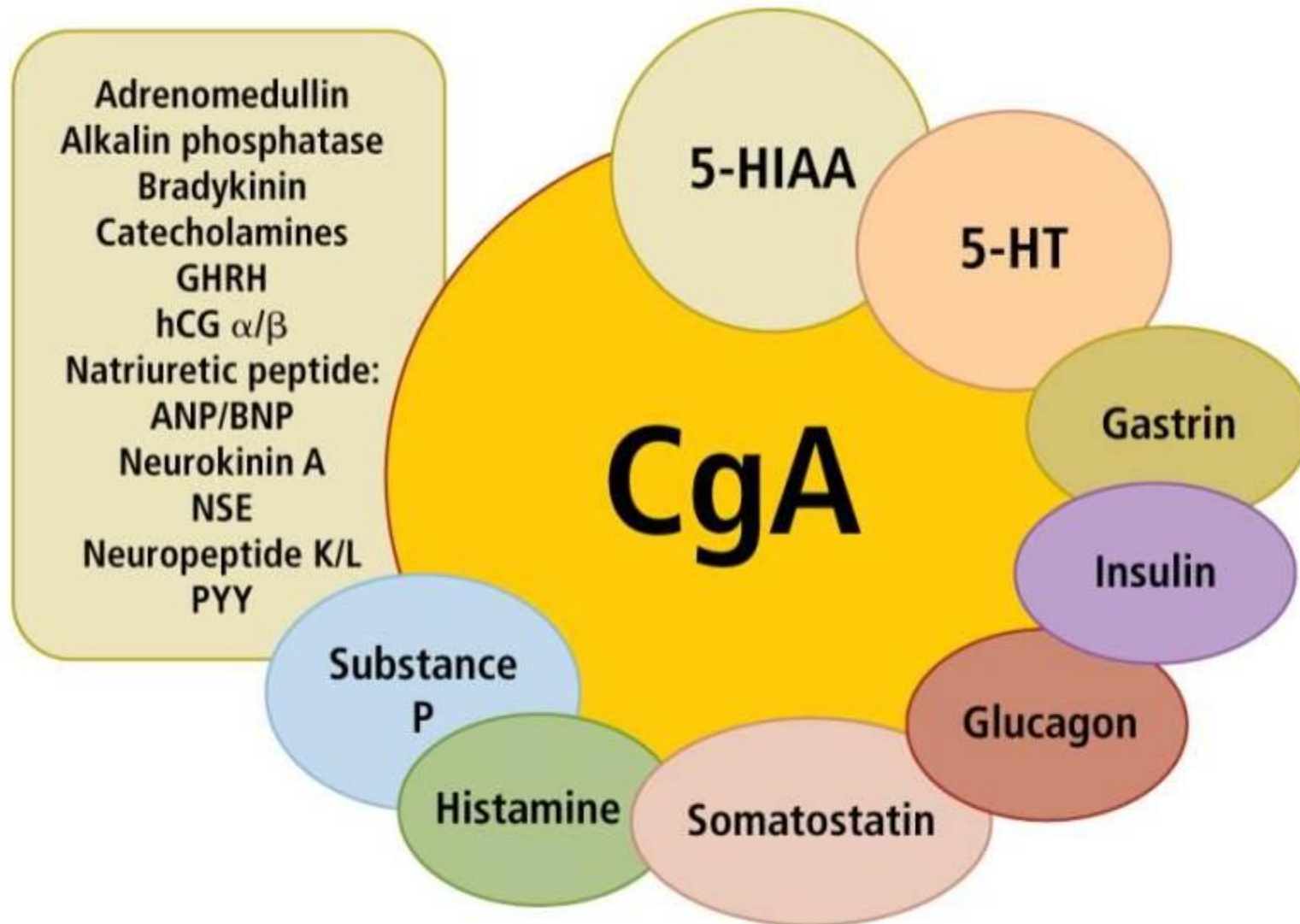
# **Introduction to Neuroendocrine Tumors (NETs)**

- **Neuroendocrine cells: migrated from the neural crest to the gut endoderm**
- **NETs: neoplasm that arise from cells of the endocrine (hormone) and nervous systems.**
- **NETs have special secretory granules and often producing biogenic amines and polypeptide hormones.**

