WHO e TNM:

Importanza della classificazione nell'approccio terapeutico

Marco Volante
Mauro Papotti

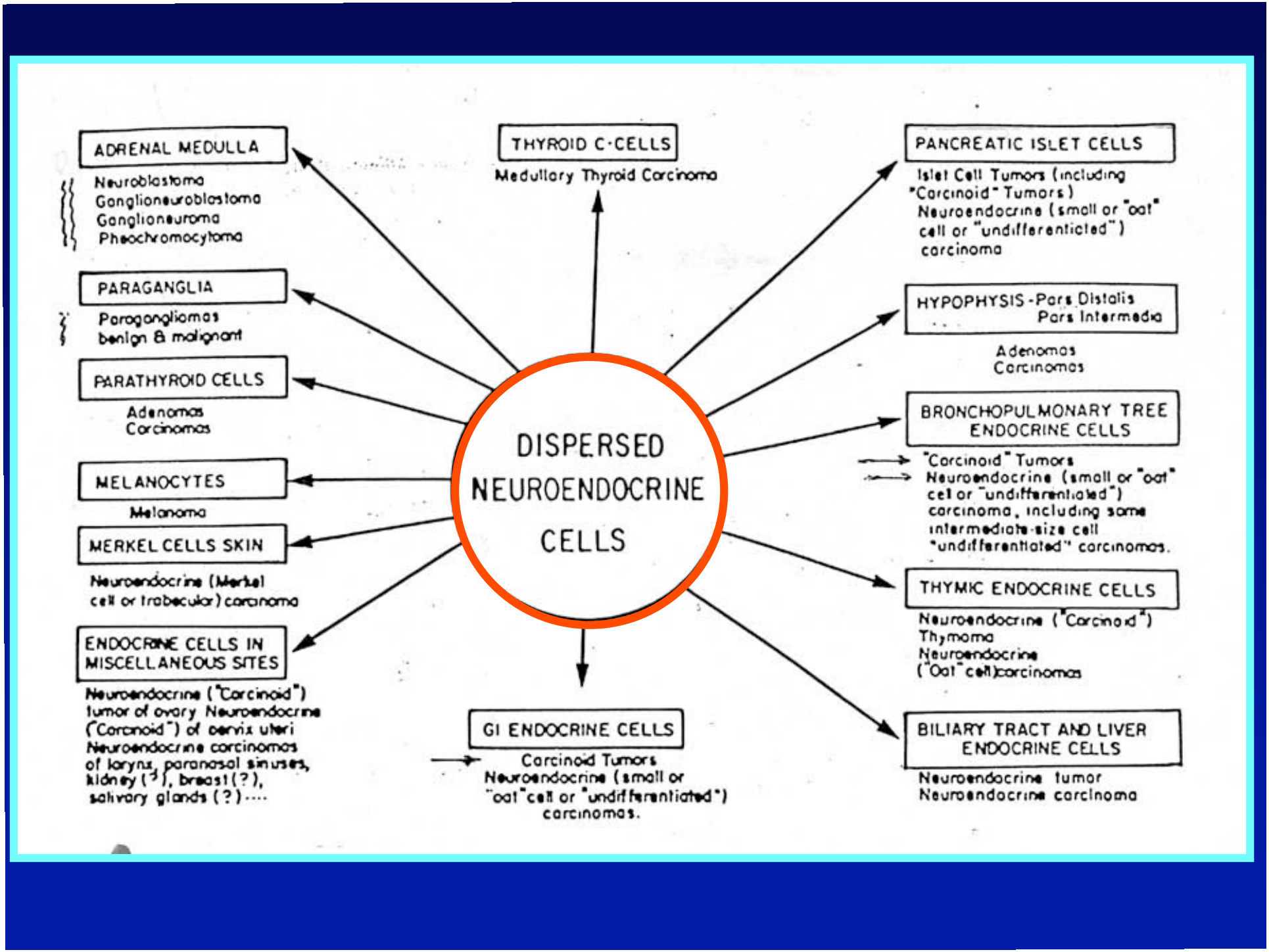
Dipartimento di Scienze Cliniche e Biologiche – Ospedale San Luigi
Orbassano, Torino

PROGRAMMA

1° SESSIONE

LA DIAGNOSI.
I trabocchetti piu' frequenti degli approcci diagnostici

- ✓ Rare tumors
- ✓ Heterogeneous lesions
- ✓ Widespread distribution
- ✓ Incomplete uniformity of terminology/classification
- ✓ Poorly defined pre-invasive lesions
- ✓ Largely unknown molecular pathways


DISPERSED NEUROENDOCRINE CELLS
ADRENAL MEDULLA
Neuroblastoma
Ganglioneuroblastoma
Ganglioneuroma
Pheochromocytoma
PARAGANGLIA
Paragangliomas
benign & malignant
PARATHYROID CELLS
Adenomas
Carcinomas
MELANOCYTES
Melanoma
MERKEL CELLS SKIN
Neuroendocrine (Merkel cell or trabecular) carcinoma
ENDOCRINE CELLS IN MISCELLANEOUS SITES
Neuroendocrine ("Carcinoid") tumor of ovary Neuroendocrine ("Carcinoid") of cervix uteri Neuroendocrine carcinomas of larynx, paranasal sinuses, kidney (?), breast (?), salivary glands (?)....
THYROID C-CELLS
Medullary Thyroid Carcinoma
GI ENDOCRINE CELLS
Carcinoid Tumors
Neuroendocrine (small or "oat" cell or "undifferentiated") carcinomas.
PANCREATIC ISLET CELLS
Islet Cell Tumors (including "Carcinoid" Tumors)
Neuroendocrine (small or "oat" cell or "undifferentiated") carcinoma
HYPOPHYSIS - Pars Distalis Pars Intermedia
Adenomas
Carcinomas
BRONCHOPULMONARY TREE ENDOCRINE CELLS
"Carcinoid" Tumors
Neuroendocrine (small or "oat" cell or "undifferentiated") carcinoma, including some intermediate-size cell "undifferentiated" carcinomas.
THYMIC ENDOCRINE CELLS
Neuroendocrine ("Carcinoid")
Thymoma
Neuroendocrine ("Oat" cell) carcinomas
BILIARY TRACT AND LIVER ENDOCRINE CELLS
Neuroendocrine tumor
Neuroendocrine carcinoma

NET: history

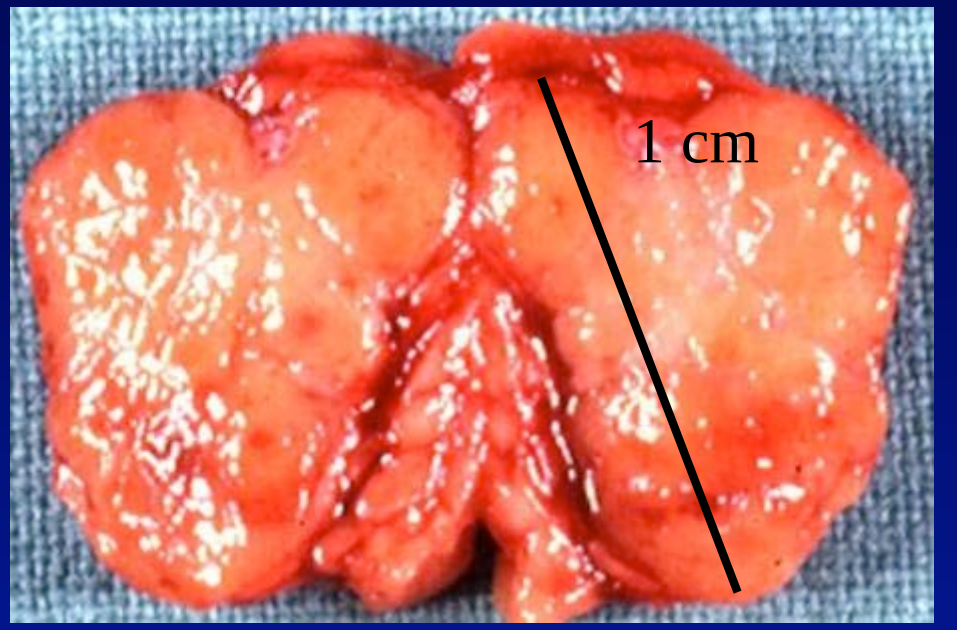
1907	“carcinoid”	*Oberndorfer*
1930	Carcinoid syndrome	*Cassidy*
1940/50	“helle zellen”	*Feyrter*
1952	Serotonin	*Erspamer & Asero*
1963	fore-, mid-, hind-gut carcinoids	*Williams & Sandler*
1965/70	APUD concept	*Pearse*
1980	Diffuse neuroendocrine system	*WHO*
1994	“neuroendocrine tumor”	*Capella et al*
2000	Classification	*WHO*

