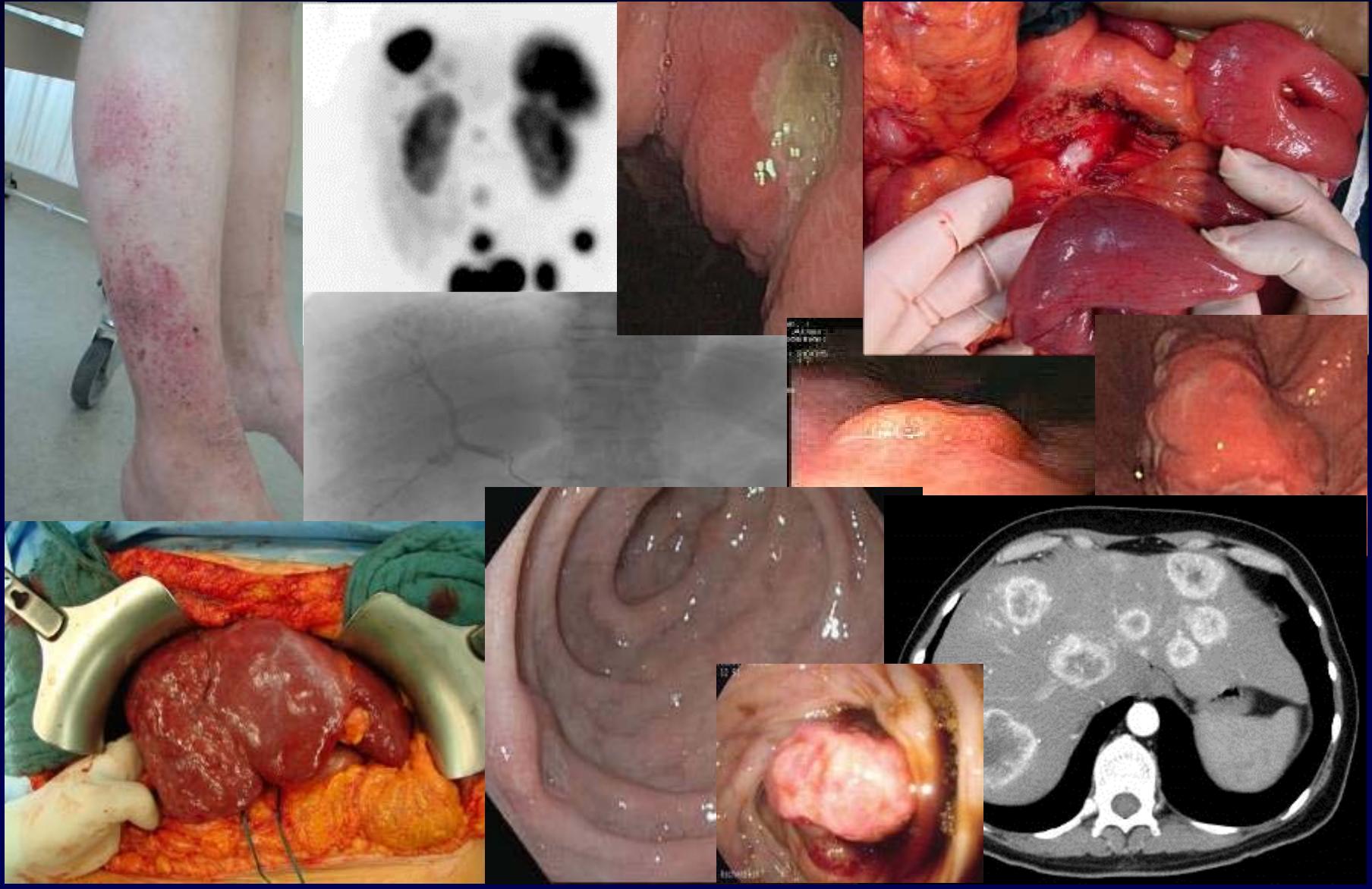


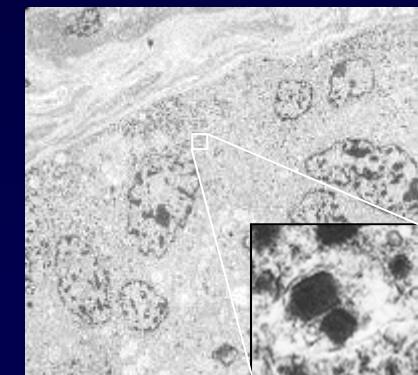
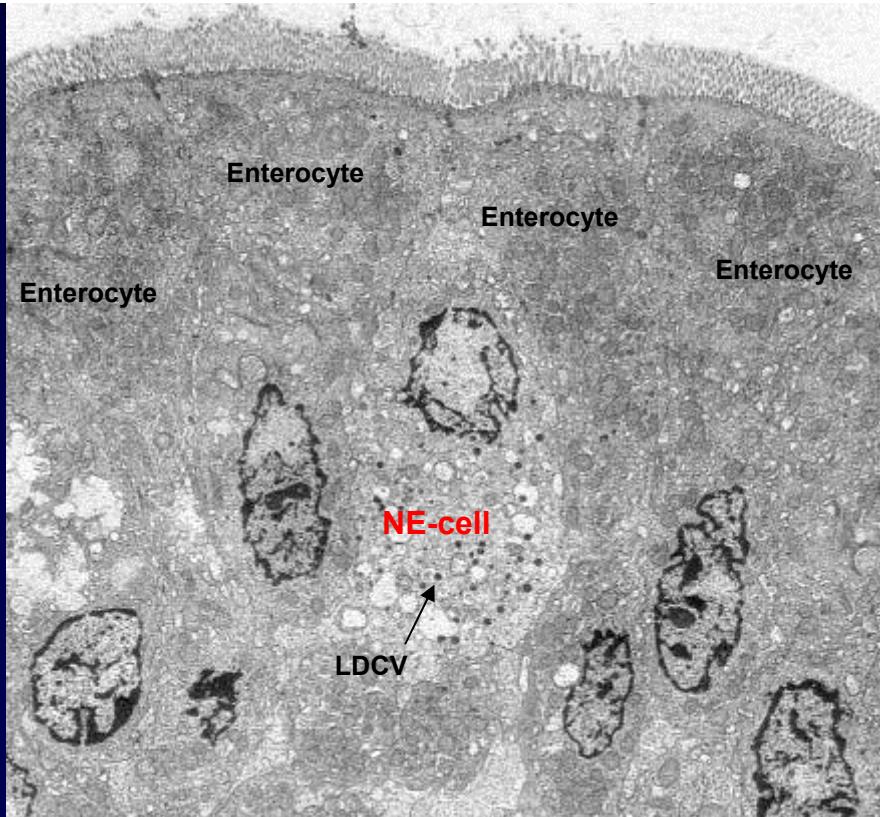
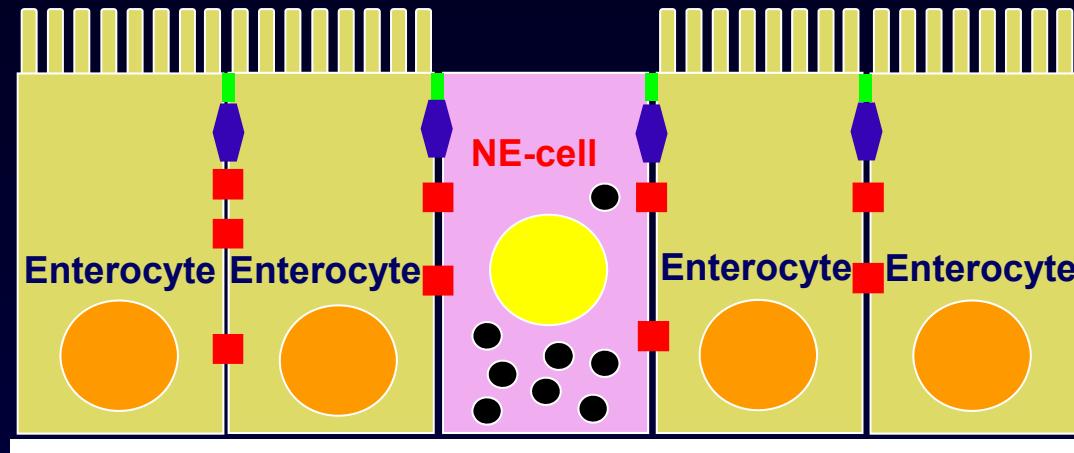
Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs): A Closer Look at the Characteristics of These Diverse Tumors

Ulrich-Frank Pape, MD
Charité University Hospital
Berlin, Germany

NET/Ns: One (?) Disease – Many Face(t)s!



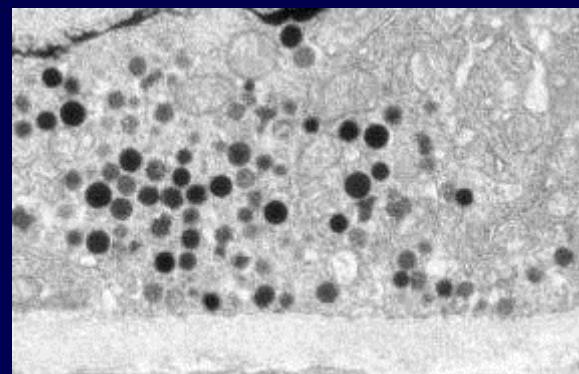
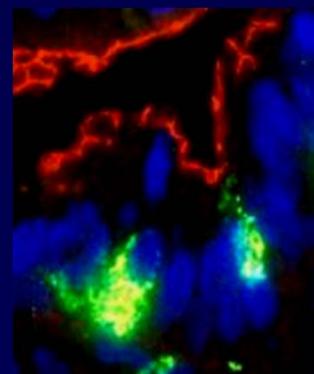
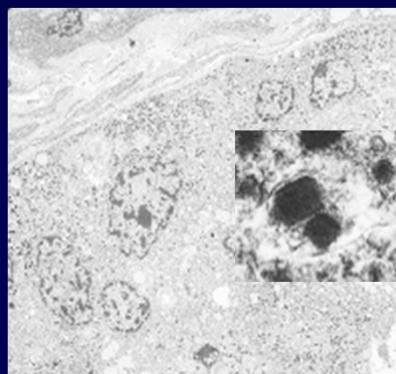
Neuroendocrine Cells in the GI Tract



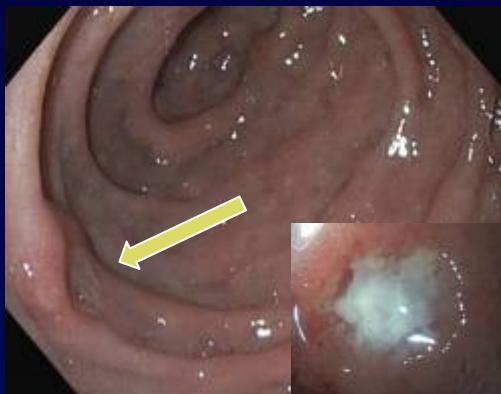
The Diffuse Endocrine System (DES) of the GI Tract

Neoplasm and cell type	Pancreas	Stomach		Small intestine			Appendix	Large intestine	
		Body fundus	Antrum	Duodenum	Jejunum	Ileum		Colon	Rectum
NET grade 1-2									
B	✓	-	-	-	-	-	-	-	-
A	✓	-	-	-	-	-	-	-	-
PP	✓	-	-	-	-	-	-	-	-
D	✓	-	-	✓	✓	-	-	-	-
EC	✓	✓	✓	✓	✓	✓	✓	✓	✓
ECL	-	✓	-	-	-	-	-	-	-
G	✓	-	✓	✓	✓	✓	-	-	-
L	-	-	-	✓	✓	✓	✓	✓	✓
P/D1	✓	✓	-	-	-	-	-	-	-
NEC grade 3									
S/L	✓	✓	✓	✓	✓	✓	✓	✓	✓