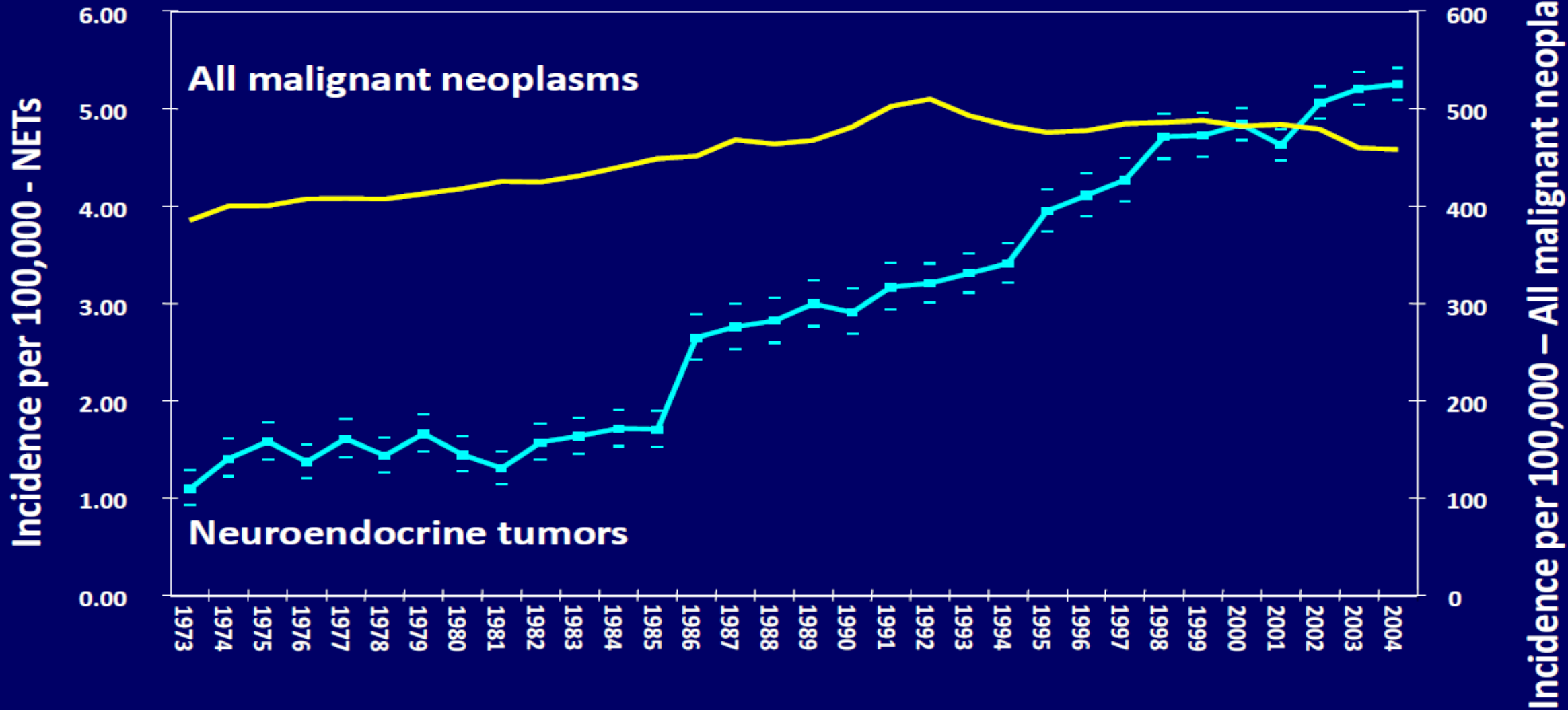
# Neuroendocrine System



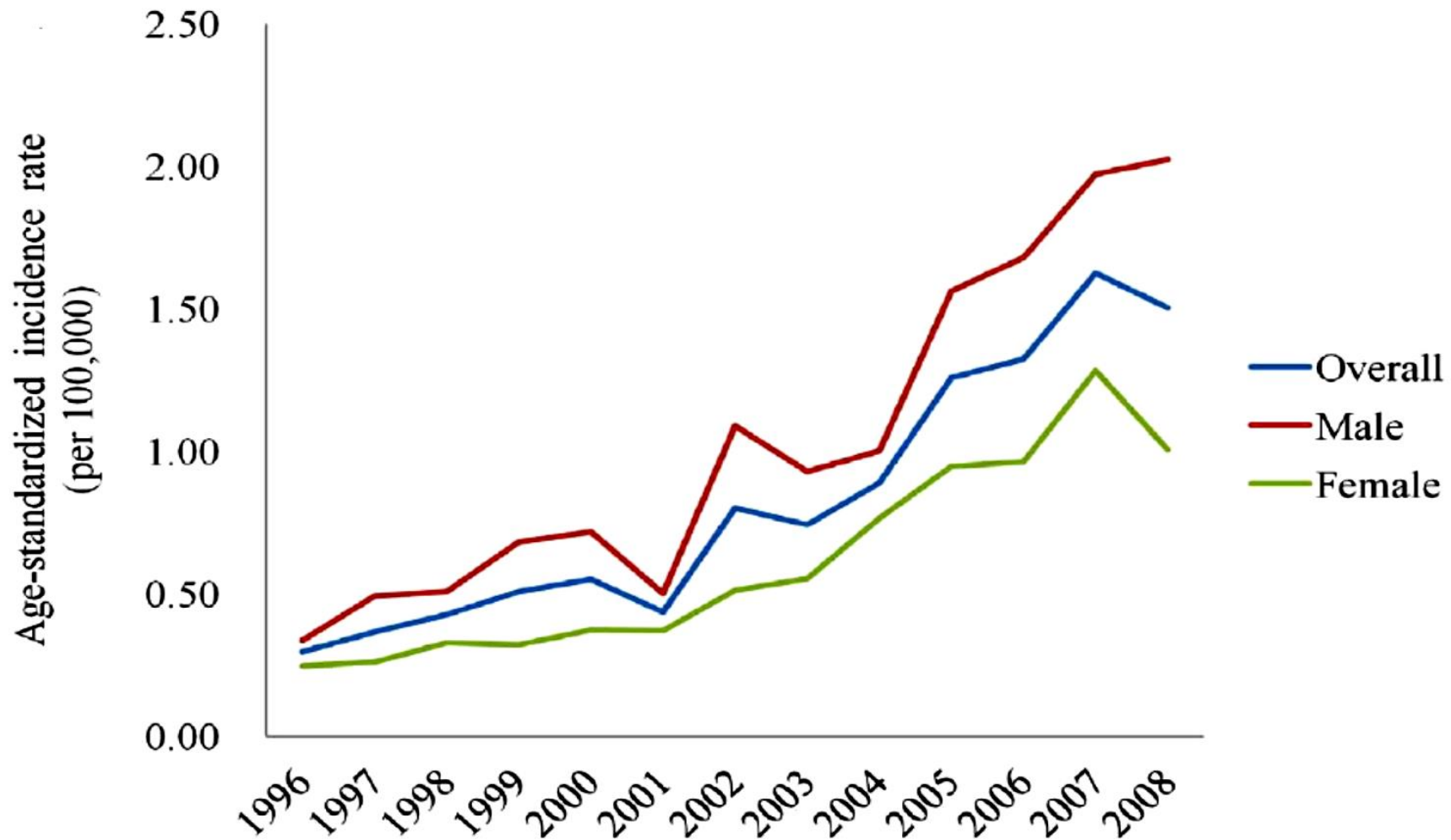
Indolent biology	Aggressive biology
Well-differentiated neuroendocrine tumor (carcinoid tumor, atypical carcinoid, many primary sites)	Small cell and large cell neuroendocrine lung cancer
Well-differentiated pancreatic neuroendocrine tumor (islet cell tumor)	High-grade poorly differentiated neuroendocrine carcinoma (small cell and large cell types, many primary sites)
Medullary carcinoma of the thyroid	Extrapulmonary small cell carcinoma (many primary sites)
Paraganglioma	Merkel cell tumor of the skin
Pheochromocytoma	Neuroblastoma