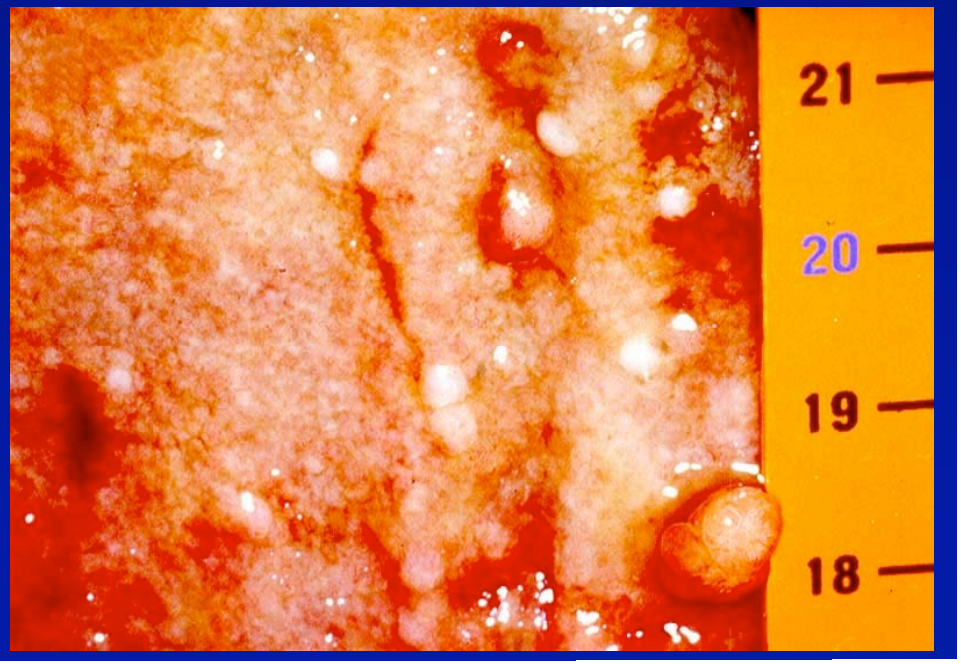
NET: glossary

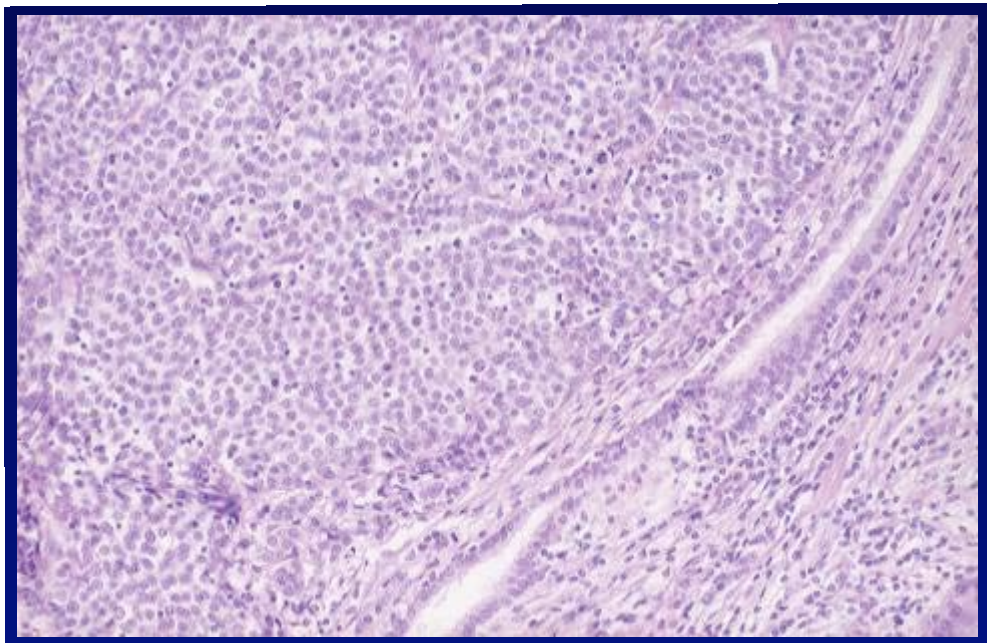
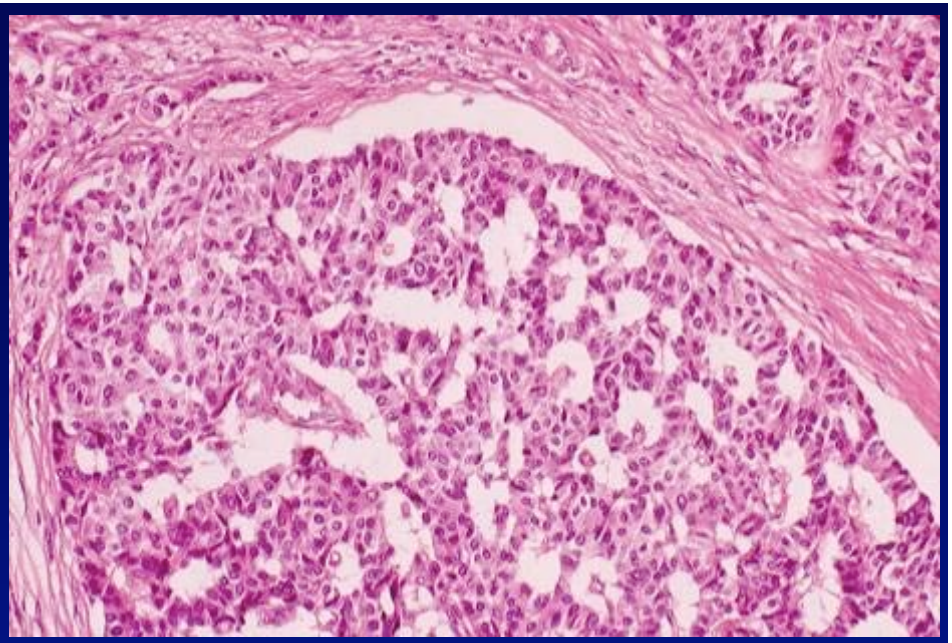
- carcinoid, malignant carinoid
- apudoma
- Islet-cell tumor (A/B/D/PP)-cell
- adenoma / microadenoma vs carcinoma
- Kultchisky cell tumor / carcinoma
- Endocrine carcinoma
- Endocrine neoplasm
- *hormone*…-oma (insulinoma, gastrinoma,..)

HETEROGENEOUS MACROSCOPY

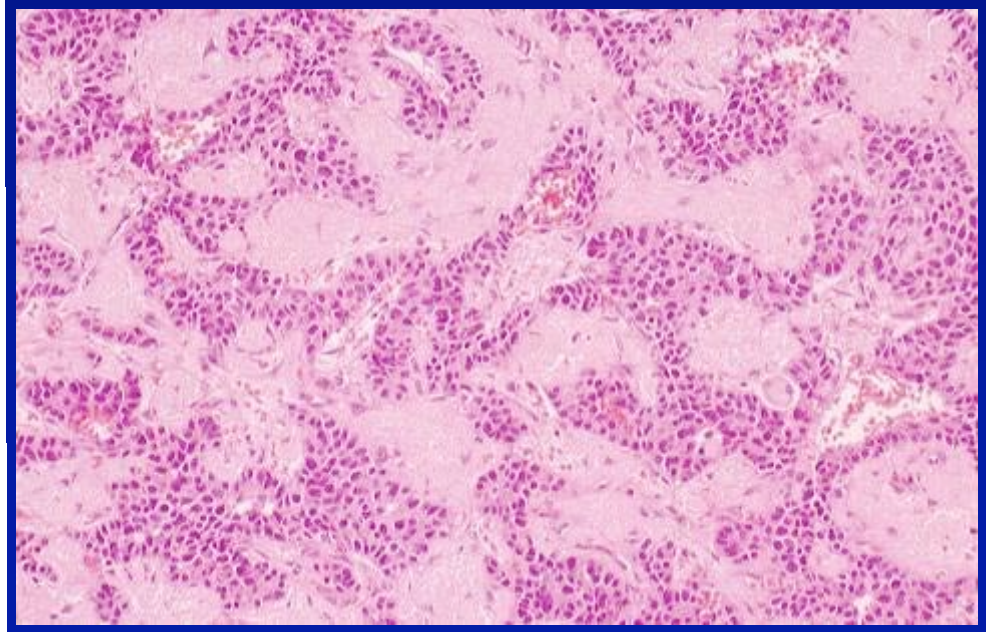
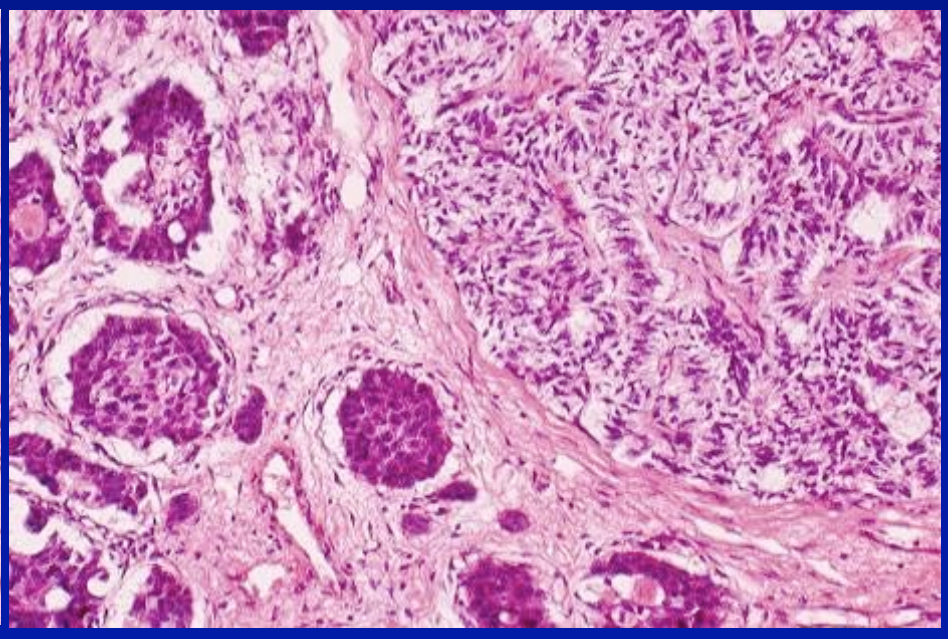
- ✓ Solitary or multiple
- ✓ well demarcated or infiltrative
- ✓ Size 0.5-15 cm.
- ✓ Solid/cystic
- ✓ LN spread
- ✓ Distant metastases





HETEROGENEOUS MICROSCOPY

WHO CLASSIFICATION

or…..