Rindi G, Wiedenmann B. *Nat Rev Endocrinol.* 2011;8(1):54-64



Hormone Hypersecretion Syndromes

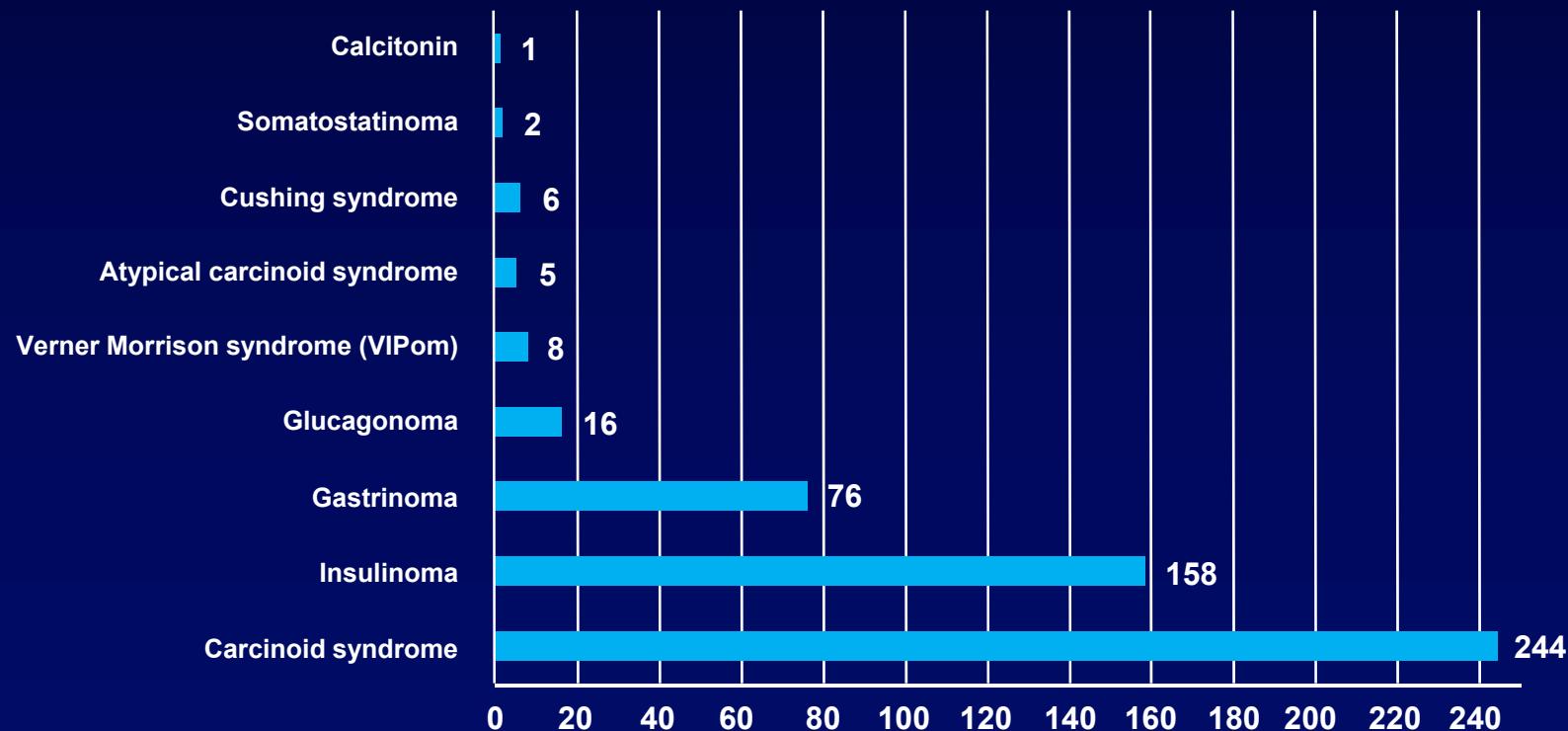


Hormone Hypersecretion Syndromes (= Functioning NET)

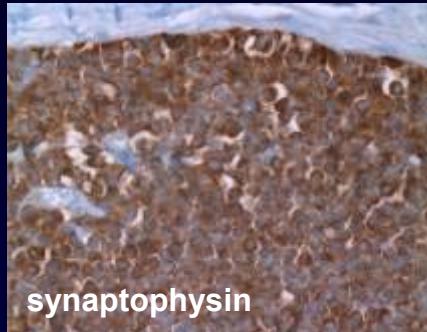
Functioning: 39.5% (553)

Non-functioning: 60.0% (836)

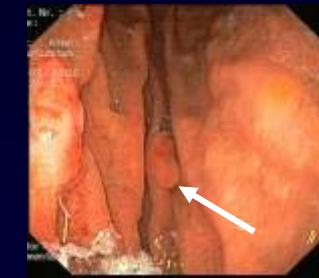
Unclear: 0.5% (11)



Origin of NET According to the Section of the Embryonic GI Tract: A First Classification



Midgut
jejunum, ileum, cecum,
ascending & transverse colon



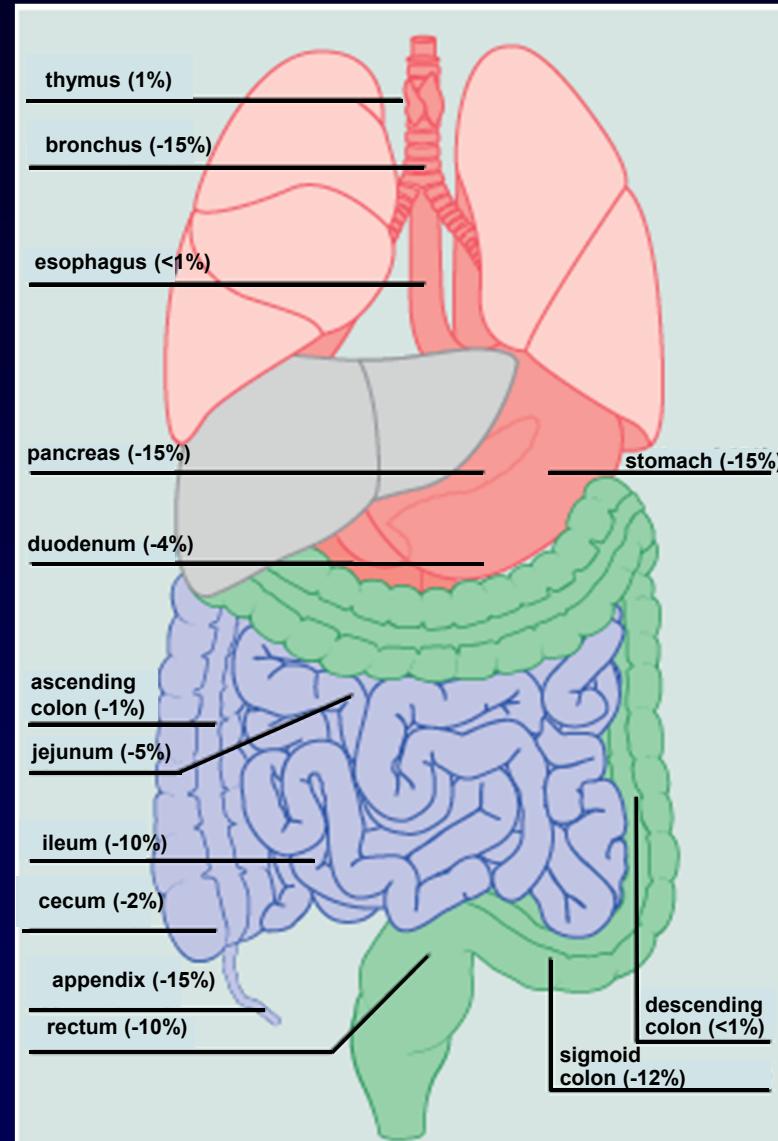
Foregut
thymus, lung,
esophagus, stomach,
duodenum, pancreas



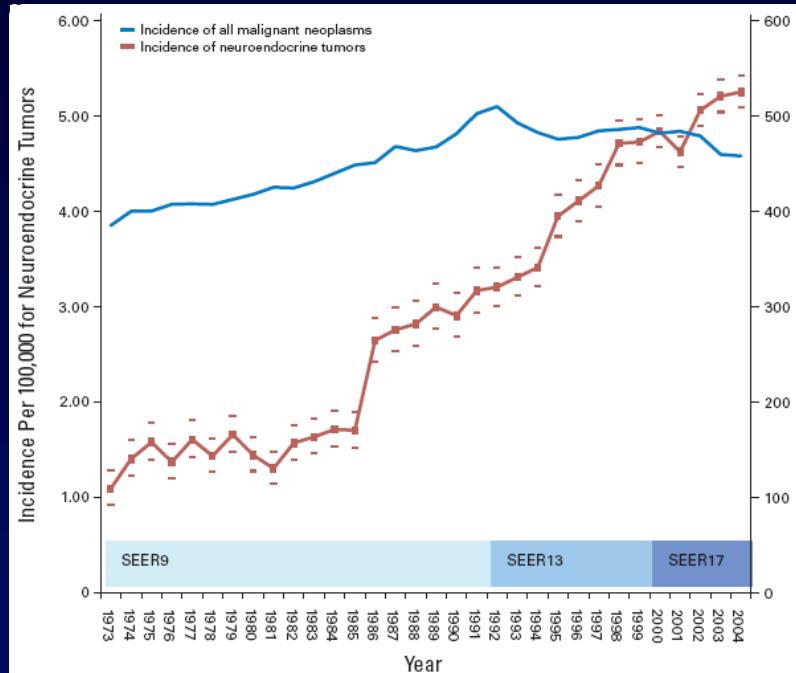
Hindgut
descending & sigmoid colon,
rectum

Primary Tumor Localizations

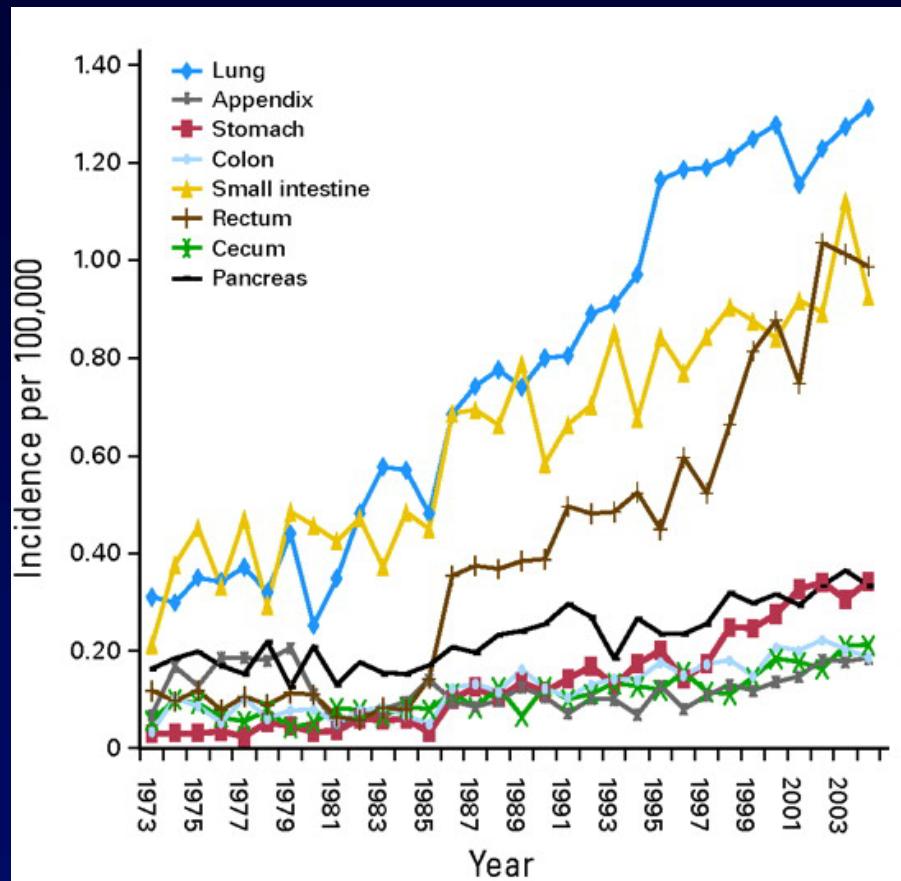
	est. % of all NEN
thymus	<1
<i>bronchus</i>	15
esophagus	<1
<i>stomach</i>	15
duodenum	4
<i>pancreas</i>	15
<i>jejunum/ileum</i>	15
cecum	2
<i>appendix</i>	15
colon	1
<i>rectum</i>	10