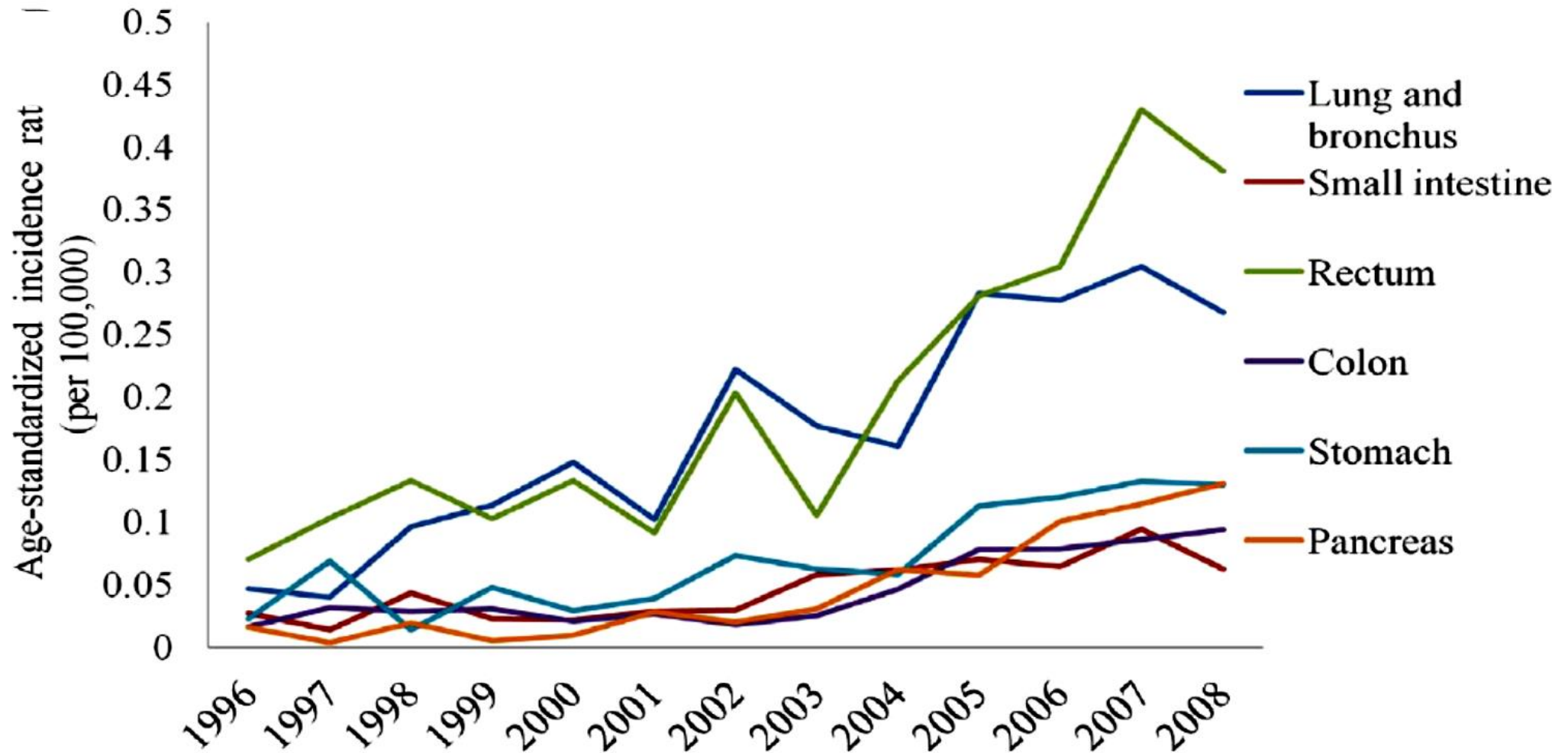
# Incidence of NETs Increasing



# Incidence of NETs in Taiwan

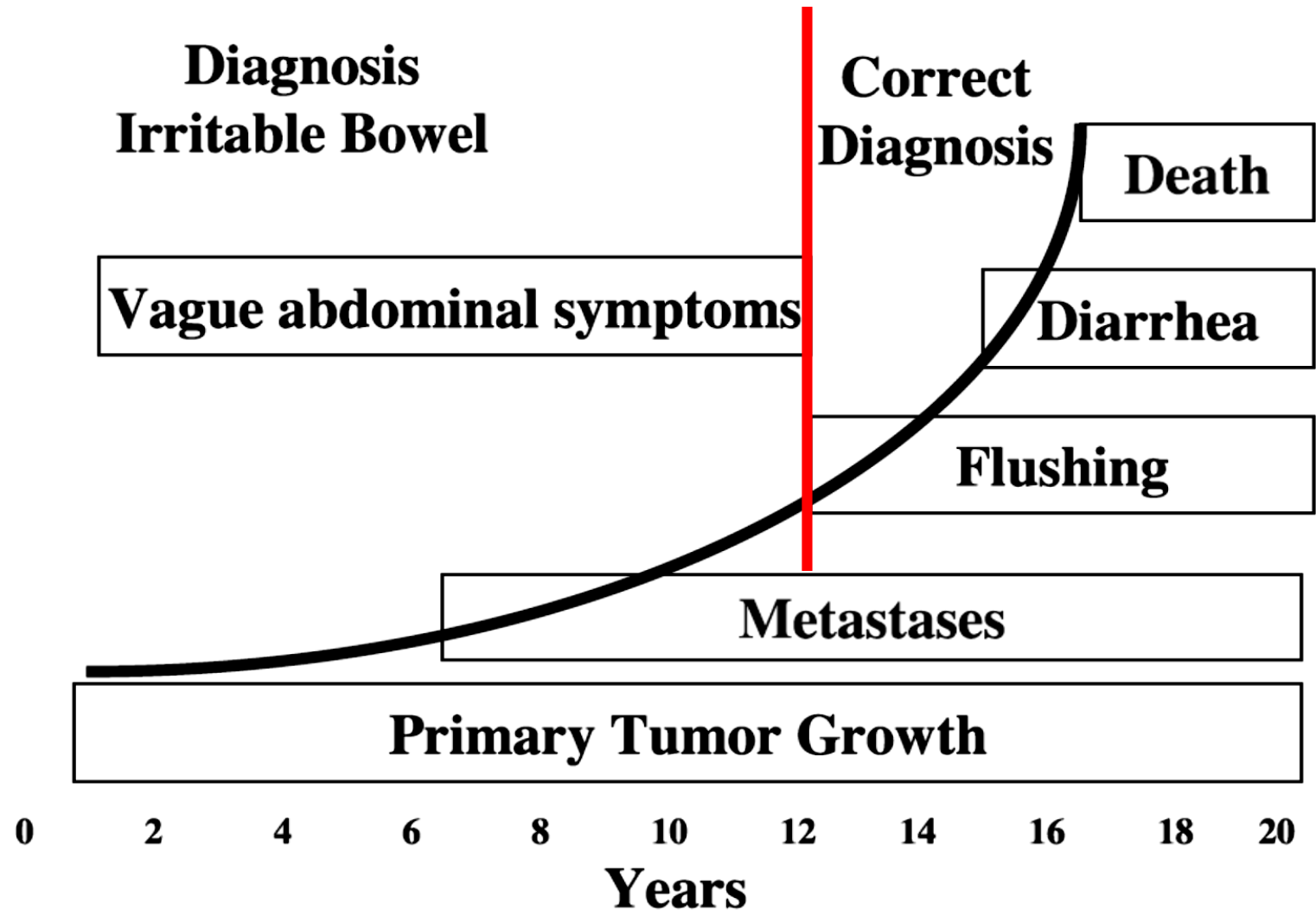


# Incidence of NETs in Taiwan





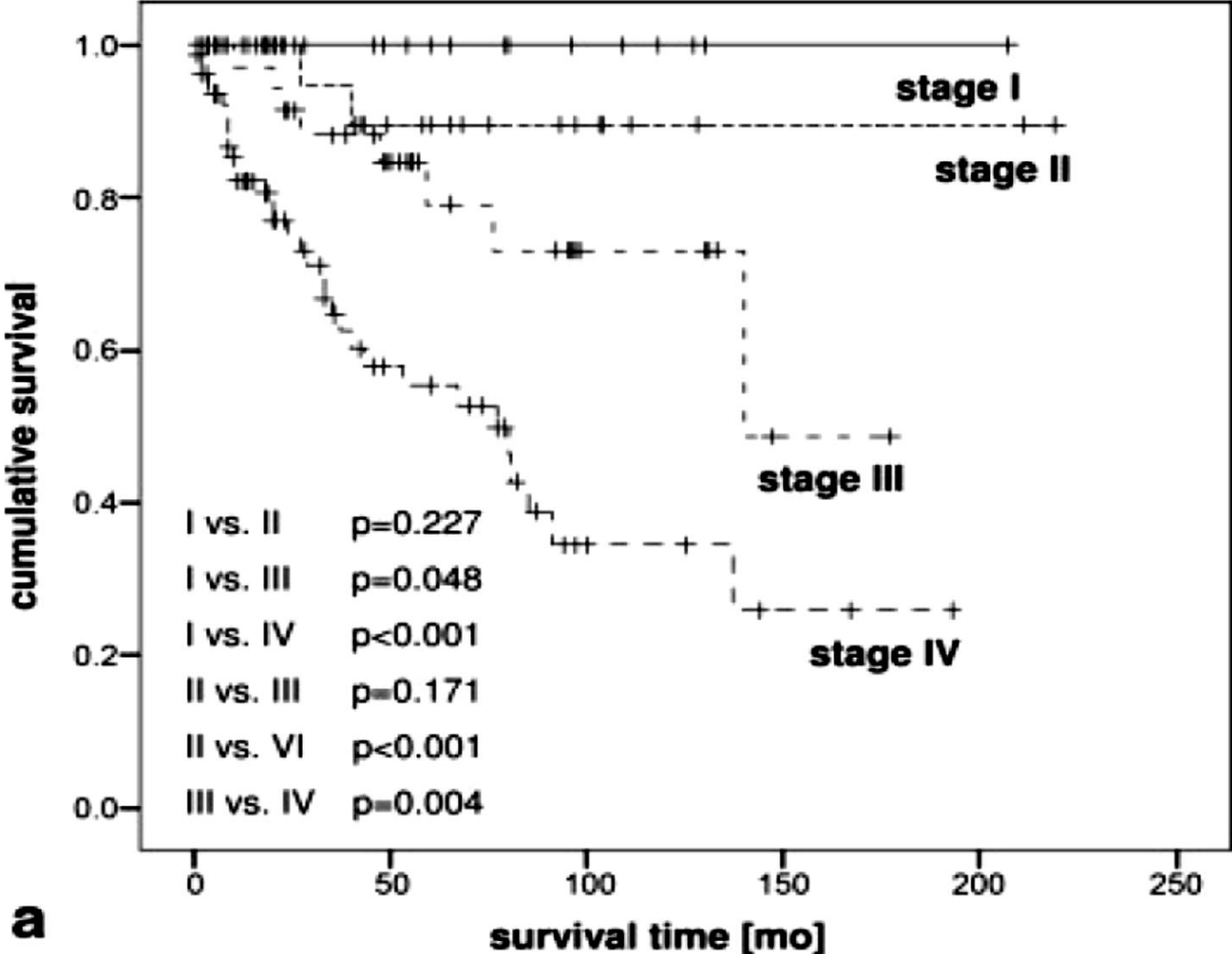
# Nature History of NETs



# Characteristics of NETs

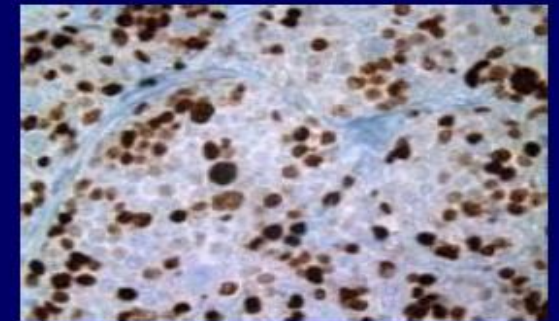
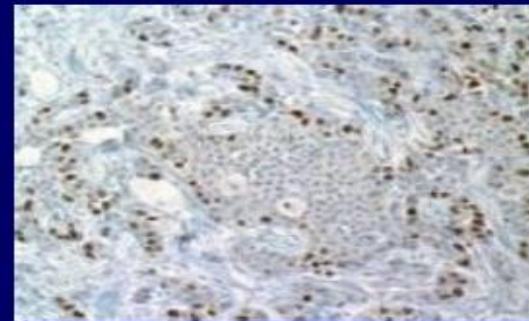
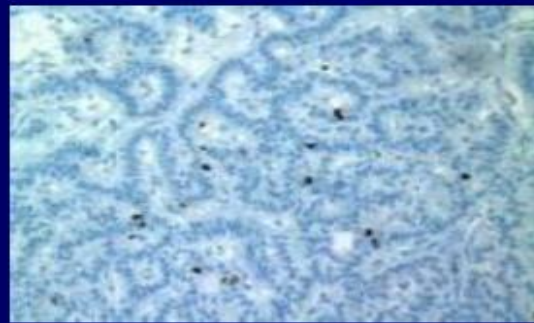
- **Rare**
- **Usually small, < 1 cm**