WHO CLASSIFICATIONS

PITUITARY

THYROID,
PARATHYROID

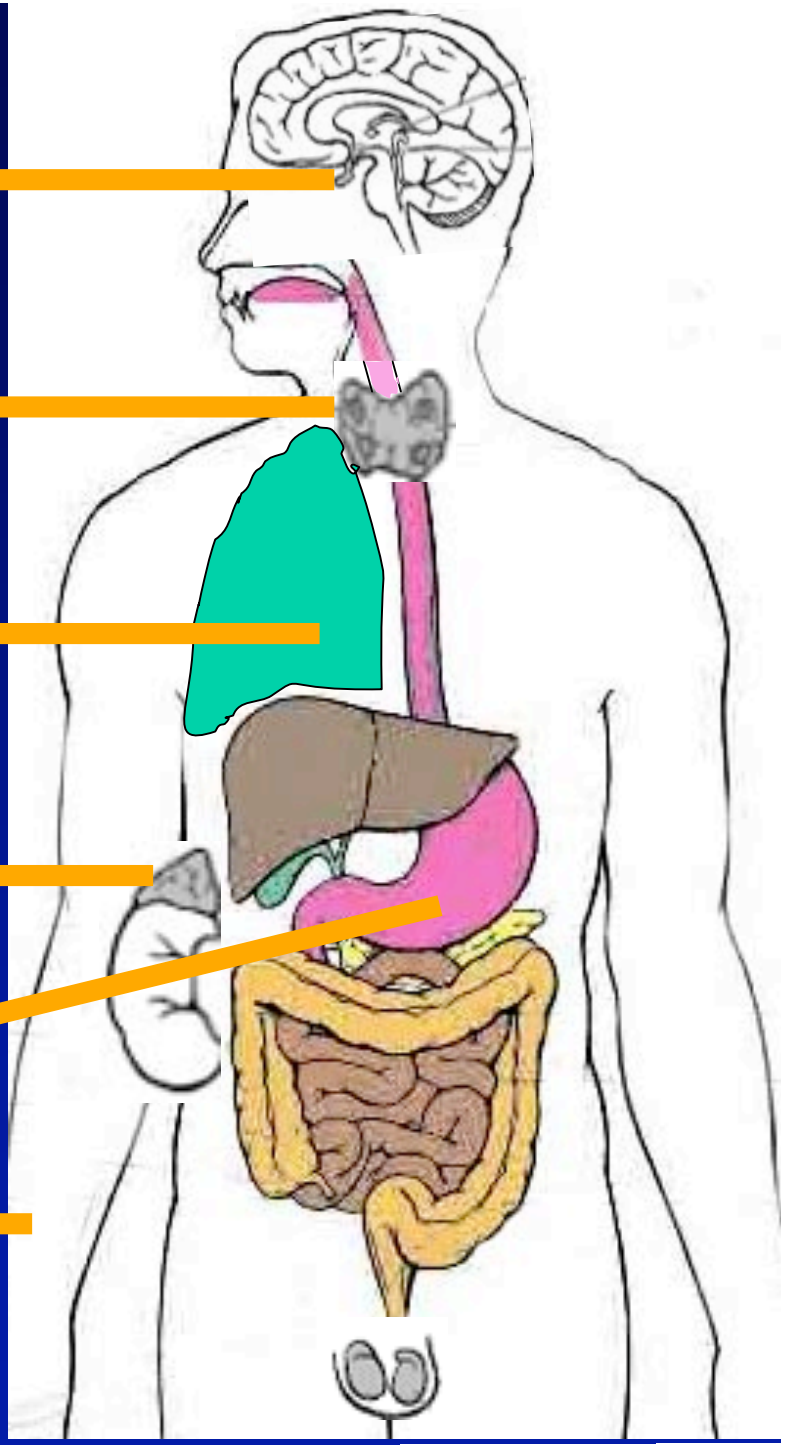
LUNG, THYMUS

ADRENAL
MEDULLA &
PARAGANGLIA

GI tract, PANCREAS

SKIN

Others (almost everywhere)



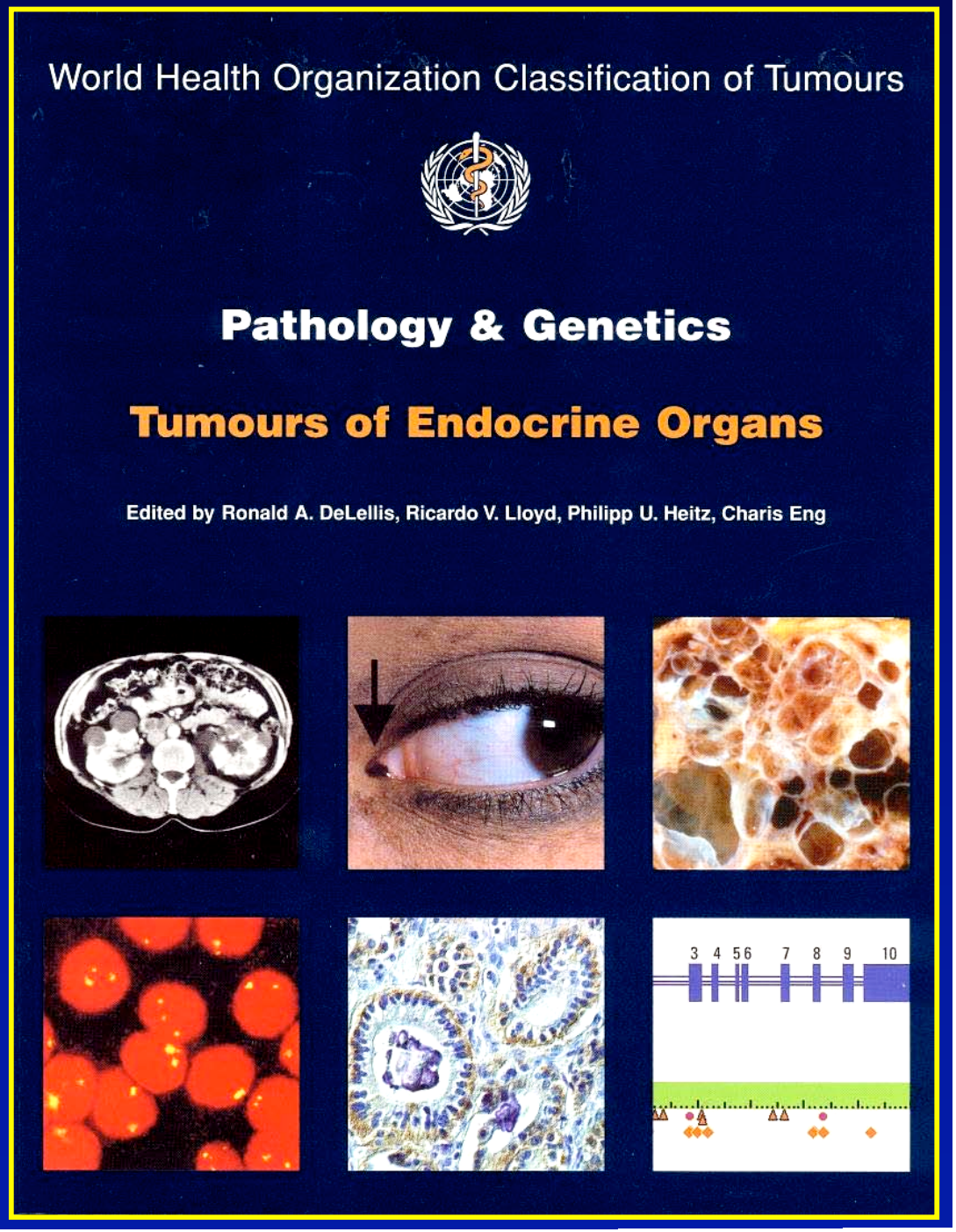
PITUITARY

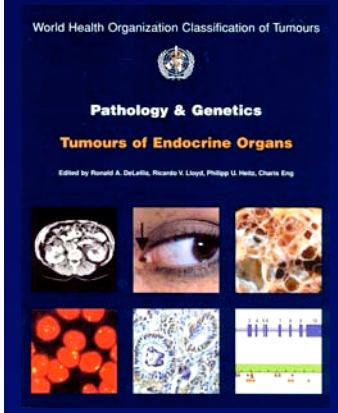
THYROID, PARATHYROID

LUNG, THYMUS

ADRENAL MEDULLA & PARAGANGLIA

GI tract, PANCREAS





VERY EASY CLASSIFICATION….

PITUITARY → **Adenoma/carcinoma**

THYROID → **Medullary carcinoma**

PARATHYROID → **Adenoma/carcinoma**

ADRENAL MEDULLA & PARAGANGLIA → **Pheochromocytoma (benign and malignant)/ paraganglioma**