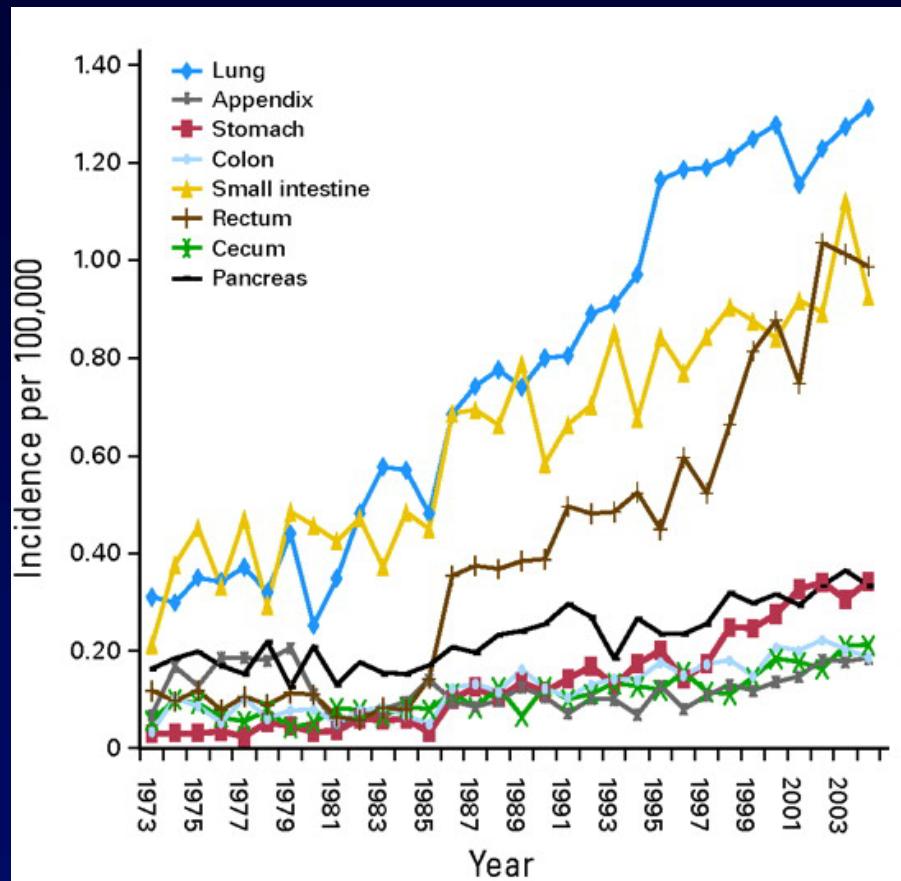
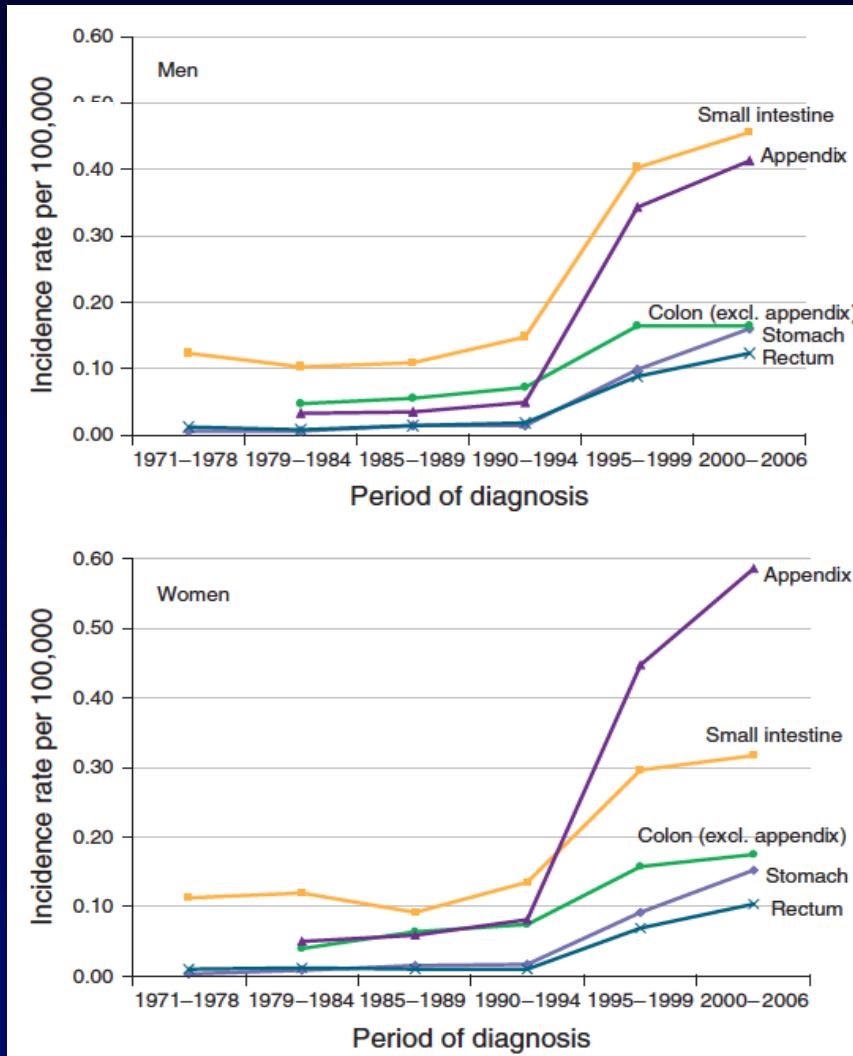
More Neuroendocrine Neoplasms (NENs)?



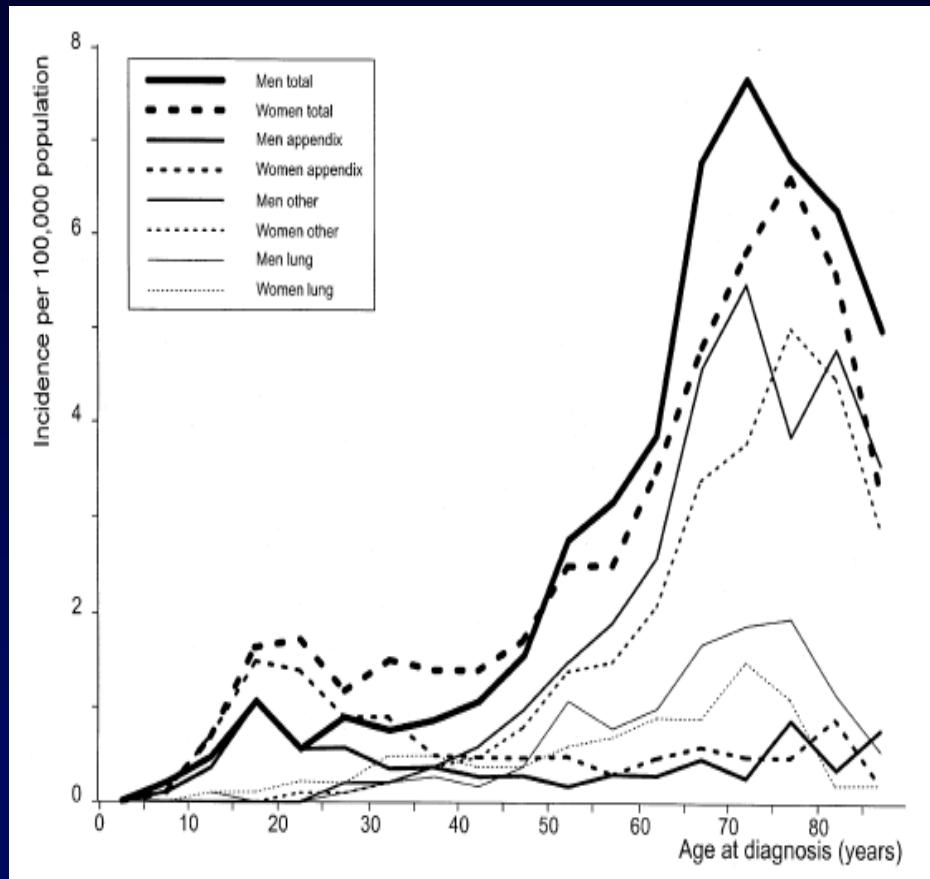
Modlin IM, et al. *Lancet Oncol.* 2008;9(1):61-72



More Neuroendocrine Neoplasms (NENs)?



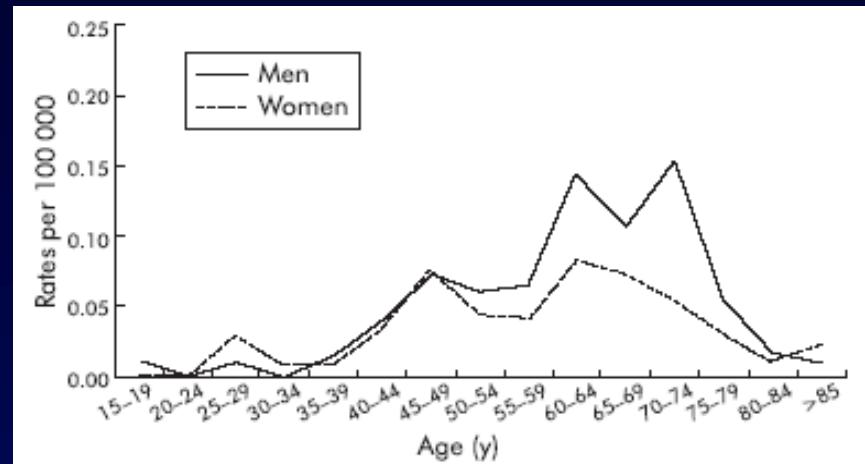
Age and Gender



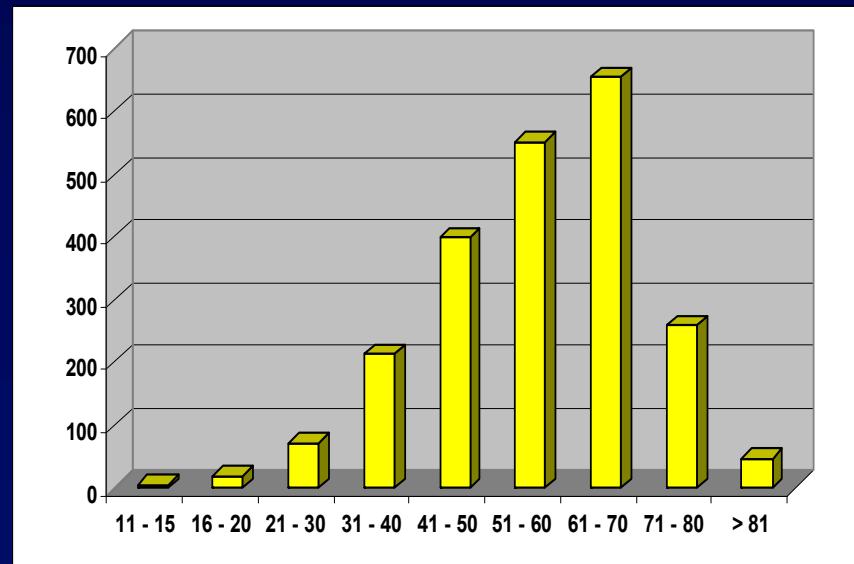
Quaedvlieg PF, et al. *Ann Oncol.* 2001;12(9):1295-1300.

Median age at ID: 57-59 years (range 10-99)

Garcia-Carbonero R, et al. *Ann Oncol.* 2010;21(9):1794-1803.