- **Slow growing, months to years**
- **Usually metastasize before becoming symptomatic, often when tumor is < 2 cm**
- **Expression is episodic, may be silent for years**
- **Symptoms mimic commonplace conditions and often are misdiagnosed**

# Correlation of Tumor Stage and Survival



# Grading of GEP-NET According to ENETS/WHO/AJCC

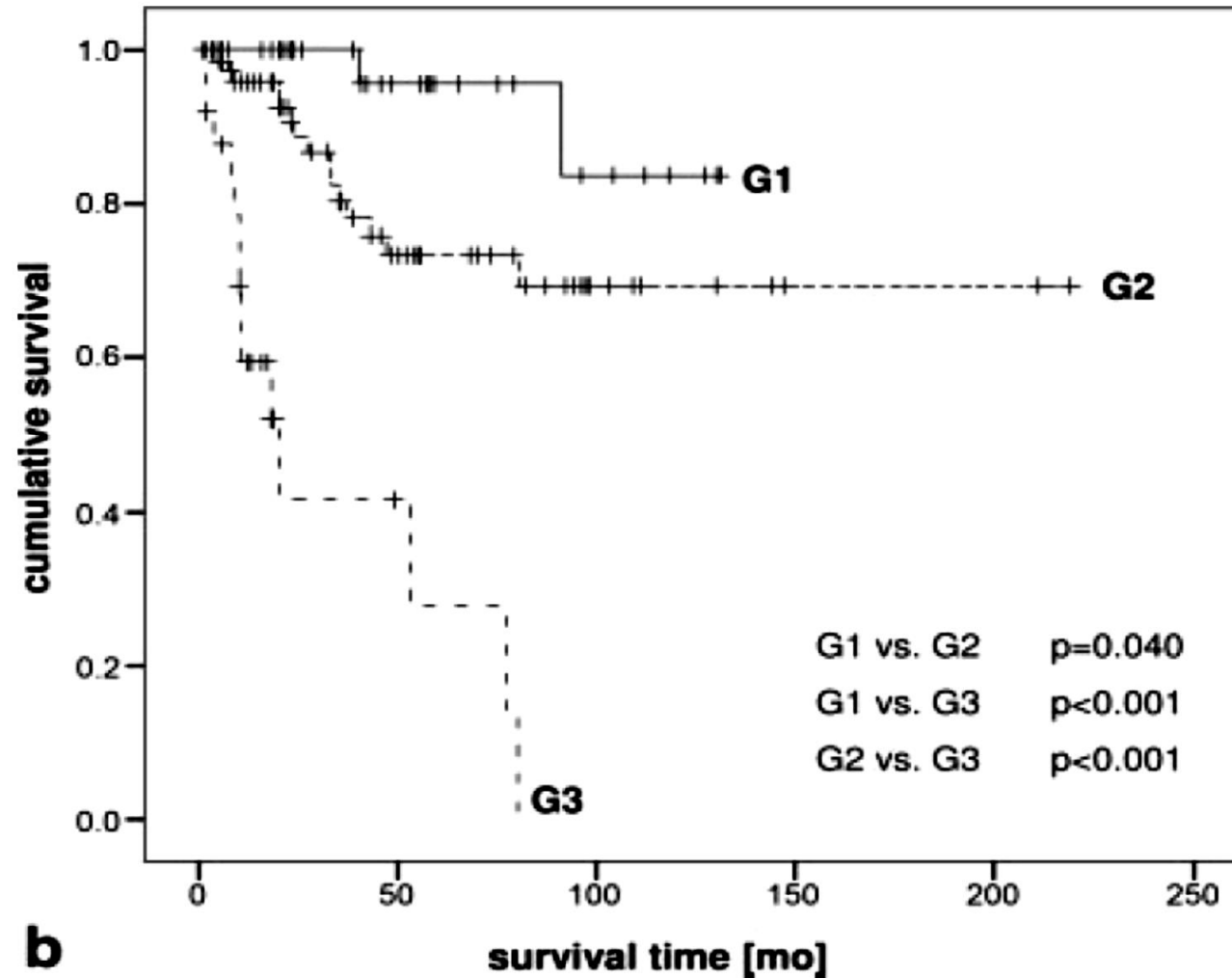
Grade	G1	G2	G3
Ki67 index (%)**	≤2	3–20	>20
MI (mitotic count)*	<2	2-20	>20