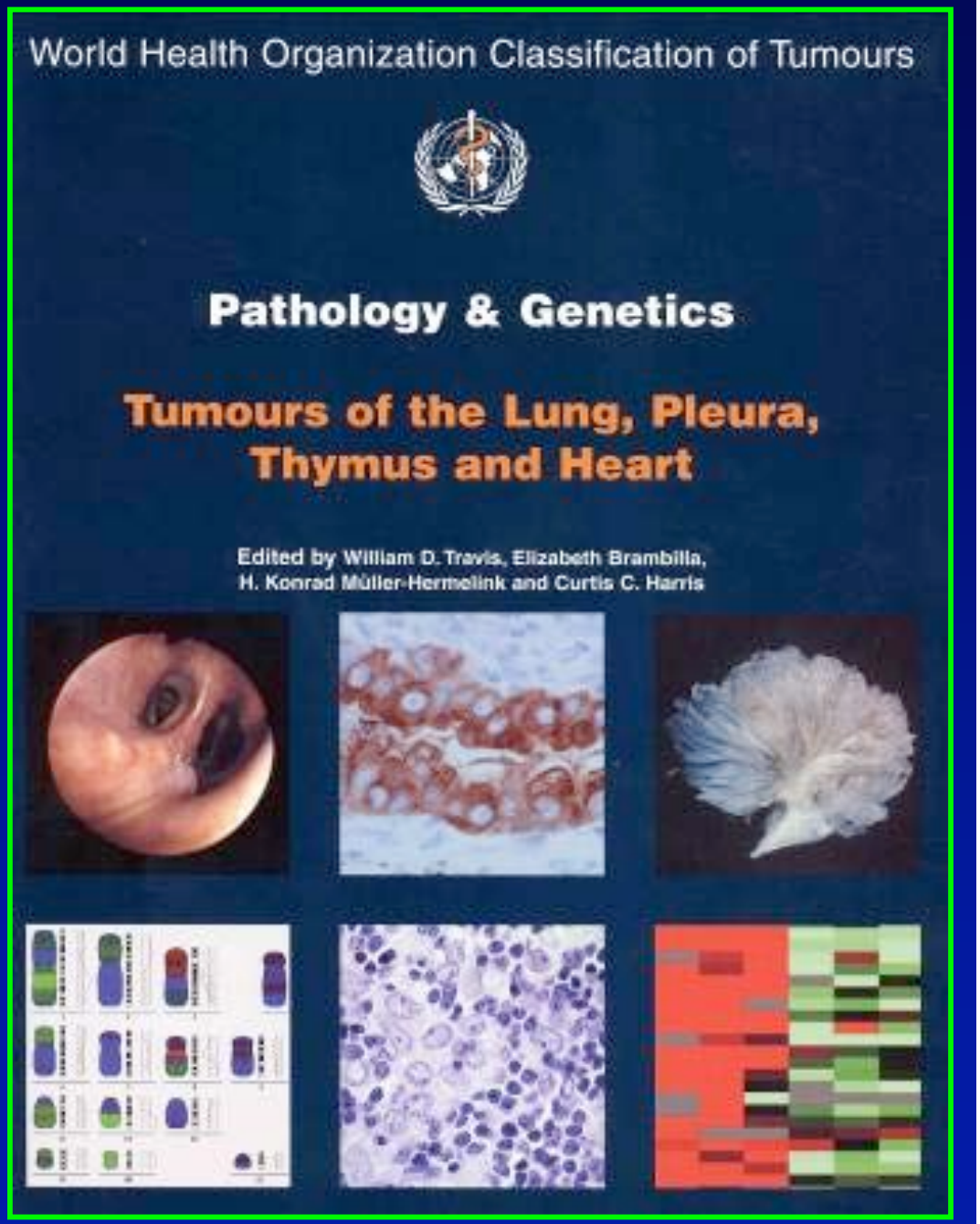
PITUITARY

THYROID, PARATHYROID

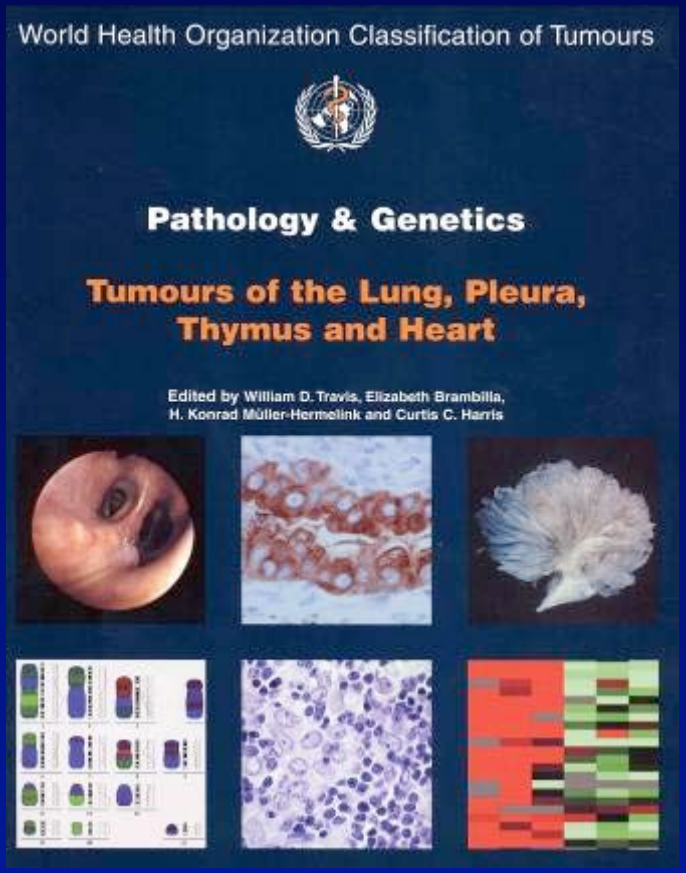
LUNG, THYMUS

ADRENAL MEDULLA & PARAGANGLIA

GI tract, PANCREAS



1999-2004 WHO CLASSIFICATIONS OF LUNG TUMORS



Splits NETs into various groups:

1.3.7 carcinoid tumors

typical

atypical

1.3.2 small cell carcinoma

1.3.4.1 large cell NE carcinoma as a variant of large cell carcinoma (1.3.4)

Combined tumors are accepted as a variant of SCC (1.3.2.1)

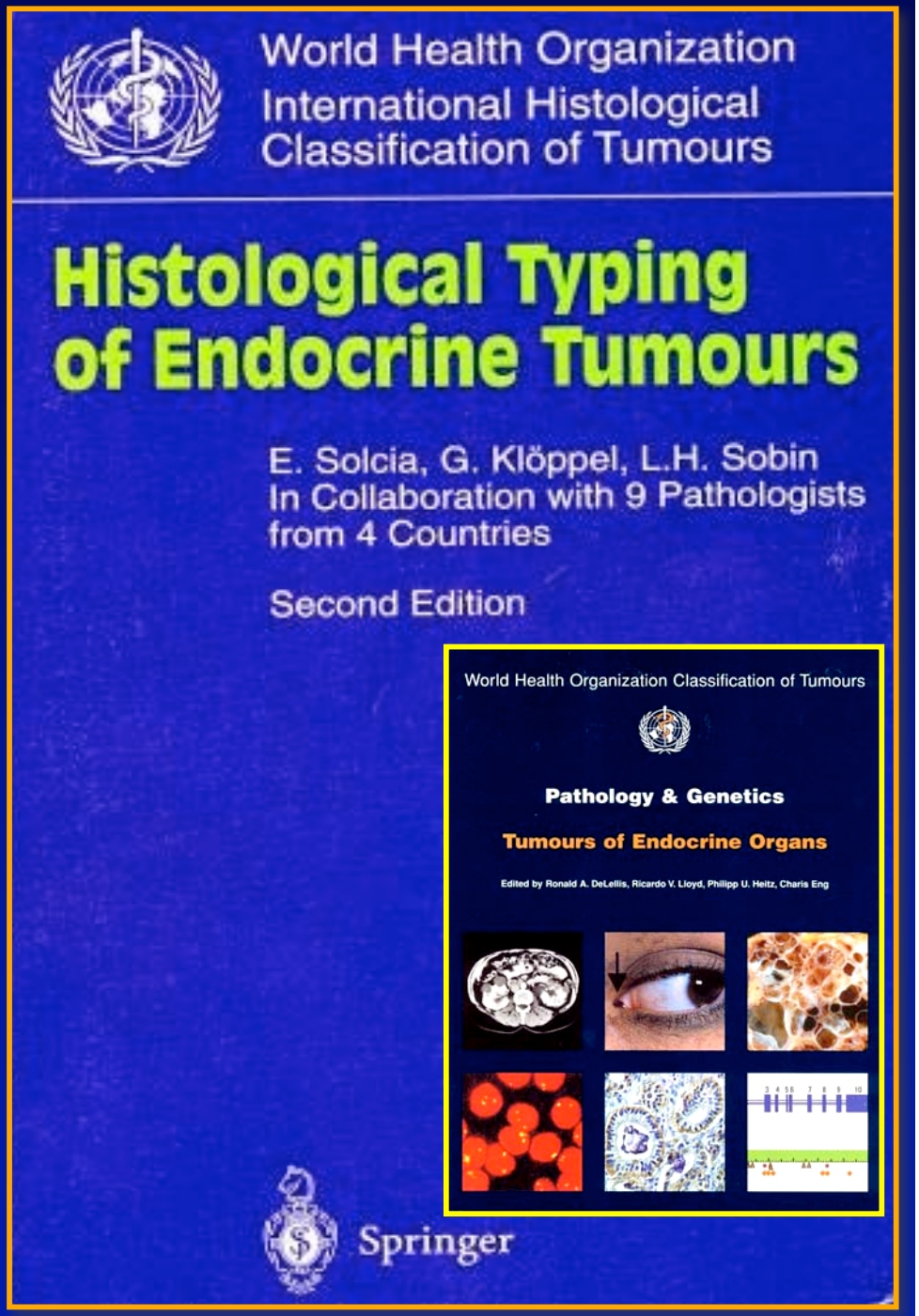
PITUITARY

THYROID, PARATHYROID

LUNG, THYMUS

ADRENAL MEDULLA & PARAGANGLIA

GI tract, PANCREAS



PROGRAMMA

1° SESSIONE

LA DIAGNOSI.
I trabocchetti piu' frequenti degli approcci diagnostici

Moderatori:
Salvo Artale, Nicola Fazio

9.00 - 9.20 **Sindrome da Carcinoide**
Marco Manzoni

9.20 - 9.40 **Marcatori neuroendocrini specifici e generici**
Luca Giovanella

9.40 - 10.00 **Octreoscan, PET, PET/TC e nuovi traccianti**
Stefano Fanti

10.00 - 10.20 **Endoscopia: nella diagnosi e nel trattamento**
Claudio De Angelis

10.20 - 10.40 **Differenziazione neuroendocrina**
Salvo Artale

10.40 - 11.00 ***Discussione***

11.00 - 11.15 *Coffe Break*

11.15 - 12.00 **LETTURA MAGISTRALE**
Introduzione: *Emilio Bajetta*
WHO e TNM: importanza della classificazione nell'approccio terapeutico
Marco Volante

12.00 - 13.00 **CASI CLINICI**
con discussione interattiva
Coordinatore:
Renato Cozzi
Renato Cozzi, Gianni Bolza