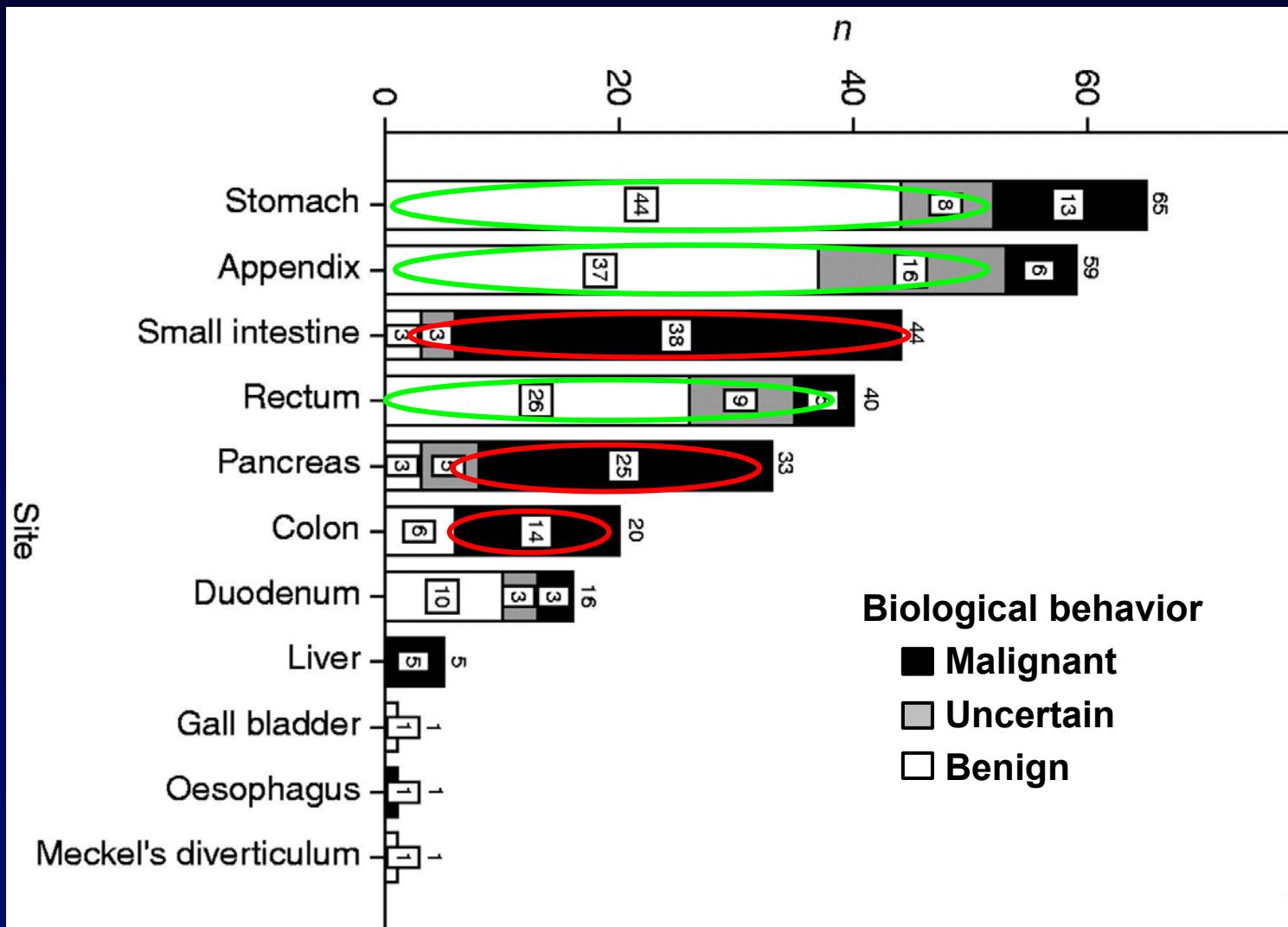


Lepage C, et al. *Gut.* 2004;53(4):549-553.



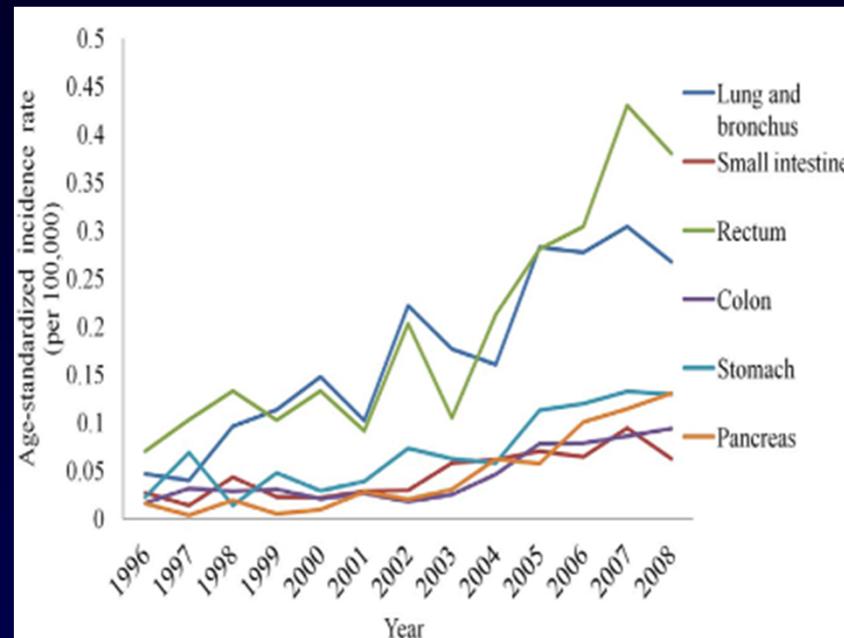
Plöckinger U, et al. *Neuroendocrinology.* 2009;90(2):159-161.

NEN: All the Same?



Niederle MD, et al. *Endocr Relat Cancer*. 2010;17(4):909-918.

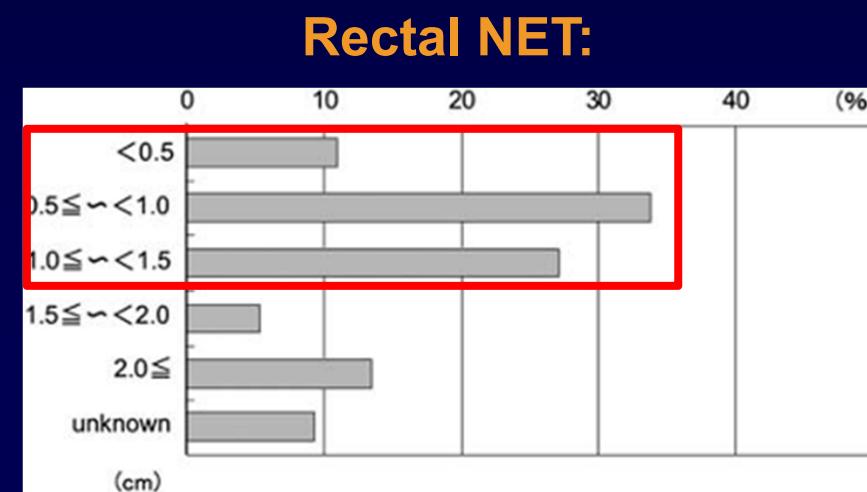
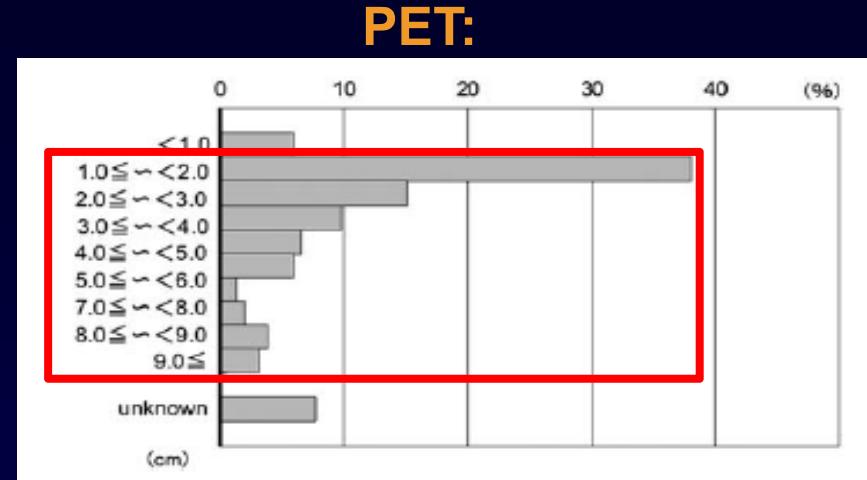
Population-Based Epidemiology: Japan



Tsai HJ, et al. PLoS One. 2013;8(4):e62487.

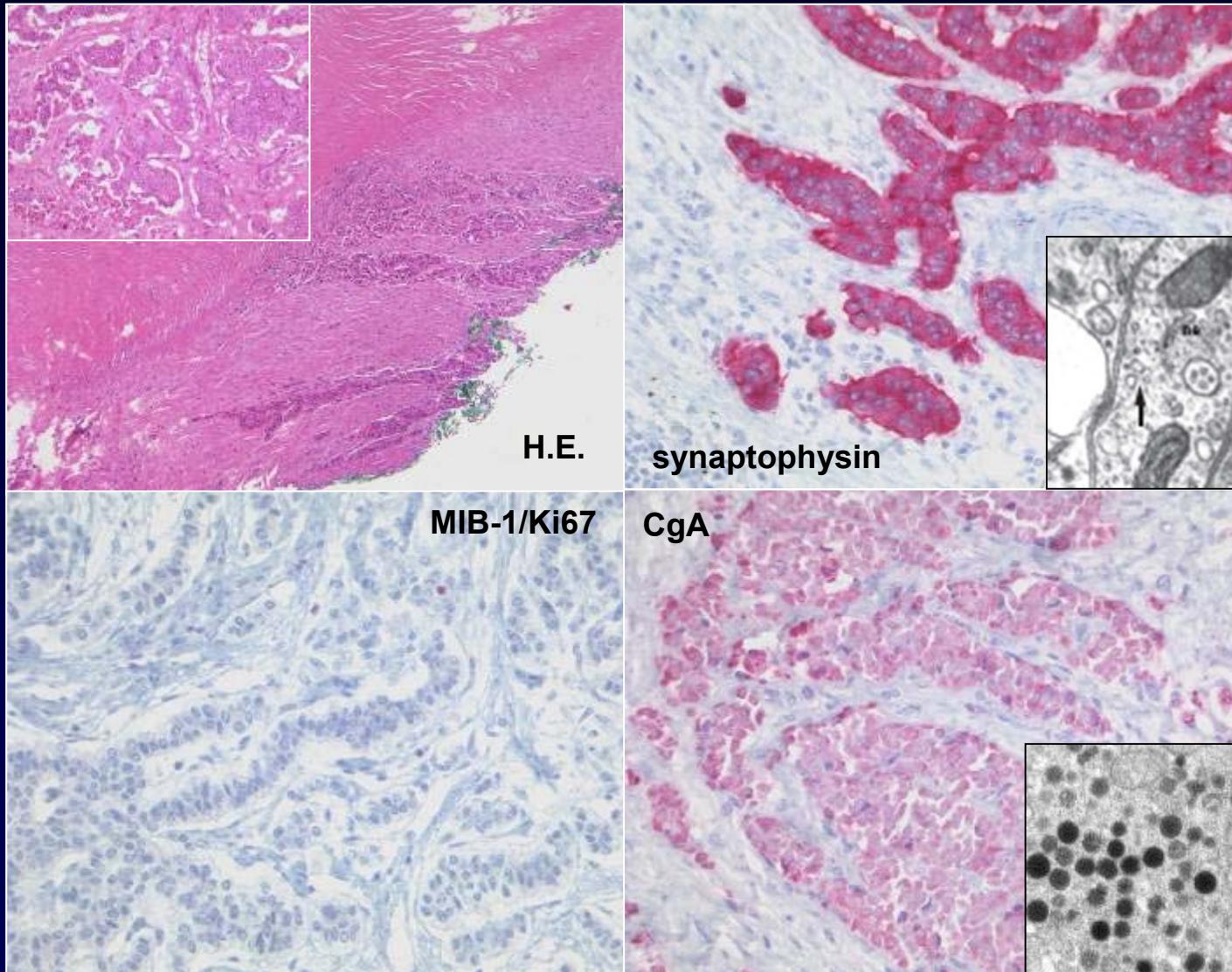
Primary GI Cancer in Japan:

Rectum	55.7 %
Duodenum	16.7 %
Stomach	15.1%
Colon	2.1 %
Jejunoileum	2.2 %



Ito T, et al. J Gastroenterol. 2010;45(2):234-243.