\*10 HPF (high power field) = 2 mm<sup>2</sup>, at least 40 fields (at 40× magnification) evaluated in areas of highest mitotic density.

\*\* MIB1 antibody; % of 2,000 tumour cells in areas of highest nuclear labeling.

# Correlation of Tumor Grade and Survival



5-year survival rate:

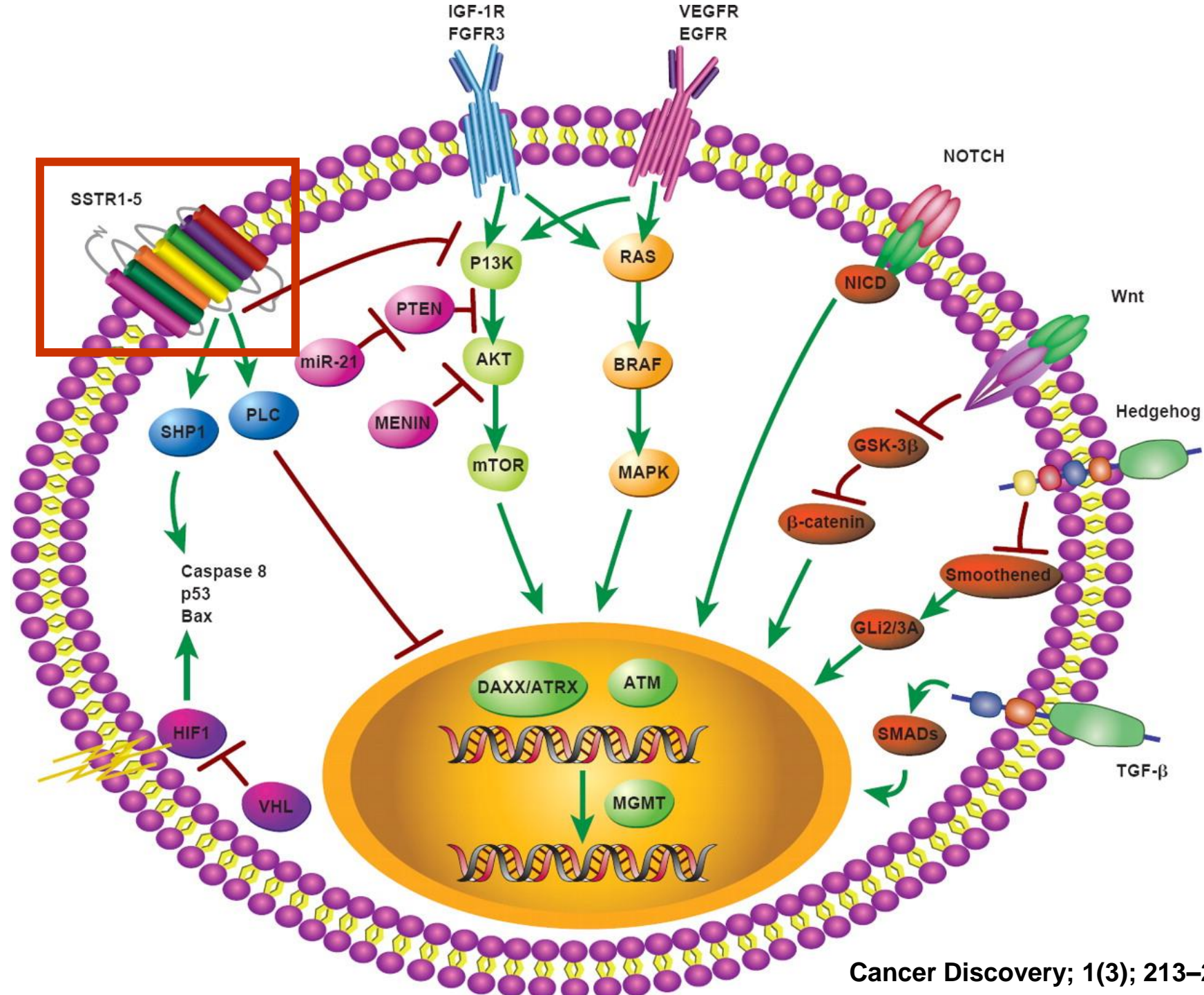
**G1: 85%**

**G2: 78%**

**G3: 9%**

# **Diagnostic & therapeutic challenges in NETs**

- **Heterogeneous group of tumors**
- **Wide variety of clinical presentations**
- **Late presentation**
- **Over 60% of NETs are advanced at the time of diagnosis**
- **The median survival for patients with advanced NET is 33 months**
- **Different terminology and classifications**
- **Histologic diagnosis may be difficult**
- **Variety of therapeutic options/approaches**
- **Limited phase III evidence for chemotherapy and Peptide Receptor Radionuclide Therapy (PRRT)**



# Somatostatin receptors

sst-positive tumours	Total no. of cases	No. of cases per pattern	sst pattern				
			sst1	sst2	sst3	sst4	sst5
<b>Tumour types with predominance of sst2</b>							
Neuroblastomas	8	8	—	+++	—	—	—
Meningiomas	6	6	—	+++	—	—	—
Medulloblastomas	5	5	—	+++	—	—	—
Breast carcinomas	31	29	—	+++	—	—	—
		1	—	++	—	—	—
		1	+++	—	—	—	—
Lymphomas	7	4	—	+++	—	—	—
		3	—	+++	—	—	+
Renal cell carcinomas	7	5	—	+++	—	—	—
		2	—	++	—	—	—
Parangliomas	10	6	—	+++	—	—	—
		2	+++	—	—	—	—
		2	—	+++	+	—	—
Small cell lung cancers	2	2	—	+++	—	—	—
Hepatomas	2	2	—	+++	—	—	—