13.00 - 14.00 *Pranzo*

2° SESSIONE

LA TERAPIA.
Approccio multidisciplinare di una patologia complessa

Moderatori:
Gianluca Aimaretti, Massimo Falconi

14.00 - 14.30 **Caso clinico**
Laura Catena

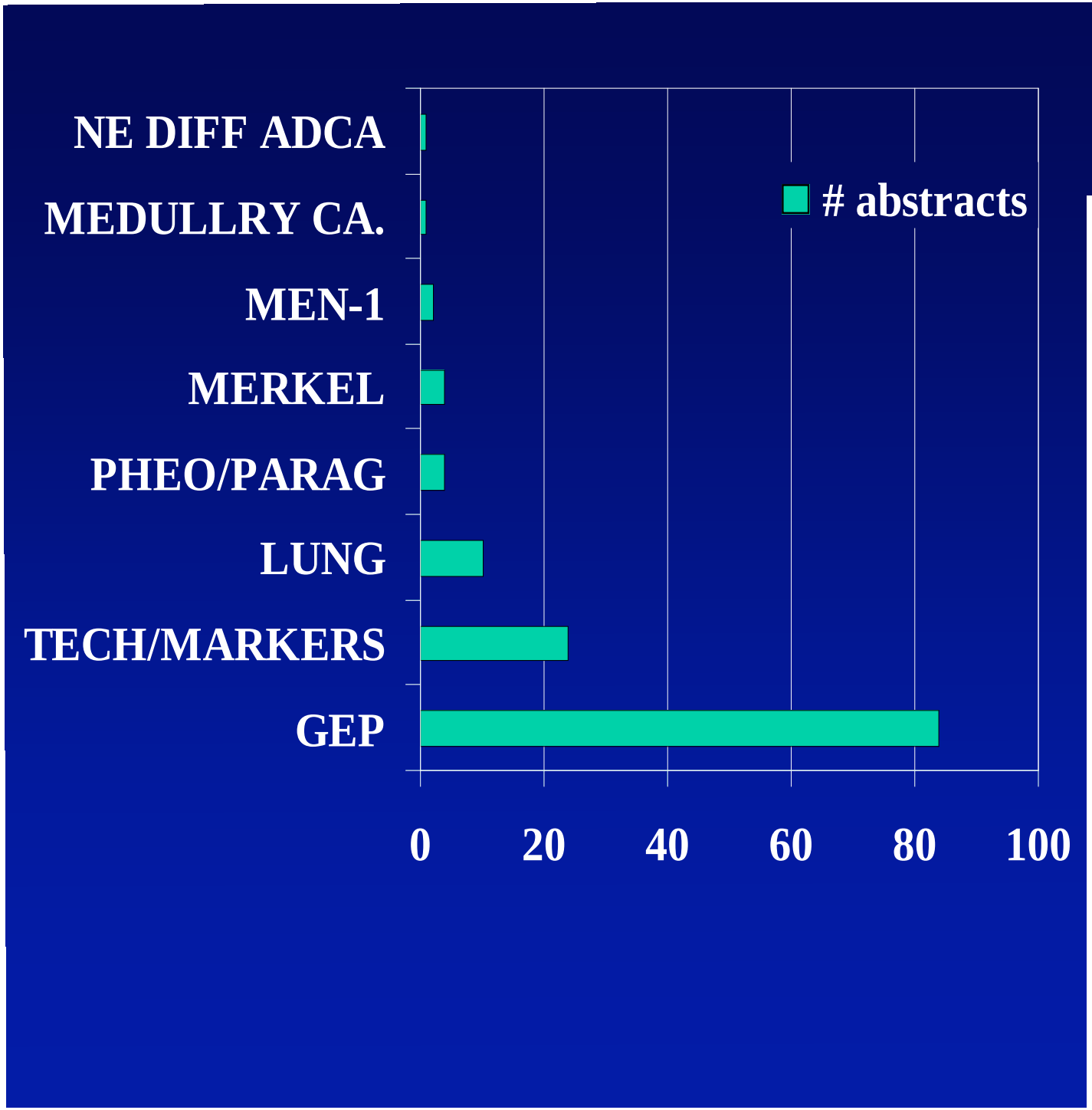
14.30 - 14.50 **Ruolo del debulking chirurgico**
Massimo Falconi

14.50 - 15.10 **Terapia radiometabolica: gli analoghi radiomarcati**
Ettore Seregni

15.10 - 15.30 **Bioterapia nel trattamento dei GEP**
Silvia Della Torre

15.30 - 15.50 **I nuovi farmaci: associazione o superamento del trattamento con analoghi**
Nicola Fazio

15.50 - 16.20 ***Conclusione lavori***



European ENETS Neuroendocrine Tumor Society

5th Annual ENETS Conference

for the

Diagnosis and Treatment of Neuroendocrine Tumor Disease

6 - 8 March 2008
Paris • France

1994

Digestion 1994;55(suppl 3):11–23

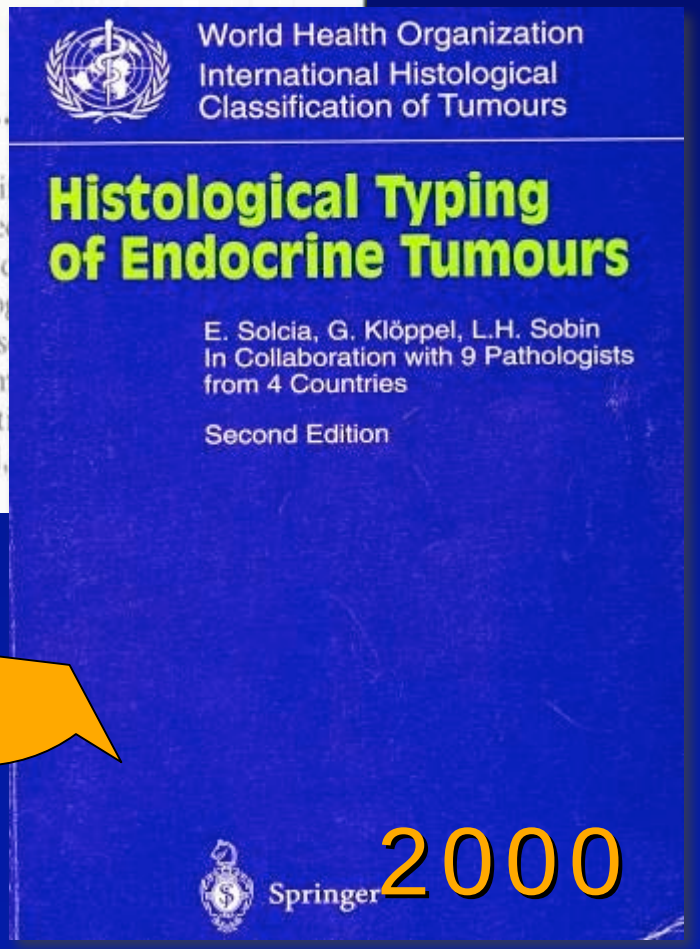
Revised Classification of Neuroendocrine Tumors of the Lung, Pancreas and Gut

Carlo Capella[a]
Philipp U. Heitz[b]
Heinz Höfler[c]
Enrico Solcia[d]
Günter Klöppel[e]

Departments of Pathology, Universities of Pavia at Varese, Italy, Zurich, Switzerland, Munich, Germany, Pavia, Italy, and Brussels, Belgium

Key Words
Neuroendocrine tumors
Lung
Pancreas
Gut
Classification

Abstract
The general use of the term carcinoid for the classi
tumors has become increasingly difficult during re
tion and prognosis varies from site to site. Second
does not cover the whole morphological and biolo
docrine tumors known today. We therefore propos
neuroendocrine tumors of the lung, pancreas, ston
ileum, appendix and colorectum. These classificat
work and attempt to con r the morphological,
features of these tumors.



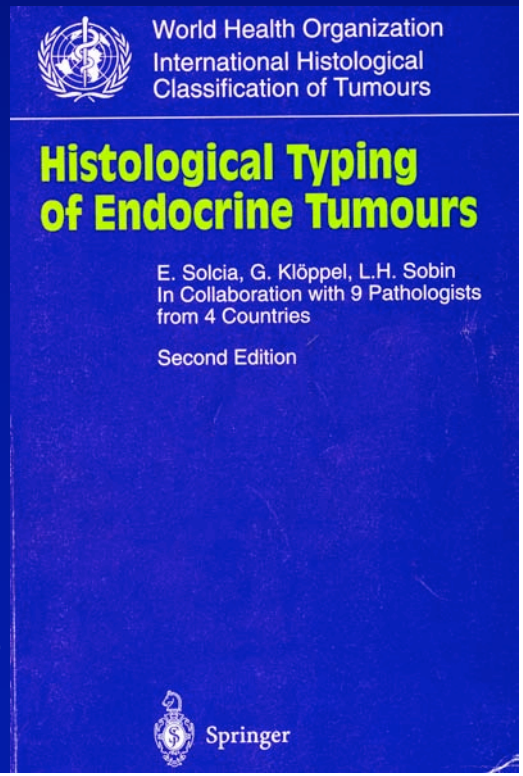
WHO 2000 classification

Combined clinico-pathological parameters…

location, diameter, angioinvasion, presence of metastases

… and funtional data (clinico-pathological correlates)

type of hormonal secretion and clinical syndrome eventually present



WHO 2000 classification

1) well differentiated endocrine tumor:

   a) benign

   b) uncertain behaviour

2) well differentiated endocrine carcinoma

   (low grade malignant)

3) poorly differentiated endocrine carcinoma

   (high grade malignant)