Neuroendocrine Neoplasms



The “Capella” - Classification of NETs

Virchows Archiv (1995) 425:547–560

REVIEW ARTICLE

Carlo Capella · Philipp U. Heitz · Heinz Höfler
Enrico Solcia · Günter Klöppel

Revised classification of neuroendocrine tumours of the lung, pancreas and gut

Table 1 Neuroendocrine tumours of the lung

Benign or low-grade malignant
Nonfunctioning well-differentiated tumour (typical carcinoid)
Functioning well-differentiated tumour
Low-grade malignant ^a
Nonfunctioning well-differentiated carcinoma (atypical carcinoid)
Functioning well-differentiated carcinoma
High-grade malignant
Functioning or nonfunctioning poorly differentiated carcinoma
Large cell type
Small or intermediate cell type

^a If metastases or gross invasion are present, tumour should be called low-grade neuroendocrine carcinoma

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Functioning well-differentiated carcinoma
High-grade malignant
Functioning or nonfunctioning poorly differentiated
Large cell type
Small or intermediate cell type

^a If metastases or gross invasion are present, tumour should be called low-grade neuroendocrine carcinoma

Table 3 Neuroendocrine tumours of the stomach

Benign
Nonfunctioning well-differentiated tumour of small size (up to 1 cm) within the mucosa-submucosa and without angioinvasion
– usually ECL-cell tumours of the fundic mucosa associated with chronic atrophic gastritis (CAG) and hypergastrinaemia
Benign or low-grade malignant
Nonfunctioning well-differentiated tumour within the mucosa-submucosa of intermediate size (>1 up to 2 cm) without angioinvasion or of small to intermediate size (up to 2 cm) with angioinvasion
– usually ECL-cell tumours of the fundic mucosa associated with CAG and hypergastrinaemia
– rarely MEN-1 associated or sporadic ECL-cell tumours
Low-grade malignant ^a
Nonfunctioning well-differentiated tumour of large size (>2 cm) or extending beyond the submucosa
– usually sporadic ECL-cell tumours; rarely serotonin producing tumours ^b or others
– rarely MEN-1 or CAG associated ECL-cell tumours
Functioning well-differentiated tumour of any size and extension
– sporadic gastrinoma, serotonin producing tumour ^b or others
High-grade malignant
Functioning or nonfunctioning poorly differentiated intermediate or small cell carcinoma

^a If metastases or gross invasion are present, tumour should be called low-grade neuroendocrine carcinoma

^b Also called EC-cell tumour

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Nonfunctioning well-differentiated carcinoma (atypical carcinoid)
Functioning well-differentiated carcinoma
High-grade malignant
Functioning or nonfunctioning poorly differentiated
Large cell type
Small or intermediate cell type

^a If metastases or gross invasion are present, tumour should be called low-grade neuroendocrine carcinoma

Table 3 Neuroendocrine tumours of the stomach

Benign
Nonfunctioning well-differentiated tumour of small (≤ 1 cm) within the mucosa-submucosa and without an
– usually ECL-cell tumours of the fundic mucosa with chronic atrophic gastritis (CAG) and hypergastrinaemia
Benign or low-grade malignant
Nonfunctioning well-differentiated tumour within the submucosa of intermediate size (>1 up to 2 cm) with invasion or of small to intermediate size (up to 2 cm) with invasion
– usually ECL-cell tumours of the fundic mucosa with CAG and hypergastrinaemia
– rarely MEN-1 associated or sporadic ECL-cell tumours
Low-grade malignant ^a
Nonfunctioning well-differentiated tumour of large size (>2 cm) or extending beyond the submucosa
– usually sporadic ECL-cell tumours; rarely serotonin producing tumours ^b or others
– rarely MEN-1 or CAG associated ECL-cell tumours
Functioning well-differentiated tumour of any size or extension
– sporadic gastrinoma, serotonin producing tumour
High-grade malignant
Functioning or nonfunctioning poorly differentiated intermediate or small cell carcinoma

^a If metastases or gross invasion are present, tumour should be called low-grade neuroendocrine carcinoma.

^b Also called EC-cell tumour.

Table 5 Neuroendocrine tumours of the jejunum and ileum

Benign
Nonfunctioning well-differentiated tumour of small size (≤ 1 cm) within the mucosa-submucosa but without angioinvasion
– usually serotonin producing ^b tumours in the terminal ileum
Benign or low-grade malignant
Nonfunctioning well-differentiated tumours of intermediate size (>1 up to 2 cm) but without angioinvasion or extension beyond the submucosa
– usually serotonin producing ^b tumours of the terminal ileum
Low-grade malignant ^a
Nonfunctioning well-differentiated tumour of large size (>2 cm) or extending beyond the submucosa and/or angioinvasive
– usually serotonin producing ^b tumours of the terminal ileum
Functioning well-differentiated tumour of any size and extension
– serotonin producing tumour ^b with carcinoid syndrome ^c
– sporadic gastrinoma (upper jejunum)
High-grade malignant
Functioning or nonfunctioning poorly differentiated intermediate or small cell carcinoma

^a If metastases or gross invasion are present, tumour should be called low-grade neuroendocrine carcinoma.

^b Also called EC-cell tumour.

^c As serotonin is metabolized and inactivated by the liver, serotonin secreting tumours of the gut only produce a syndrome if liver metastases are already present

The “Capella” - Classification of NETs

Virchows Archiv (1995) 425:547–560

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Table 1 Neuroendocrine tumours of the lung

Benign or low-grade malignant
Nonfunctioning well-differentiated (typical carcinoid)
Functioning well-differentiated tu-
Low-grade malignant*
Nonfunctioning well-differentiated (atypical carcinoid)
Functioning well-differentiated car-
High-grade malignant
Functioning or nonfunctioning poor
Large cell type
Small or intermediate cell type

^a If metastases or gross invasion are called low-grade neuroendocrine carcinoma.

Table 2 Neuroendocrine tumours of the stomach

Benign	Functioning well-differentiated non-angioinvasive tumour of small size
insulinoma	(size <2 cm)
others ^b	(size <1 cm)
Nonfunctioning well-differentiated non-angioinvasive tumour of small size	(<2 cm)
Benign or low-grade malignant	Functioning well-differentiated non-angioinvasive tumour of intermediate size
insulinoma	(size 2–3 cm)
others ^b	(size 1–2 cm)
Nonfunctioning well-differentiated non-angioinvasive tumour of intermediate size (2–3 cm)	
Low-grade malignant	Functioning well-differentiated tumour of large size and/or with angioinvasion
insulinoma	(size >3 cm)
others ^b	(size >2 cm)
Nonfunctioning well-differentiated tumour of large size (>3 cm) and/or with angioinvasion	
High-grade malignant	Functioning or nonfunctioning poorly differentiated intermediate or small cell carcinoma

^a If metastases or gross invasion are present, tumour should be called low-grade neuroendocrine carcinoma.

b Other functioning tumours: gastrinoma, vipoma, glucagonoma, serotonin producing tumour, others

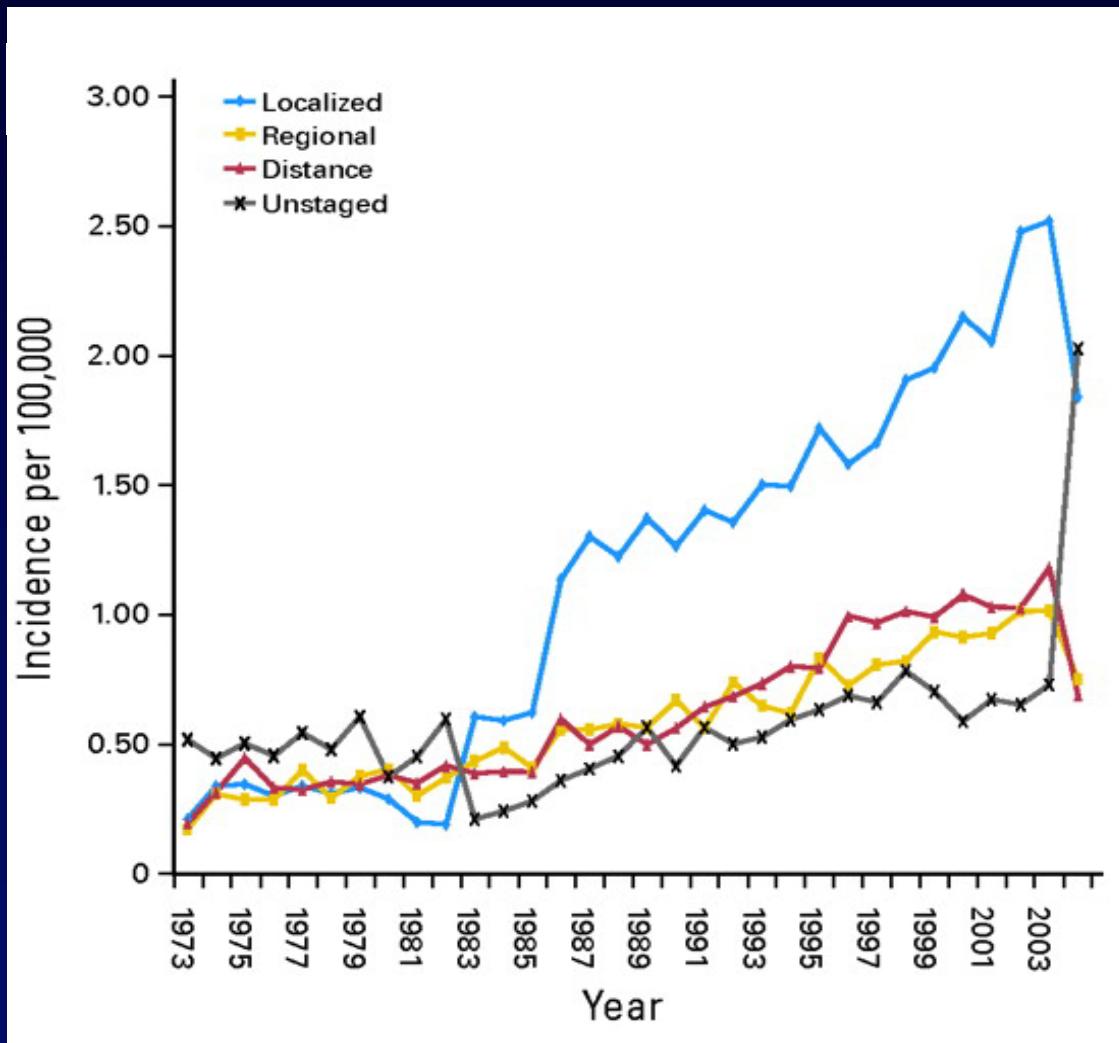
Table 5. Nonwandosing tumours of the jejunum and ileum

- ed tumour of small size (≤ 1 cm)
ut without angioinvasion
- ^{g^b} tumours in the terminal ileum
- ed tumours of intermediate size
oinvasion or extension beyond
- ^{g^b} tumours of the terminal
- ed tumour of large size (> 2 cm)
osa and/or angioinvasive
- ^{g^b} tumours of the terminal ileum
- utour of any size and extension
- ^{r^b} with carcinoid syndrome^c
jejunum)

are present, tumour should be carcinoma

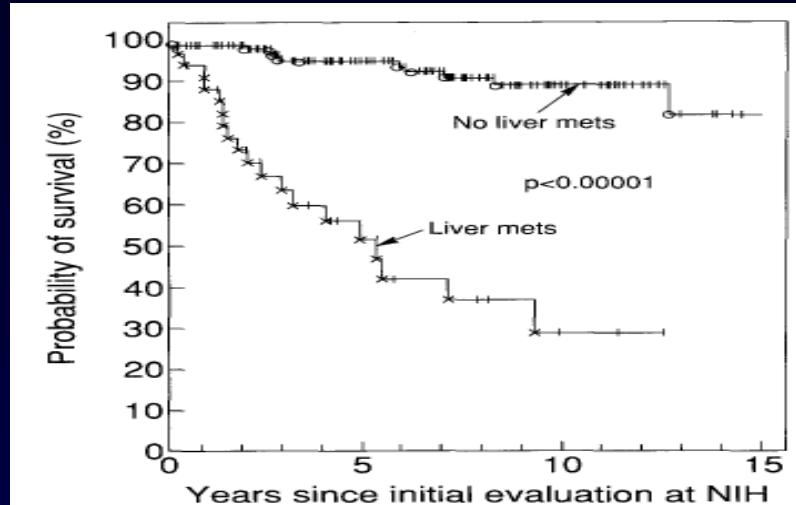
inactivated by the liver, serotonin produce a syndrome if liver

Primary Tumor Localization and Extent of Tumor Disease

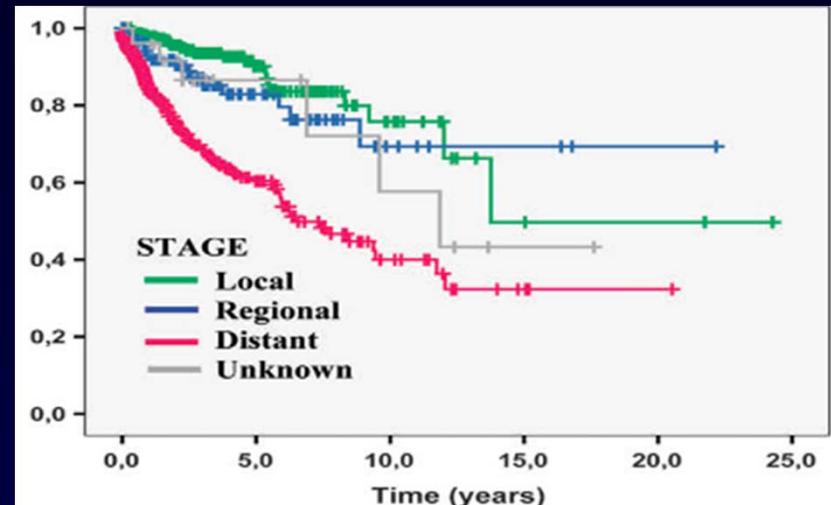


Yao JC, et al. *J Clin Oncol*. 2008;26(18):3063-3072.