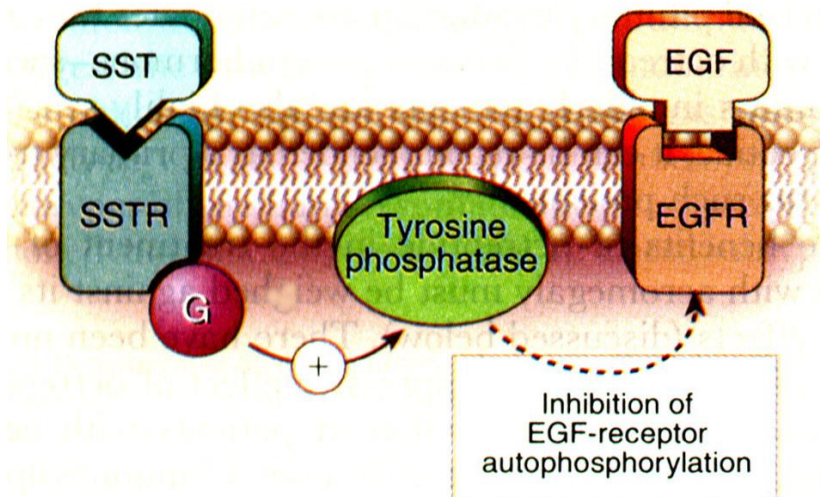
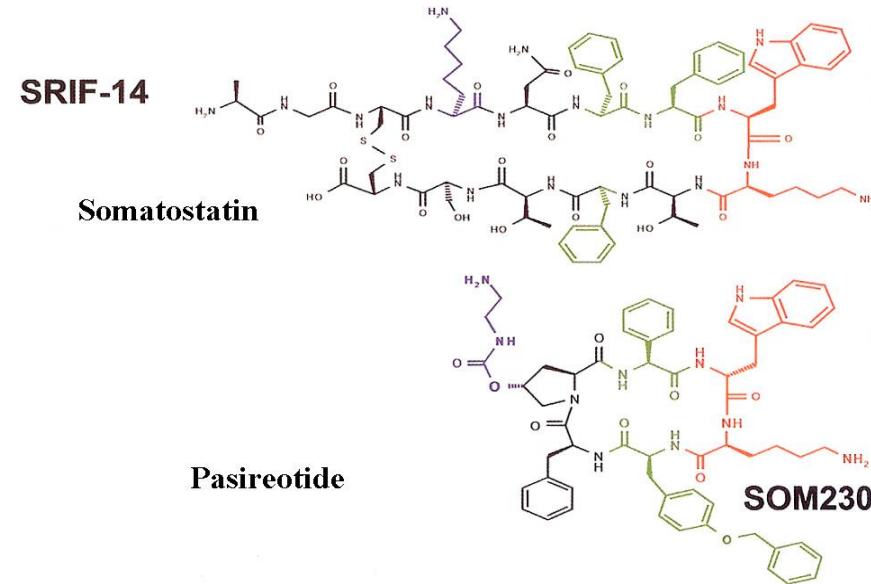
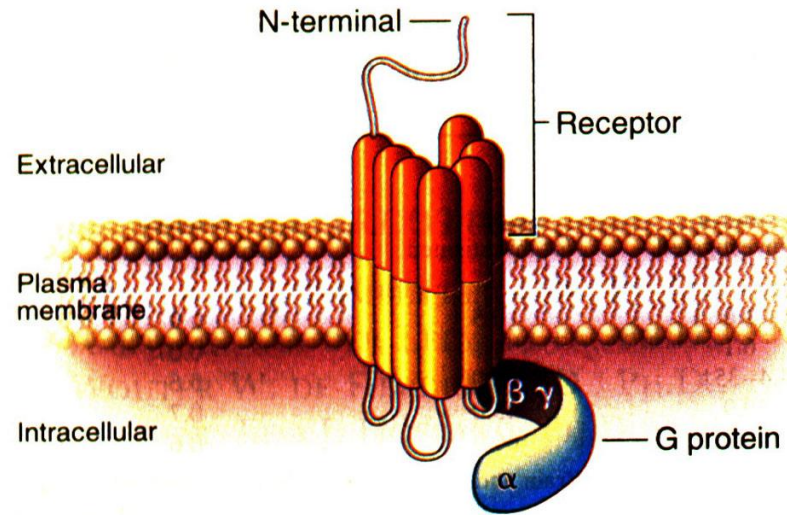
# Somatostatin receptors

sst-positive tumours	Total no. of cases	No. of cases per pattern	sst pattern				
			sst1	sst2	sst3	sst4	sst5
<b>Tumour types with predominance of sst3</b>							
<b>Inactive pituitary adenomas</b>	<b>30</b>	<b>12</b>	-	-	+++	-	-
		8	-	+++	-	-	-
		4	-	+	+++	-	-
		3	-	++	-	-	+
		1	+++	-	-	-	-
		1	-	++	++	-	-
		1	-	-	-	-	++
<b>Tumour types with predominance of sst2 + sst5</b>							
<b>GH pituitary adenomas</b>	<b>24</b>	<b>9</b>	-	+++	-	-	-
		7	-	++	-	-	++
		4	-	++	-	-	-
		2	-	-	-	-	++
		1	-	++	+	-	-
		1	-	+	+	-	++
<b>Phaeochromocytomas</b>	<b>19</b>	<b>13</b>	-	+++	-	-	-
		3	+++	-	-	-	-
		1	++	-	-	-	-
		1	-	++	-	-	+
		1	++	++	-	-	-
<b>Other tumours</b>							
<b>Gastric carcinomas</b>	<b>5</b>	<b>2</b>	+++	-	-	-	-
		1	-	+++	-	-	-
		1	-	-	-	-	+++
		1	+	-	-	-	+++

# Somatostatin receptors

sst-positive tissues	No. of cases	sst pattern				
		sst1	sst2	sst3	sst4	sst5
Vessels (veins)	22	-	+++	-	-	-
Nerve plexus (myenteric)	7	-	+++	-	-	-
Pancreatic islets	4	-	+++	-	-	-
Adrenal medulla	1	-	+++	-	-	-
Prostatic stroma	2	-	+++	-	-	-
Gastric mucosa	4	+++	-	-	-	-
Colon mucosa	2	-	++	-	-	-
Spleen	2	-	+++	-	-	-
Lymphoid tissues (tonsils + lymph nodes)						
Germinal centre	11	-	+++	-	-	-
Lymphoreticular tissue	11	-	+	+	-	+

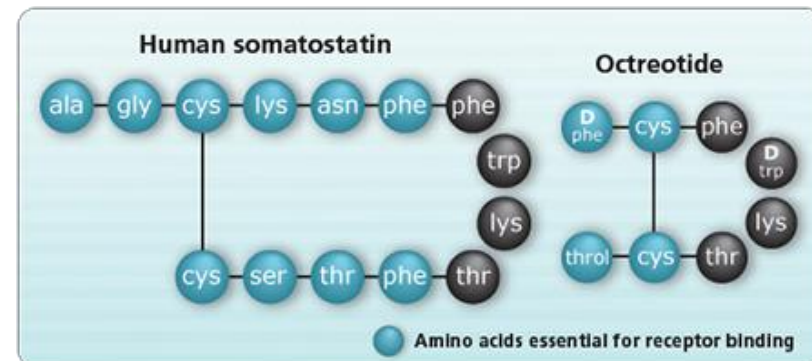
# Somatostatin-Receptor (SSTR) Scanning



- 5 sub-classes of somatostatin receptors
- SST has affinity for all but SSA have differing affinity