Table 11. Clinicopathological correlations of endocrine tumours of the stomach

1	Well-differentiated tumour - carcinoid
1.1	Benign behaviour: confined to mucosa-submucosa, nonangioinvasive, ≤ 1 cm in size[a], nonfunctioning
1.1.1	ECL cell tumour of corpus-fundus associated with hypergastrinaemia and chronic atrophic gastritis (CAG) or MEN1 syndrome
1.1.2	Serotonin-producing tumour
1.1.3	Gastrin-producing tumour
1.2	Uncertain behaviour: confined to mucosa-submucosa, >1 cm in size, or angioinvasive
1.2.1	ECL cell tumour with CAG or MEN1 syndrome or sporadic
1.2.2	Serotonin-producing tumour
1.2.3	Gastrin producing tumour
2	Well-differentiated endocrine carcinoma - malignant carcinoid
2.1	Low grade malignant, deeply invasive (muscularis propria or beyond), or with metastasis
2.2	Nonfunctioning
2.2.1	ECL cell carcinoid, usually sporadic, rarely in CAG or MEN1 syndrome
2.2.2	Serotonin-producing carcinoid
2.2.3	Gastrin producing carcinoma
2.3	Functioning
2.3.1	ECL cell carcinoid with atypical carcinoid syndrome
2.3.2	Serotonin-producing carcinoid with carcinoid syndrome
2.3.3	Gastrin-producing carcinoma - malignant gastrinoma
2.3.4	ACTH-producing carcinoma with Cushing syndrome
3	Poorly differentiated endocrine carcinoma - small cell carcinoma, high grade malignant, usually nonfunctioning, occasionally with Cushing syndrome

[a] <1 cm approaches to 100% probability of benign behaviour; <2 cm corresponds to 80% probability

stomach

World Health Organ
International Histolo
Classification of Tu

Histological Typi
of Endocrine Tu

E. Solcia, G. Klöppel, L
In Collaboration with 9
from 4 Countries

Second Edition

Table 12. Clinicopathological correlations of endocrine tumours of the duodenum and upper jejunum

1	Well-differentiated endocrine tumour - carcinoid
1.1	Benign behaviour: nonfunctioning, confined to mucosa-submucosa, ≤1 cm in size, nonangioinvasive
1.1.1	Gastrin-producing tumour (proximal duodenum)
1.1.2	Serotonin-producing tumour
1.1.3	Gangliocytic paraganglioma, any size and extension (ampullary region)
1.2	Uncertain behaviour: confined to mucosa-submucosa, >1 cm in size or angioinvasive
1.2.1	Gastrin-producing tumour, functioning (gastrinoma) or nonfunctioning, sporadic, or MEN-1-associated
1.2.2	Somatostatin-producing tumour (ampullary region) with or without Recklinghausen disease
1.2.3	Serotonin-producing tumour, nonfunctioning
2	Well-differentiated endocrine carcinoma - malignant carcinoid
2.1	Low grade malignant, extending beyond submucosa or with metastasis
2.2	Gastrin-producing carcinoma, functioning (gastrinoma) or nonfunctioning, sporadic, or MEN-1-associated
2.3	Somatostatin-producing carcinoma (ampullary region) with or without Recklinghausen disease
2.4	Serotonin-producing carcinoid, nonfunctioning or functioning (any size or extension) with carcinoid syndrome
2.5	Malignant gangliocytic paraganglioma
3.	Poorly differentiated endocrine carcinoma - small cell carcinoma

duodenum

Table 13. Clinicopathological correlations of endocrine tumours of the ileum, caecum, colon, and rectum

1	Well-differentiated endocrine tumour - carcinoid
1.1	Benign behaviour: nonfunctioning, confined to mucosa-submucosa, nonangioinvasive, ≤1 (small int.) or ≤2 cm (large int.) in size
1.1.1	Serotonin-producing tumour
1.1.2	Enteroglucagon-producing tumour
1.2	Uncertain behaviour: nonfunctioning, confined to mucosa-submucosa, >1 cm (small int.) or >2 cm (large int.) in size, or angioinvasive
1.2.1	Serotonin-producing tumour
1.2.1	Enteroglucagon-producing tumour
2	Well-differentiated endocrine carcinoma - malignant carcinoid, low grade malignant, deeply invasive (muscularis propria or beyond), or with metastases
2.1	Serotonin-producing carcinoid with or without carcinoid syndrome
2.2	Enteroglucagon-producing carcinoma
3	Poorly differentiated endocrine carcinoma - small cell carcinoma, high grade malignant
4	Mixed exocrine-endocrine carcinoma - moderate to high grade malignant

ileum/rectum

Table 14. Clinicopathological correlations of endocrine tumours of the appendix

1	Well-differentiated endocrine tumour - carcinoid, benign behaviour, nonfunctioning, confined to appendiceal wall, nonangioinvasive, ≤2 cm in size
1.1.1	Serotonin-producing tumour
1.1.2	Enteroglucagon-producing tumour of uncertain behaviour, nonfunctioning, confined to submucosa, >2 cm in size, or angioinvasive tumour
2	Well-differentiated endocrine carcinoma - malignant carcinoid
2.1	Low grade malignant, invading the mesoappendix or beyond, and/or with metastasis
2.2	Serotonin-producing carcinoid with or without carcinoid syndrome
3	Mixed exocrine-endocrine carcinoma
3.1	Low grade malignant - goblet-cell carcinoid

appendix

2000/2004 WHO CLASSIFICATION OF PANCREATIC NETs

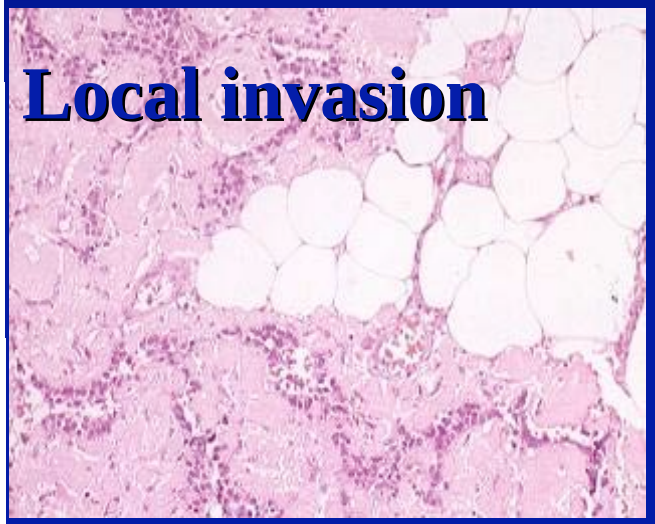
WELL DIFFERENTIATED ENDOCRINE TUMOR

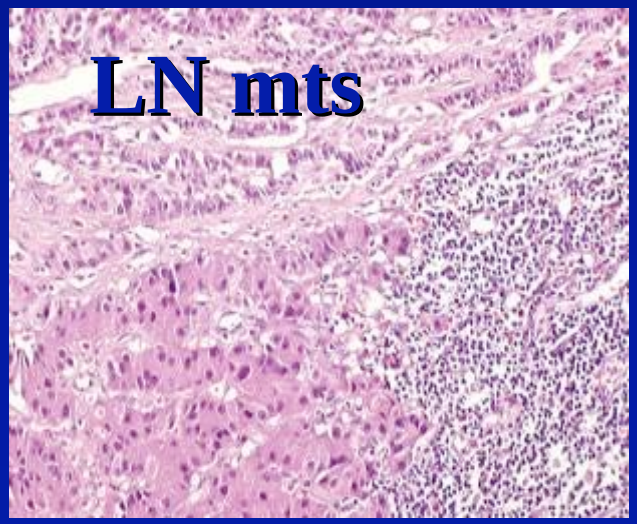
	BEHAVIOUR	
	Benign	Uncertain
Extrapancreatic extension	no	no
Angioinvasion	no	yes
Diameter >=2 cm	no	yes
Mitoses >2 /10HPF	no	yes
Ki67 >2%	no	yes

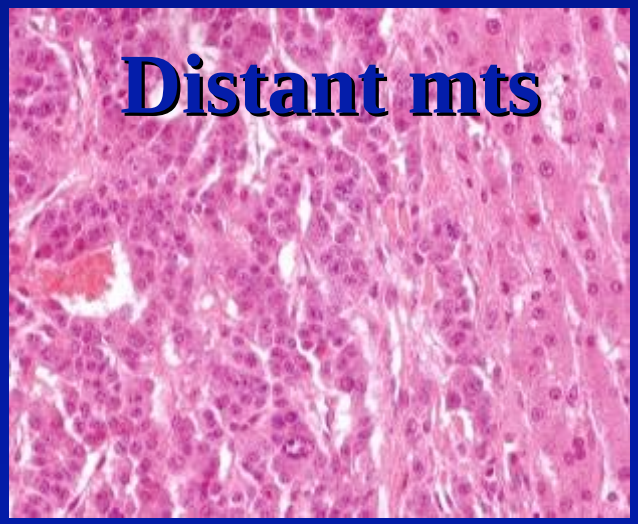
2000/2004 WHO CLASSIFICATION OF PANCREATIC NETs