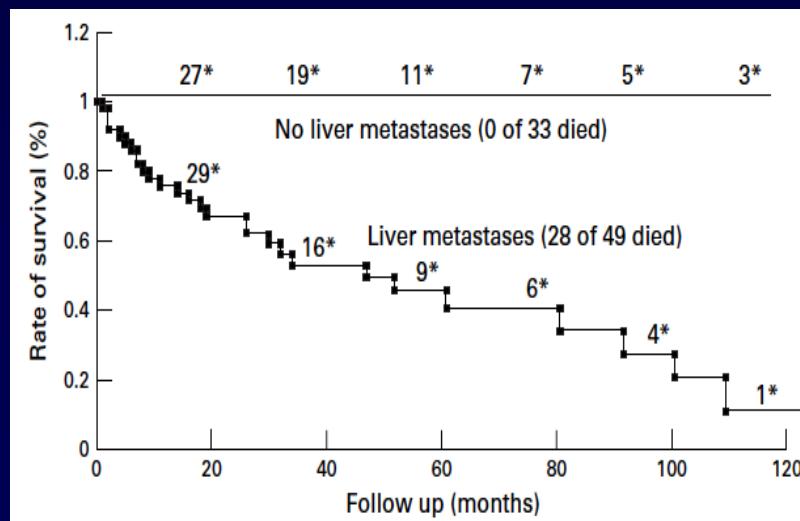
Prognosis: Metastatic vs Non-Metastatic Disease



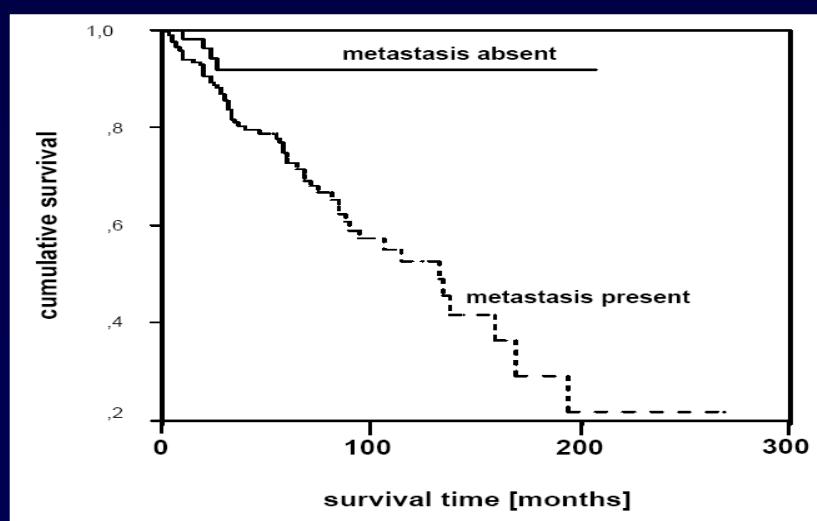
Weber HC, et al. *Gastroenterology*. 1995;108(6):1637-1649.



Garcia-Carboero R, et al. *Ann Oncol*. 2010;21(9):1794-1803.

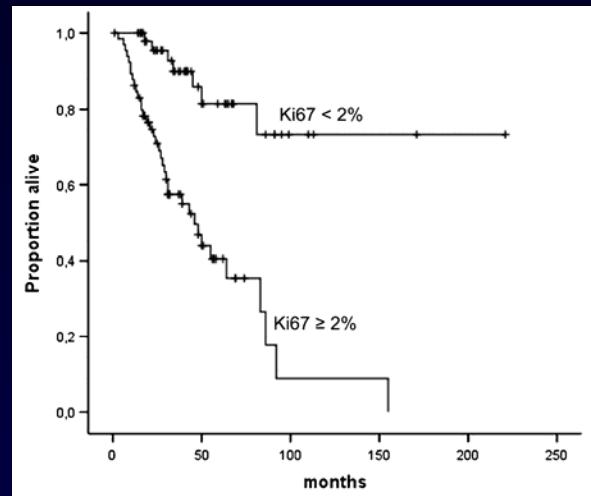


Madeira I, et al. *Gut*. 1998;43(3):422-427

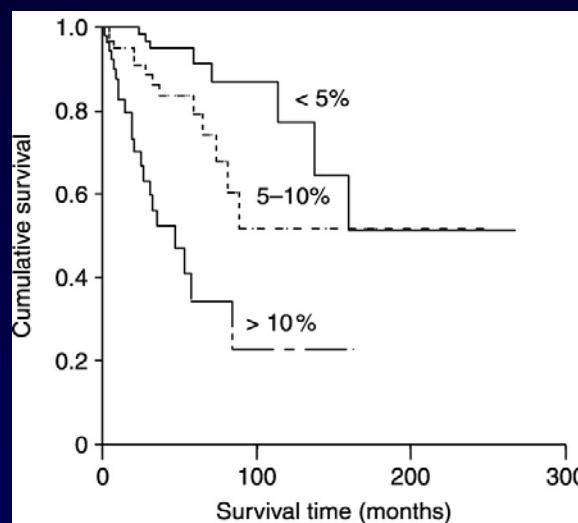
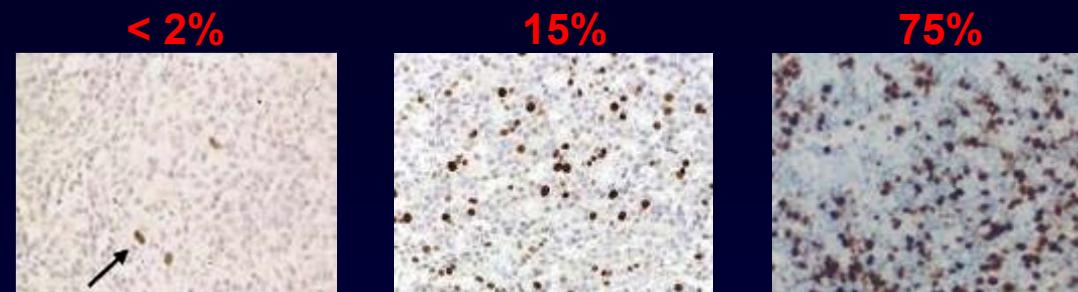


Pape UF, et al. *Endocr Relat Cancer*. 2008;15(4):1083-1097.

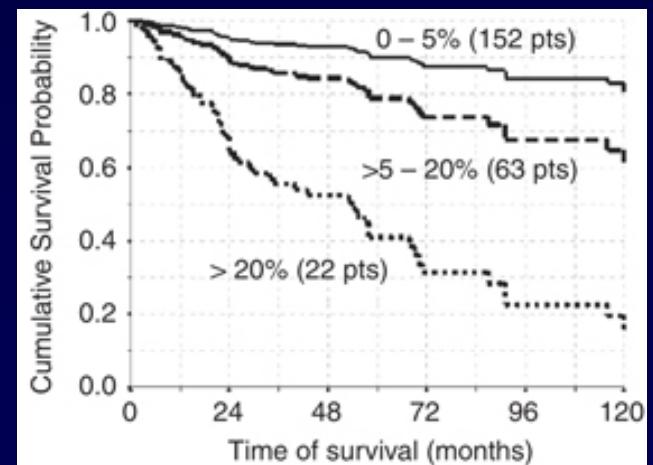
Prognostic Influence of Ki67-Labelling



Ekeblad S, et al. *Clin Cancer Res.* 2008;14(23):7798-7803.
Vilar E, et al. *Endocr Relat Cancer.* 2007;14(2):221-232.



Pape UF, et al. *Endocr Relat Cancer.* 2008;15(4):1083-1097.



Scarpa A, et al. *Mod Pathol.* 2010;23(6):824-833.

Slide not available

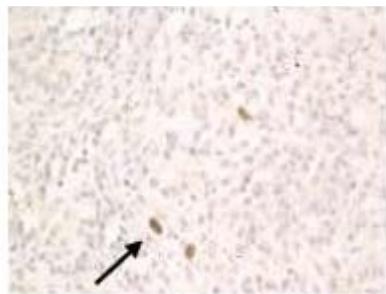
Current Classification: WHO 2010 ... Who Else?

WHO 1980	WHO 2000	Histological differentiation	Size	metas- tases	WHO 2010	Ki67-Index (%)
Carcinoid(s) Islet cell Tm	WDET	well	≤ 1-2 cm	-	NET - G1	≤2
	WDEC	well	> 2 cm	+	NET - G2	3 - 20
	PDEC	poorly small or large cell phenotype	any	+	NEC - G3	>20

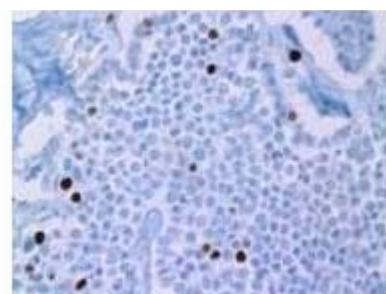
Capella C, et al. *Virchows Arch.* 1995;425(6):547-560
Solcia E, Klöppel G, Sabin LH. *WHO*. 2000
Klimstra DS, et al. *Pancreas*. 2010;39(6):707-712

Rindi G, et al. *Virchows Arch.* 2006;449(4):395-401.
Rindi G, et al. *Virchows Arch.* 2007;451(4):757-762.

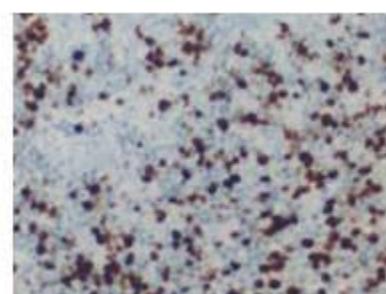
Current Classification: WHO 2010 ... Who Else?



G1 ($\leq 2\%$)



G2 (3-20%)



G3 ($>20\%$)

Size	metas-tases	WHO 2010	Ki67-Index (%)
$\leq 1\text{-}2\text{ cm}$	-	NET - G1	≤ 2
$> 2\text{ cm}$	+	NET - G2	3 - 20
any	+	NEC - G3	>20

Virchows Arch (2006) 449:395–401
DOI 10.1007/s00428-006-0250-1

ORIGINAL ARTICLE

TNM staging of foregut (neuro)endocrine tumors:
a consensus proposal including a grading system

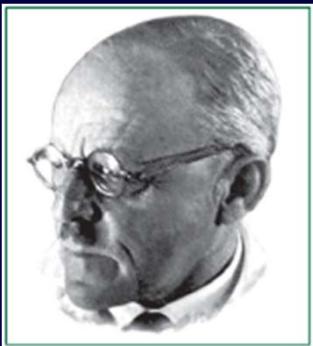
Virchows Arch
DOI 10.1007/s00428-007-0452-1

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TNM staging of midgut and hindgut (neuro) endocrine
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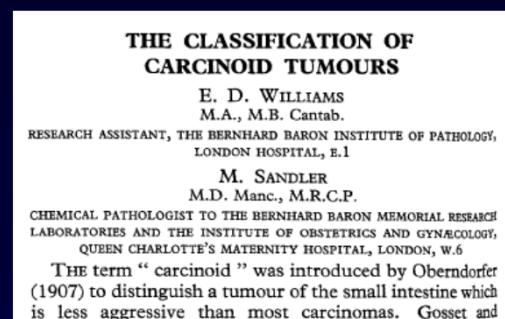
Rindi G, et al. *Virchows Arch.* 2006;449(4):395-401.
Rindi G, et al. *Virchows Arch.* 2007;451(4):757-762.