# Octreoscan

- **Indium-111 octreotide**
  - Half-life: 67 hrs
- **Binding to the somatostatin receptor subtype 2 (SSTR2), which is predominant in NETs**
- **Sensitivity: 80-100% (?)**
- **FDA approval in 1994**



# Octreoscan – “false positive”

- **Other tumoral uptake**
  - Astrocytoma, meningioma
  - Lymphoma
  - Breast cancer
  - Renal cell carcinoma
  - Gastric cancer
  - Differentiated thyroid cancer
  - Prostate cancer
  - Sarcoma
- **Non-tumoral uptake**
  - Sarcoidosis
  - Rheumatoid arthritis
  - Graves’ disease
  - Bacterial pneumonia, radiation pneumonitis

# Gallium-68 tracers

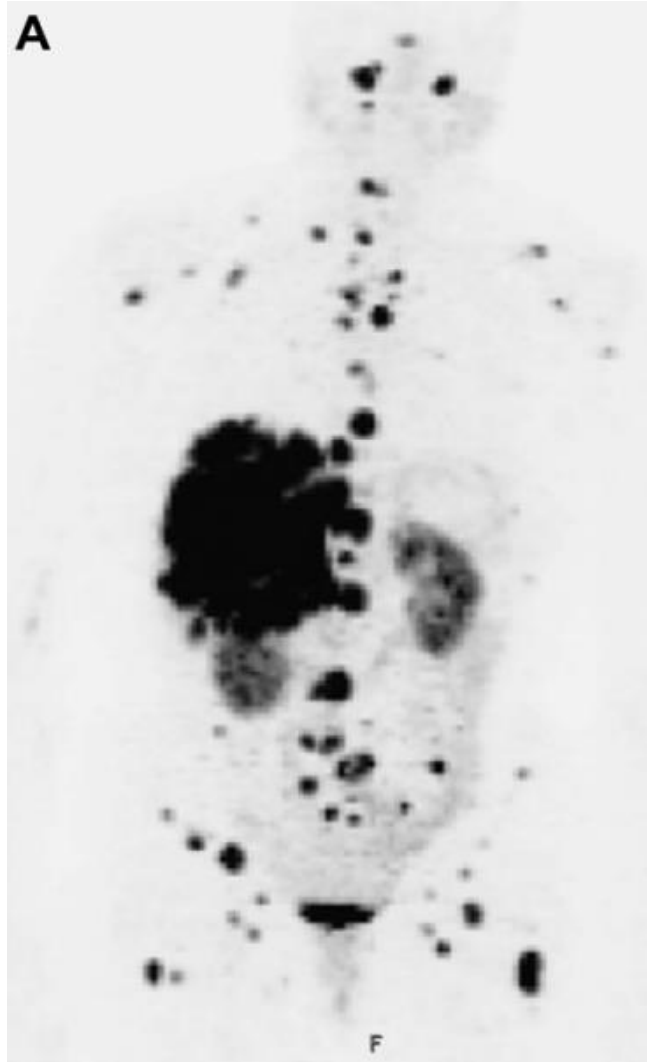
- **Gallium-68**
  - Half-life 68.3 min
  - Eluted from a generator
- **Tracers**
  - Ga-68 DOTA-TATE
  - Ga-68 DOTA-TOC
  - Ga-68 DOTA-NOC

# Gallium-68 tracers

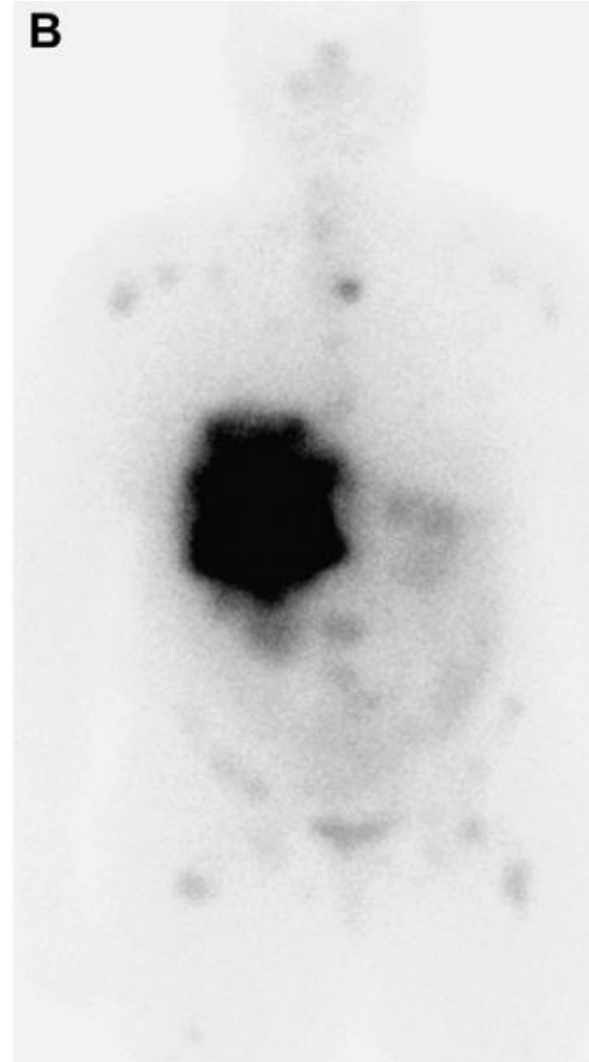
## Affinity-Profiles of Somatostatin-Analogues (IC50-Values, nmol/L)

Peptide	SSR1	SSR2	SSR3	SSR4	SSR5
Somatostatin-28	3,8	2,5	5,7	4,2	3,7
Gallium-68-DOTATOC	>10000	2,5	612	>1000	73
Gallium-68-DOTATATE	>10000	0,2	>1000	300	377
Gallium-68-DOTANOC	>10000	1,9	40	260	7,2
Indium-111-DTPA-Octreotide	>10000	22	182	>1000	273

IC50: half maximal inhibitory concentration,  
the effectiveness of a substance in inhibiting a specific biological or biochemical function