WELL DIFFERENTIATED ENDOCRINE CARCINOMA

Clear-cut signs of malignancy



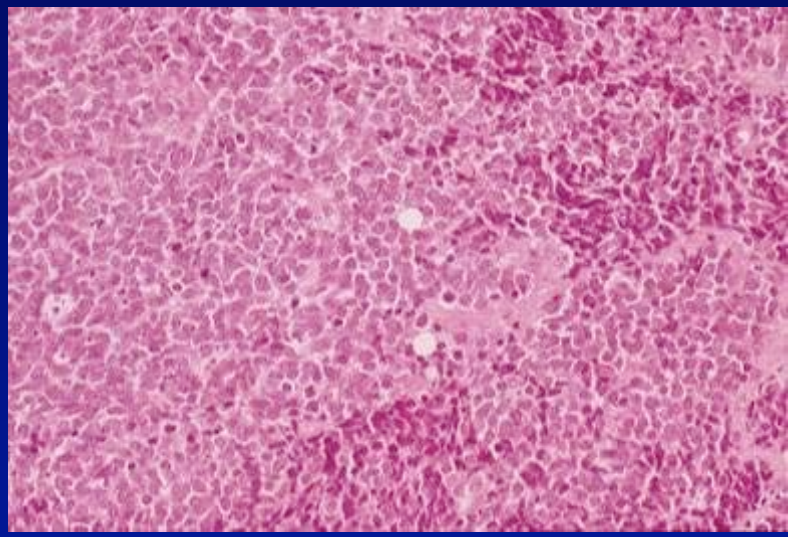


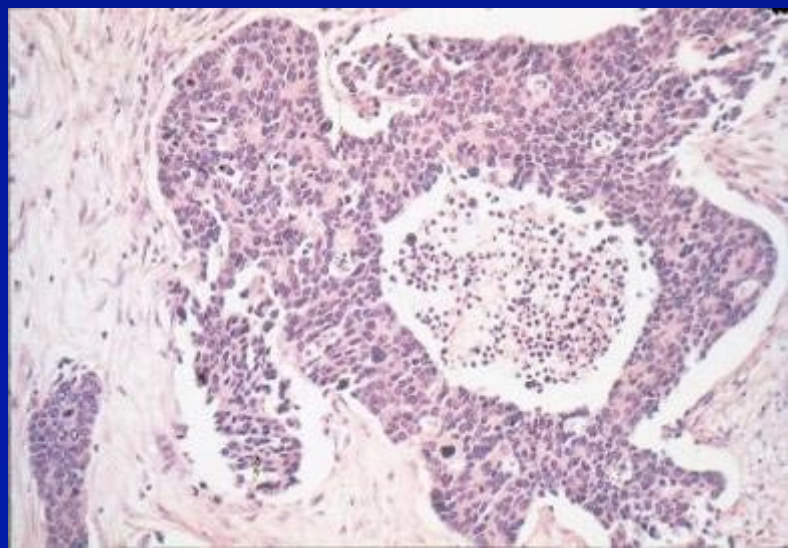


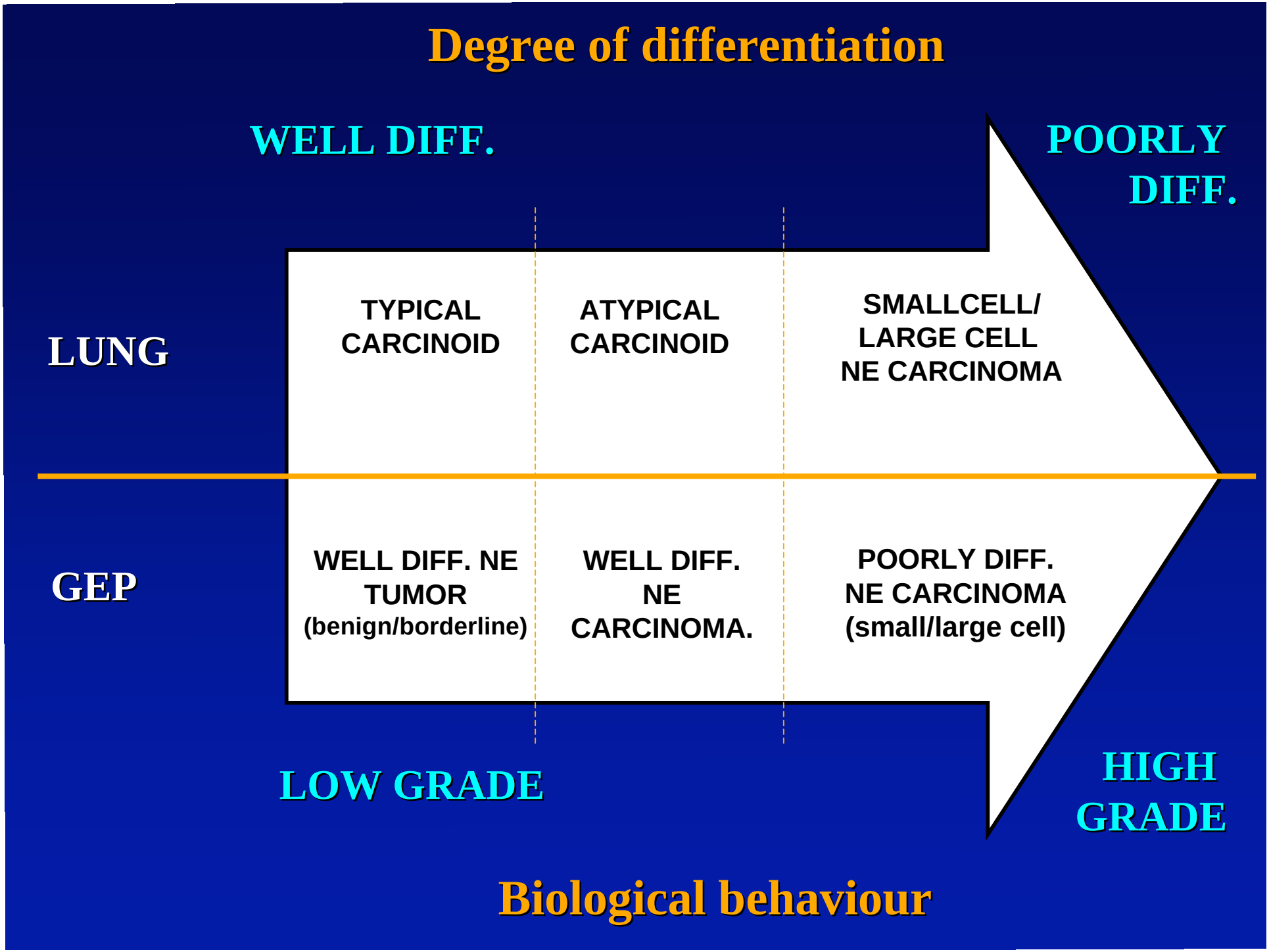
2000/2004 WHO CLASSIFICATION OF PANCREATIC NETs

POORLY DIFFERENTIATED ENDOCRINE CARCINOMA

- ✓ Solid growth
- ✓ High grade nuclear features
- ✓ Necrosis
- ✓ High mitotic activity
- ✓ High Ki67






Degree of differentiation
WELL DIFF.
POORLY DIFF.
LUNG
TYPICAL CARCINOID
ATYPICAL CARCINOID
SMALLCELL/ LARGE CELL NE CARCINOMA
GEP
WELL DIFF. NE TUMOR (benign/borderline)
WELL DIFF. NE CARCINOMA.
POORLY DIFF. NE CARCINOMA (small/large cell)
LOW GRADE
HIGH GRADE
Biological behaviour

WHO CLASSIFICATION(S)

OR

SOMETIMES EQUIVOCAL DIAGNOSTIC CRITERIA

…..Cell size…

….Mitotic index….

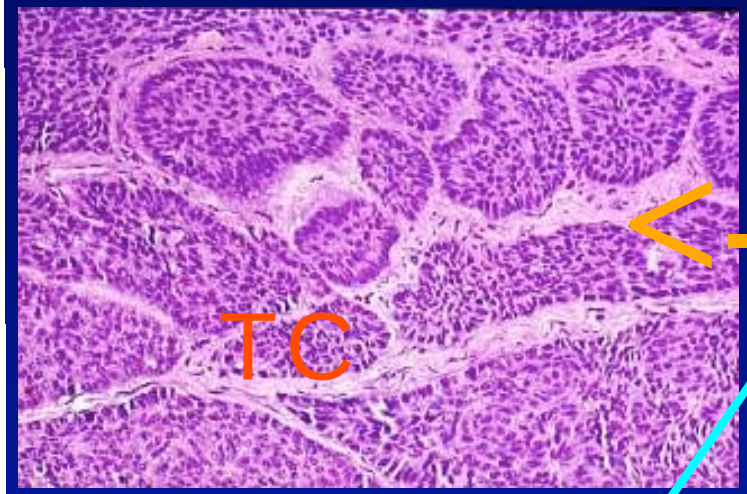
…..Presence (or even extent) of necrosis….

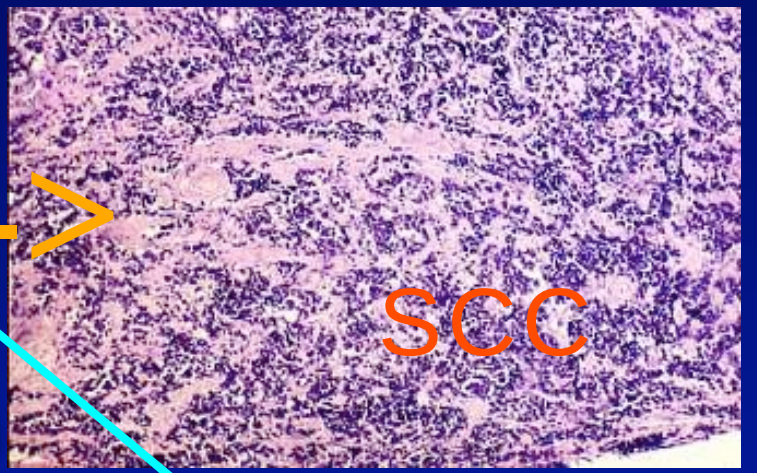
SPECTRUM of NE TUMORS of THE LUNG

TC	AC	LCNEC	SCLC
<2 mitoses no necrosis	2-9 mitoses or necrosis	≥10 mitoses (necrosis)	small cells (necrosis)