NEN-Classification: ... As Time Goes By...



Siegfried Oberndorfer

1907

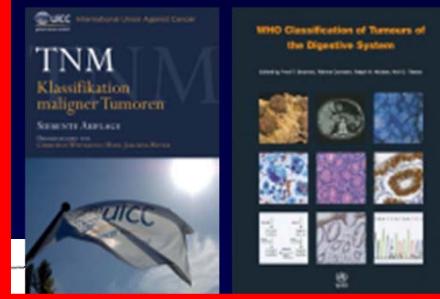


TNM staging of midgut and hindgut (neuro)endocrine tumors: a consensus proposal including a grading system

G. Rindi • G. Klöppel • A. Couvelard • P. Komminoth •
M. Körner • J. M. Lopes • A-M. McNicol • O. Nilsson •
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A. Scarpa • J-Y. Scouazec • B. Wiedenmann •
and all other Frascati Consensus Conference
participants



Virchows Archiv (1995) 425:547–560

REVIEW ARTICLE

Carlo Capella • Philipp U. Heitz • Heinz Höfler
Enrico Sclaria • Günter Klöppel

Revised classification of neuroendocrine tumours of the lung,
pancreas and gut

WHO
1980

WHO
2000
AJCC/WHO
UICC 2010
ENETS

1995 2000 2006/7 2009 2010



p/c-Staging of Gastric NEN

TNM staging of foregut (neuro)endocrine tumors:
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A. Scarpa • J.-Y. Scouazec • B. Wiedenmann •
and all other Frascati Consensus Conference
participants

Rindi G, et al. *Virchows Arch.* 2006;449(4):395-401.

<i>T – Primary tumor</i>		<i>Stage</i>
Tx	Primary tumor cannot be assessed	
T0	No evidence of a primary tumor	0
Tis	in situ tumor (only for stomach)	I
T1	Tumor invades lamina propria or submucosa and $\leq 1\text{cm}$	IIa
T2	Tumor invades muscularis propria or subserosa or $> 1\text{cm}$	
T3	Tumor penetrates serosa	IIb
T4	Tumor invades adjacent structures	IIIa
for any T	add (m) for multiple tumors	
<i>N - Regional Lymph nodes</i>		
Nx	Regional lymph nodes cannot be assessed	
N0	No regional lymph node metastasis	
N1	Regional lymph node metastasis	IIIb
<i>M – Distant metastasis</i>		
Mx	Distant metastasis cannot be assessed	
M0	No distant metastasis	
M1	Distant metastasis	IV

Clinico-Pathological Classification of Gastric NEN



	Type 1	Type 2	Type 3	Type 4
Percentage of gastric NEN [%]	70-80	5-6	10-20	<5
Tumor characteristics	mostly small (< 1-2 cm), 65% multiple, 78% polypoid	mostly small (<1-2 cm) and multiple, polypoid	solitary, often large (>2cm), polypoid, maybe ulcerated	solitary, mostly large (>2cm), polypoid and mostly ulcerated
Association	chronic atrophic gastritis	Gastrinoma & ZES MEN1	none	none
Pathology	G1/2-NET	G1/2-NET	mostly G2-NET	G3-NEC
Serum-gastrin	↑	↑↑	normal	normal
Gastric pH	↑↑	↓↓	normal	normal
Metastases [%]	2-5	5-15	30-80	50-100
Tumor-associated deaths [%]	0	<10	25-30	60-95

ZES, Zollinger-Ellison-syndrome

Klöppel G, et al. *Yale J Biol Med.* 1996;69(1):69-74.



p/c-Staging of Duodenal NEN

**TNM staging of foregut (neuro)endocrine tumors:
a consensus proposal including a grading system**

G. Rindi • G. Klöppel • H. Alhman • M. Caplin •
A. Couvelard • W. W. de Herder • B. Eriksson •
A. Falchetti • M. Falconi • P. Komminoth • M. Körner •
J. M. Lopes • A.-M. McNicol • O. Nilsson • A. Perren •
A. Scarpa • J.-Y. Scouazec • B. Wiedenmann •
and all other Frascati Consensus Conference
participants

Rindi G, et al. *Virchows Arch.* 2006;449(4):395-401.

<i>T – Primary tumor</i>		<i>Stage</i>
Tx	Primary tumor cannot be assessed	
T0	No evidence of a primary tumor	I
T1	Tumor invades lamina propria or submucosa and ≤ 1cm	
T2	Tumor invades muscularis propria or subserosa or > 1cm	IIa
T3	Tumor invades pancreas or retroperitoneum	
T4	Tumor invades peritoneum or other organs	IIb
for any T	add (m) for multiple tumors	IIIa
<i>N - Regional Lymph nodes</i>		
Nx	Regional lymph nodes cannot be assessed	
N0	No regional lymph node metastasis	
N1	Regional lymph node metastasis	IIIb
<i>M – Distant metastasis</i>		
Mx	Distant metastasis cannot be assessed	
M0	No distant metastasis	
M1	Distant metastasis	IV

P, pathological; c, clinical



p/c-Staging of Pancreatic NEN

TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system

G. Rindi • G. Klöppel • H. Ahlman • M. Caplin •
A. Couvelard • W. W. de Herder • B. Eriksson •
A. Falchetti • M. Falconi • P. Komminoth • M. Körner •
J. M. Lopes • A.-M. McNicol • O. Nilsson • A. Perren •
A. Scarpa • J.-Y. Scauzec • B. Wiedenmann •
and all other Frascati Consensus Conference
participants

Rindi G, et al. *Virchows Arch.* 2006;449(4):395-401.

<i>T – Primary tumor</i>		<i>Stage</i>
Tx	Primary tumor cannot be assessed	
T0	No evidence of a primary tumor	
T1	Tumor limited to the pancreas and size < 2cm	
T2	Tumor limited to the pancreas and size 2 – 4cm	
T3	Tumor limited to the pancreas and size > 4cm or invading duodenum or bile duct	
T4	Tumor invades peritoneum or other organs or the wall of large vessels (celiac trunk or SMA)	
for any T	add (m) for multiple tumors	
<i>N - Regional Lymph nodes</i>		<i>IIa</i>
Nx	Regional lymph nodes cannot be assessed	
N0	No regional lymph node metastasis	
N1	Regional lymph node metastasis	
<i>M – Distant metastasis</i>		<i>IIb</i>
Mx	Distant metastasis cannot be assessed	
M0	No distant metastasis	
M1	Distant metastasis	<i>IIIa</i>
		<i>IIIb</i>
		<i>IV</i>



p/c-Staging of Jejunoileal NEN

TNM staging of midgut and hindgut (neuro) endocrine tumors: a consensus proposal including a grading system

G. Rindi • G. Klöppel • A. Couvelard • P. Komminoth •
M. Körner • J. M. Lopes • A-M. McNicol • O. Nilsson •
A. Perren • A. Scarpa • J-Y. Scosazec • B. Wiedenmann

Rindi G, et al. *Virchows Arch.* 2007;451(4):757-762.

<i>T – Primary tumor</i>		<i>Stage</i>
Tx	Primary tumor cannot be assessed	I
T0	No evidence of a primary tumor	
T1	Tumor invades lamina propria or submucosa and ≤ 1cm	
T2	Tumor invades muscularis propria or subserosa or > 1cm	IIa
T3	Tumor invades subserosa	IIb
T4	Tumor invades peritoneum or other organs	IIIa
for any T	add (m) for multiple tumors	
<i>N - Regional Lymph nodes</i>		
Nx	Regional lymph nodes cannot be assessed	
N0	No regional lymph node metastasis	
N1	Regional lymph node metastasis	IIIb
<i>M – Distant metastasis</i>		
Mx	Distant metastasis cannot be assessed	
M0	No distant metastasis	
M1	Distant metastasis	IV

p/c-Staging of Appendiceal NEN

TNM staging of midgut and hindgut (neuro) endocrine tumors: a consensus proposal including a grading system

G. Rindi • G. Klöppel • A. Couvelard • P. Komminoth •
M. Körner • J. M. Lopes • A-M. McNicol • O. Nilsson •
A. Perren • A. Scarpa • J-Y. Scoazec • B. Wiedenmann

Rindi G, et al. Virchows Arch. 2007;451(4):757-762.

<i>T – Primary tumor</i>		<i>Stage</i>
Tx	Primary tumor cannot be assessed	
T0	No evidence of a primary tumor	
T1	Tumor ≤ 1cm invading lamina propria and submucosa and	I
T2	Tumor ≤ 2cm invading lamina propria, submucosa and/or minimally (up to 3mm) invading subserosa/mesoappendix	IIa
T3	Tumor > 2cm and/or extensive (> 3mm) invasion of subserosa/mesoappendix	IIb
T4	Tumor invades peritoneum or other organs	IIIa
for any T	add (m) for multiple tumors	
<i>N - Regional Lymph nodes</i>		
Nx	Regional lymph nodes cannot be assessed	
N0	No regional lymph node metastasis	
N1	Regional lymph node metastasis	IIIb
<i>M – Distant metastasis</i>		
Mx	Distant metastasis cannot be assessed	
M0	No distant metastasis	
M1	Distant metastasis	IV



p/c-Staging of Colonic and Rectal NEN

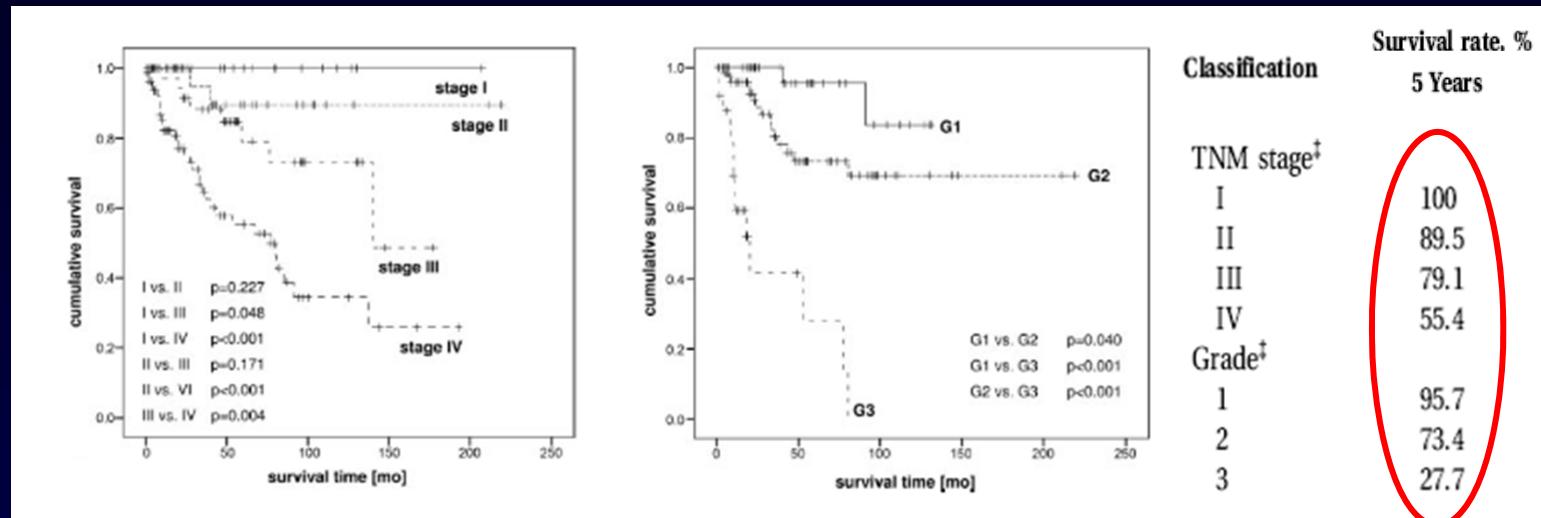
TNM staging of midgut and hindgut (neuro) endocrine tumors: a consensus proposal including a grading system