**Ga-68 DOTATOC**

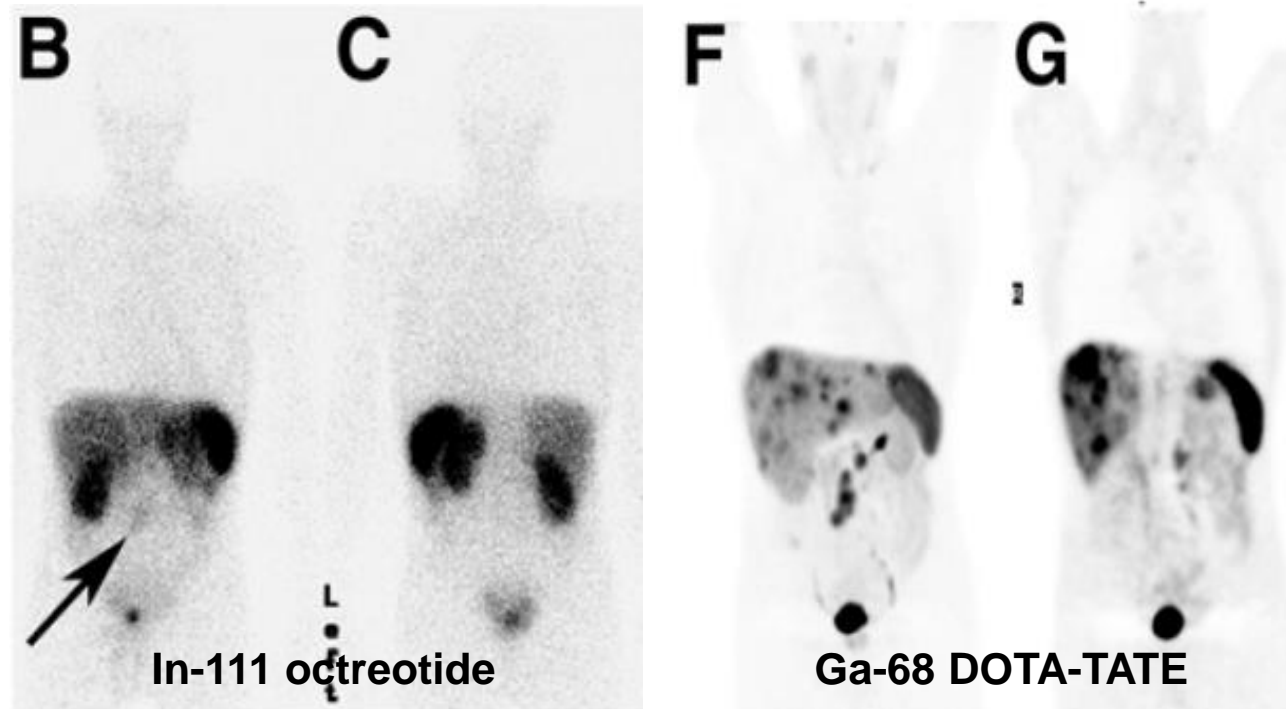


**In-111 octreotide**



# Ga-68 DOTA-TATE

- 51 patients with negative or equivocal In-111 octreotide
  - Ga-68 DOTATATE (+) in 41 patients



# Ga-68 DOTA-TOC

- **84 patients**
  - **13 detection of unknown primary**
  - **36 initial staging**
  - **35 follow-up after therapy**

Parameter	PET (%)	SPECT (%)	CT (%)
Sensitivity	97 (69/71)	52 (37/71)	61 (41/67)
Specificity	92 (12/13)	92 (12/13)	71 (12/17)
Accuracy	96 (81/84)	58 (49/84)	63 (53/84)

# Comparison of FDG, SRS (SPECT)

96 consecutive NET patients

- Overall sensitivity
  - SRS: 89%
  - FDG: 57%
- Ki-67 > 15% (n=13)
  - SRS: 69%
  - FDG: 92%

# Comparison of FDG and DOTATATE

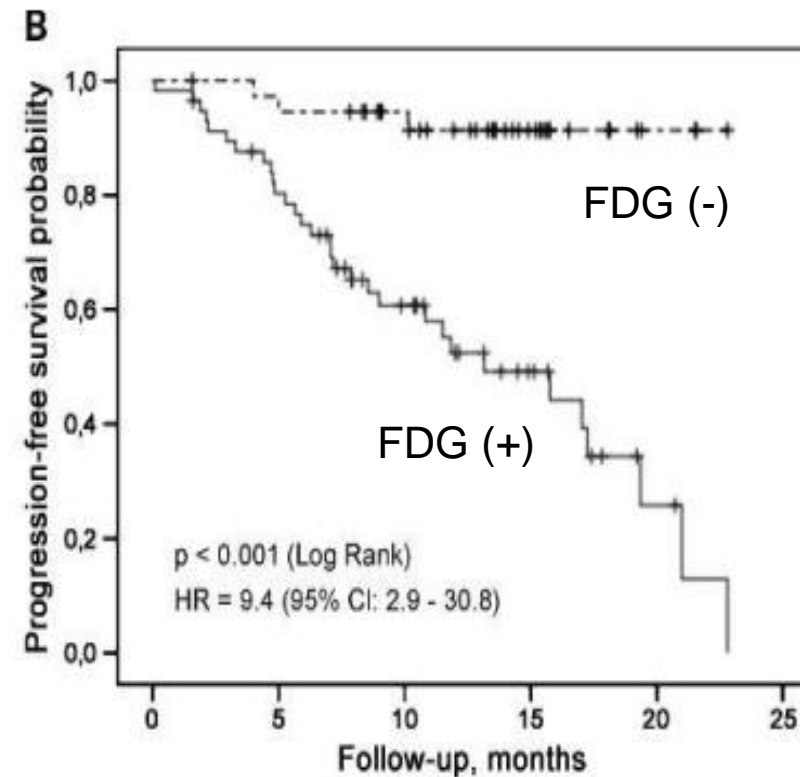
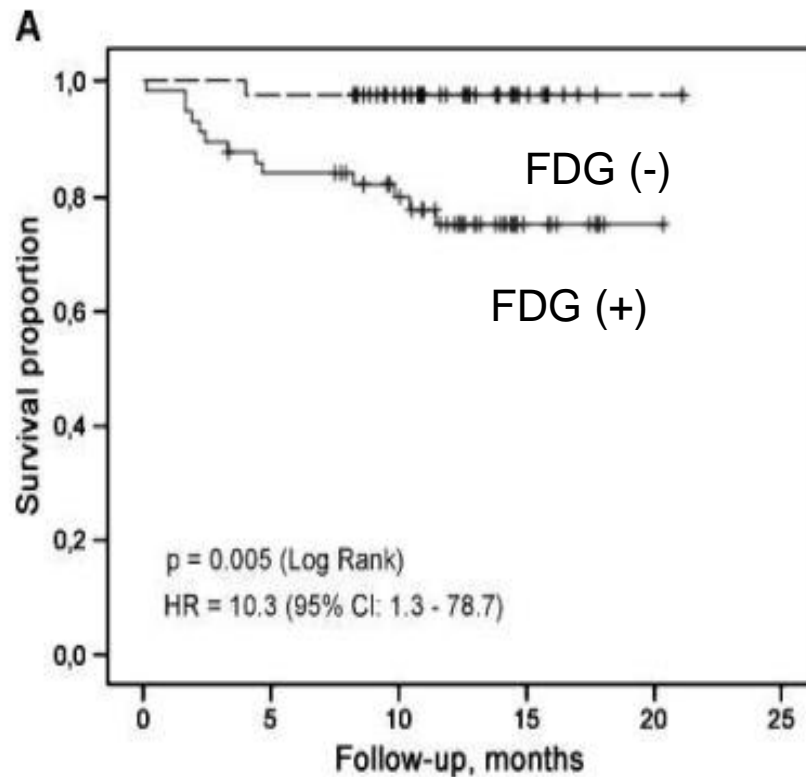
38 consecutive NET patients

– Sensitivity

- DOTATATE: 31/38 (82%)
- FDG: 25/38 (66%)
- DOTATATE + FDG: 35/38 (92%)

# FDG predicts NET survival

- 98 patients



# Conclusions

- **Ga-68 DOTATOC imaging is a sensitive tool to detect primary tumor localization in patients with suspicious neuroendocrine tumor.**
- **F-18 FDG PET provides a complementary role for detection high grade neuroendocrine tumor as compared to Ga-68 DOTATOC imaging.**