G. Rindi • G. Klöppel • A. Couvelard • P. Komminoth •
M. Körner • J. M. Lopes • A-M. McNicol • O. Nilsson •
A. Perren • A. Scarpa • J-Y. Scoazec • B. Wiedenmann

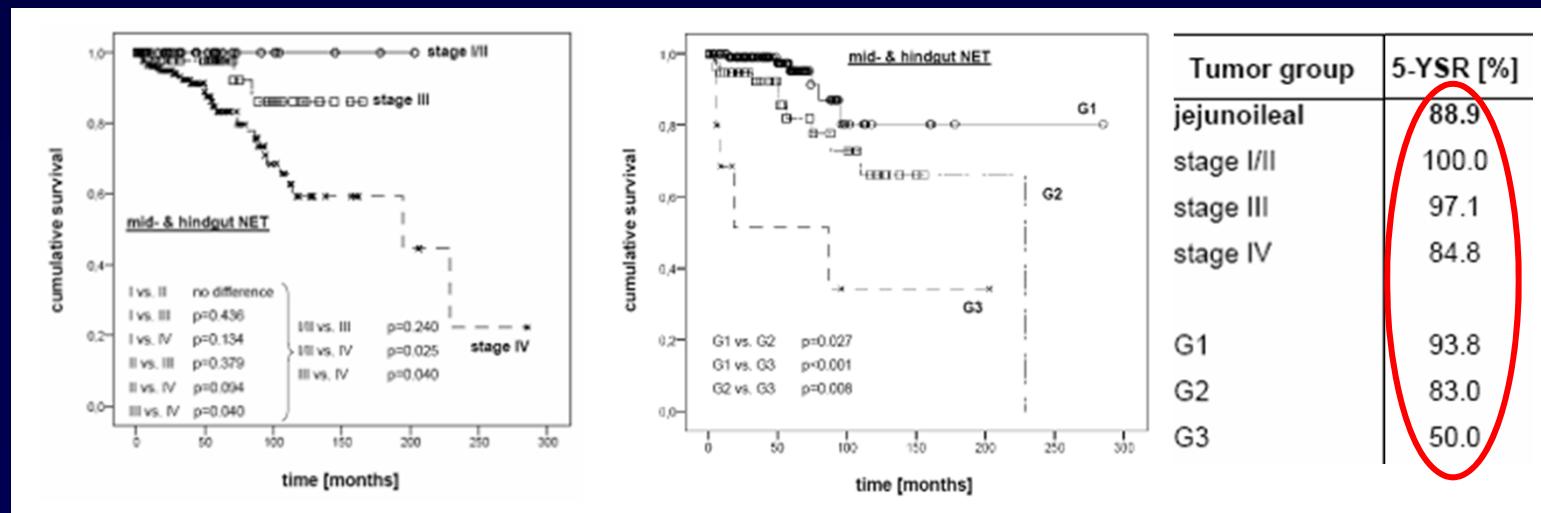
Rindi G, et al. *Virchows Arch.* 2007;451(4):757-762.

<i>T – Primary tumor</i>		<i>Stage</i>
Tx	Primary tumor cannot be assessed	
T0	No evidence of a primary tumor	
T1 T1a T1b	Tumor invades mucosa or submucosa Size < 1cm Size 1-2 cm	Ia Ib
T2	Tumor invades muscularis propria or size > 2cm	IIa
T3	Tumor invades subserosa/pericolic/perirectal fat	IIb
T4	Tumor directly invades other organs/structures and/or perforates visceral peritoneum	IIIa
for any T	add (m) for multiple tumors	
<i>N - Regional Lymph nodes</i>		
Nx	Regional lymph nodes cannot be assessed	
N0	No regional lymph node metastasis	
N1	Regional lymph node metastasis	IIIb
<i>M – Distant metastasis</i>		
Mx	Distant metastasis cannot be assessed	
M0	No distant metastasis	
M1	Distant metastasis	IV

Prognosis of NEN: TNM-Staging and Grading



Pape UF, et al. *Cancer*. 2008;113(2):256-265.

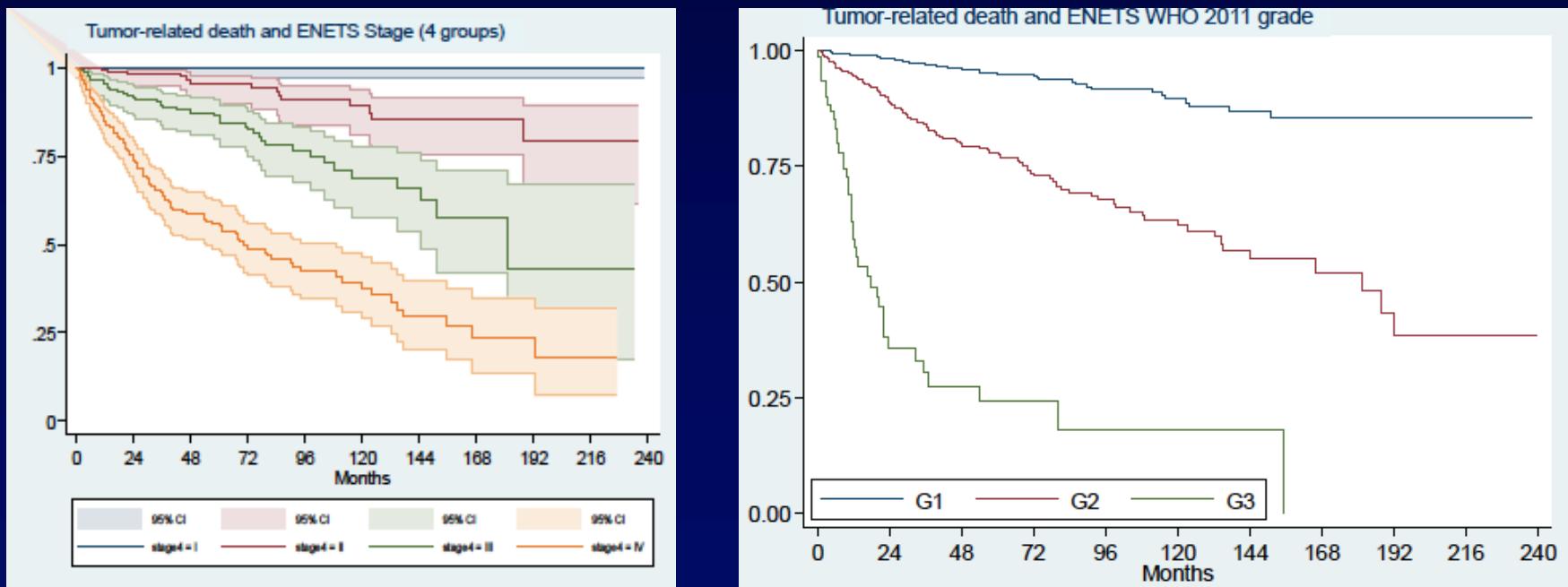


Jann H, et al. *Cancer*. 2011;117(15):3332-3341.

TNM-Staging and Grading of Pancreatic NEN

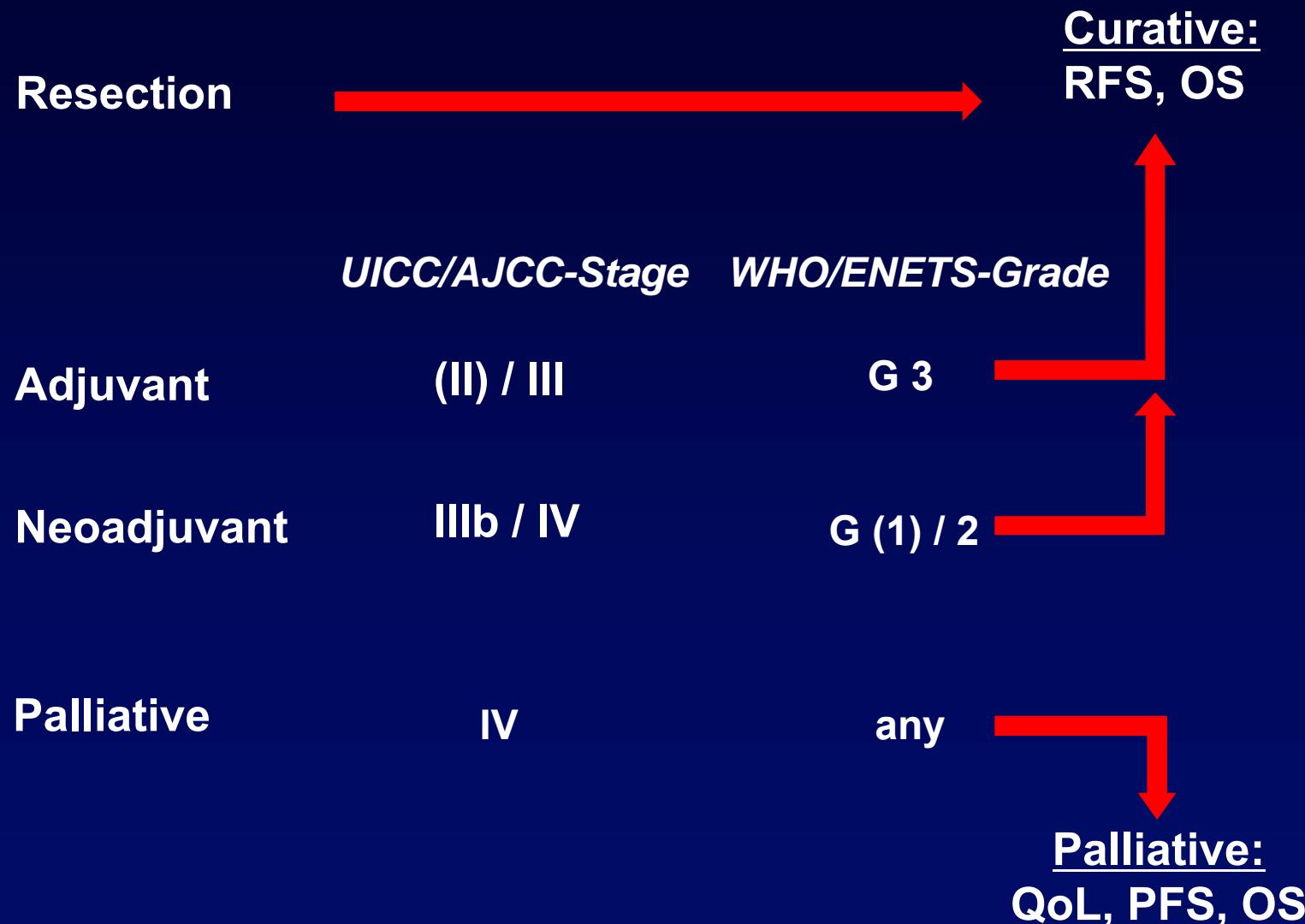
TNM Staging of Neoplasms of the Endocrine Pancreas: Results From a Large International Cohort Study

G. Rindi, M. Falconi, C. Klersy, L. Albarello, L. Boninsegna, M. W. Buchler, C. Capella, M. Caplin, A. Couvelard, C. Doglioni, G. Delle Fave, L. Fischer, G. Fusai, W. W. de Herder, H. Jann, P. Komminoth, R. R. de Krijger, S. La Rosa, T. V. Luong, U. Pape, A. Perren, P. Ruszniewski, A. Scarpa, A. Schmitt, E. Solcia, B. Wiedenmann



Rindi G, et al. *J Natl Cancer Inst.* 2012;104(10):764-777.

Treatment Situations for Systemic Options



Summary and Conclusions

-  **Staging according to UICC/ENETS criteria and grading according to WHO/ENETS criteria clearly differentiates prognostic subgroups of NEN.**
-  **Therapeutic strategies should be decided upon according to these classification systems.**
-  **A composite endpoint of tumor biology, tumor load and treatment predicts stage- and grade-dependent survival.**
-  **However, further improvements to the classification and reconfirmation of tumor grading as the disease progresses are needed.**



***Thank you very
much for your attention!***