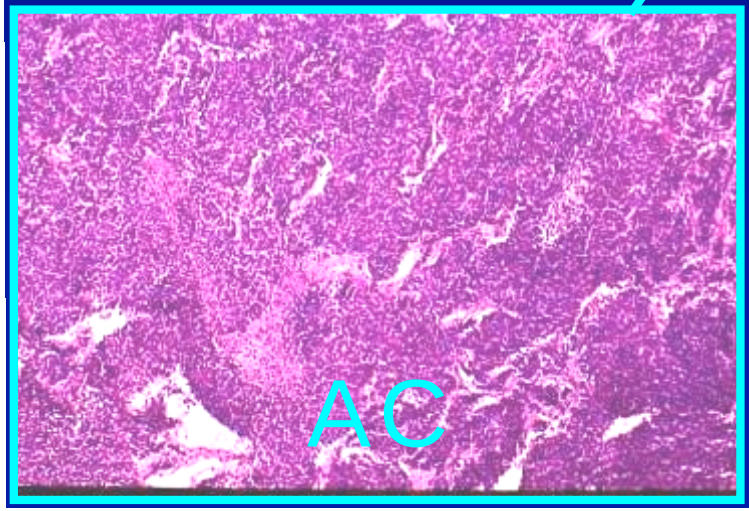
DIAGNOSIS OF LUNG NET

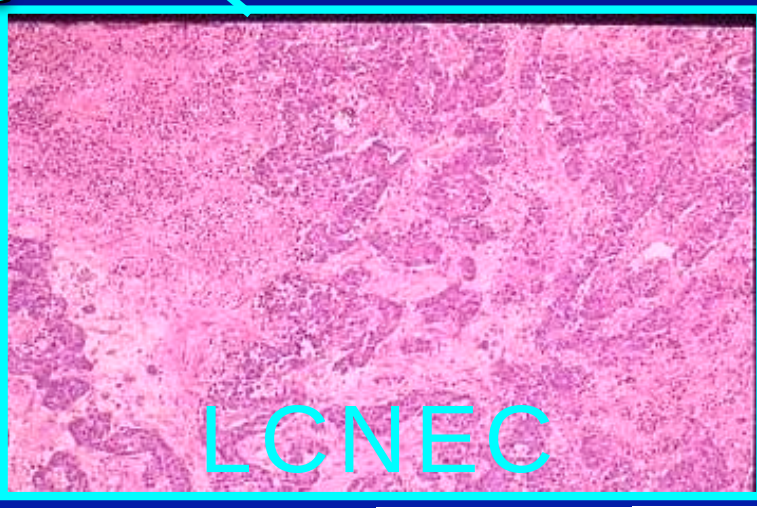
No major diagnostic problems for the two entities at the extremes of the spectrum





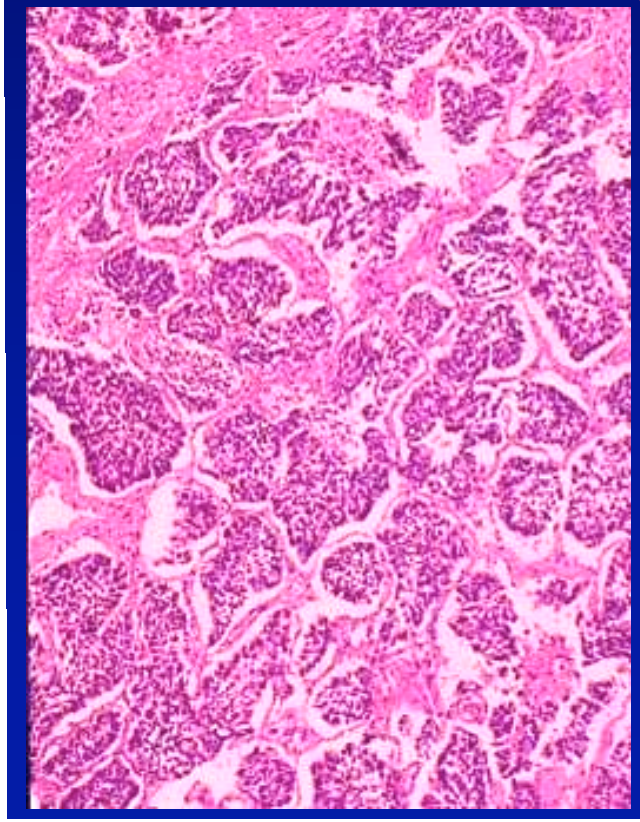
Difficulties in identifying the intermediate entities

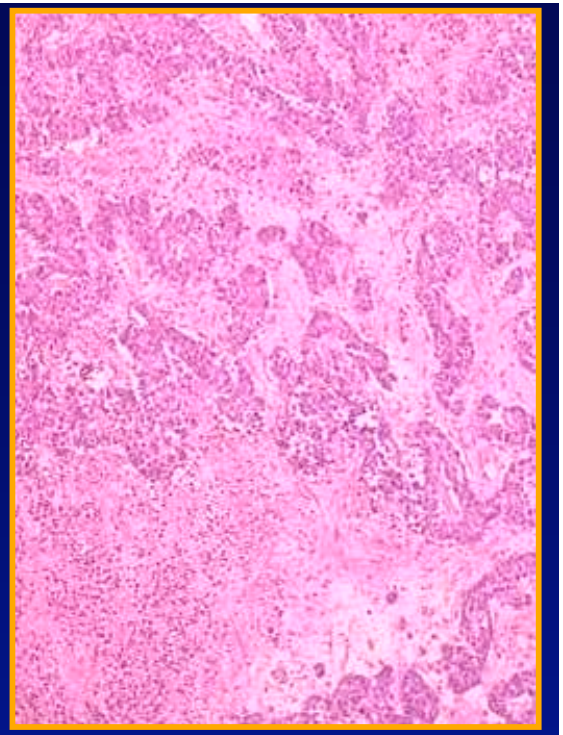




ATYPICAL CARCINOID - AC

A NE tumor having an organoid pattern of growth, necrosis *or* 2-9 mitoses/10 HPF





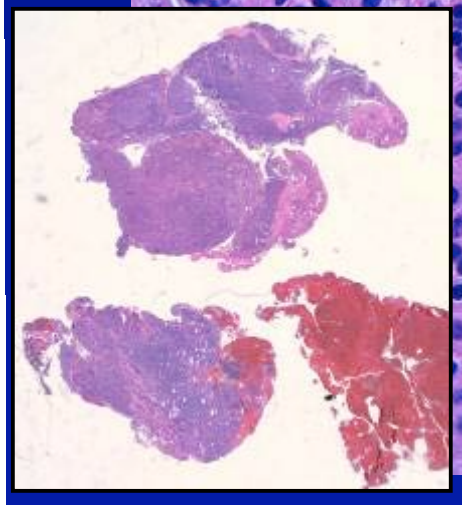
LARGE CELL NEUROENDOCRINE CARCINOMA – LCNEC

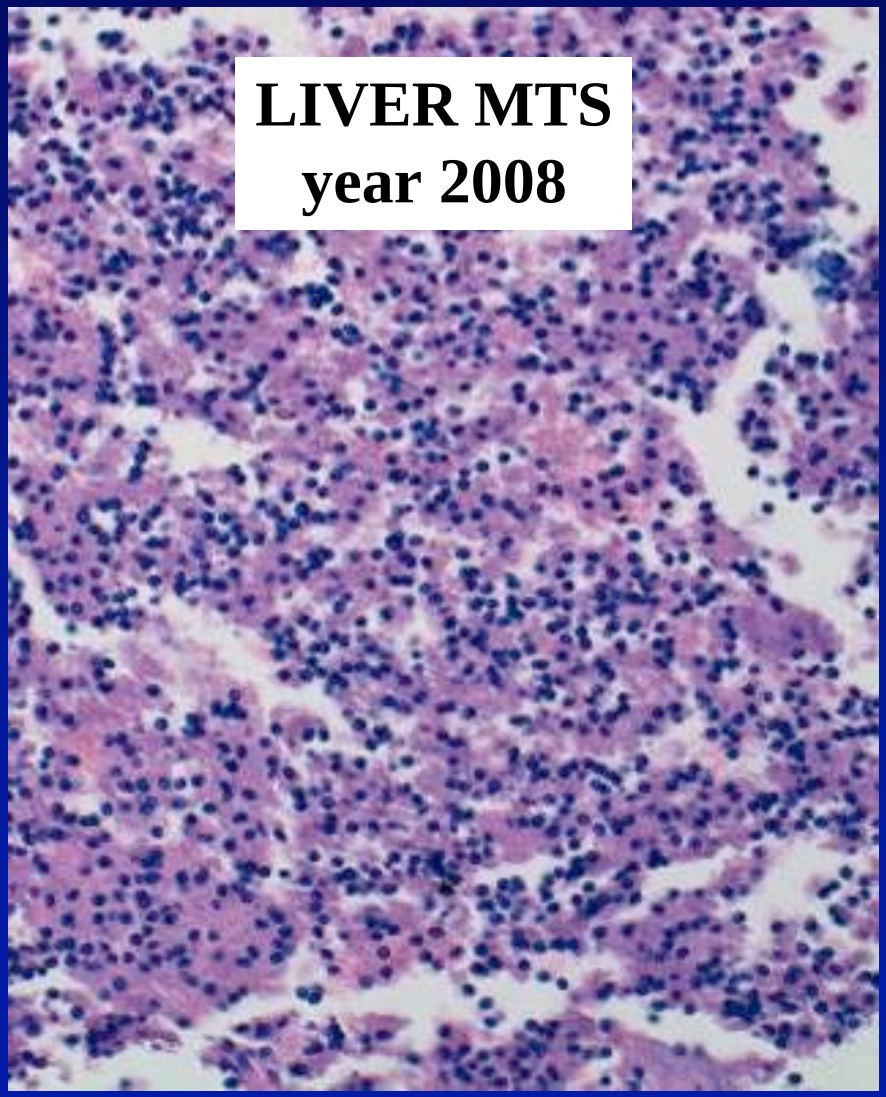
A NE tumor having an organoid pattern of growth, large atypical cells, >10 mitoses/10 HPF, generally extensive necrosis.

WHO CLASSIFICATION(S) *OR* SOMETIMES EQUIVOCAL DIAGNOSTIC CRITERIA:

biopsy material

BRONCHIAL LESION
year 2005





LIVER MTS
year 2008

WHO CLASSIFICATION(S)

OR

THE NEED OF AN APPROPRIATE APPROACH TO IMMUNOHISTOCHEMICAL MARKERS

Immunohistochemical NE markers

pan-endocrine markers

- cytosolic (NSE, PGP 9.5)
- related to secretory granules (chromogranins)
- related to synaptic vescicles (synaptophisin, VMAT)
- intermediate filaments (NF, CK HMW)
- adhesion molecules (N-CAM)

hormone markers

proliferation markers

Immunohistochemical NE markers

pan-endocrine markers

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- **related to secretory granules (chromogranins)**
- **related to synaptic vescicles (synaptophisin, VMAT)**
- **intermediate filaments (NF, CK HMW)**
- **adhesion molecules (N-CAM)**

→ hormone markers

proliferation markers

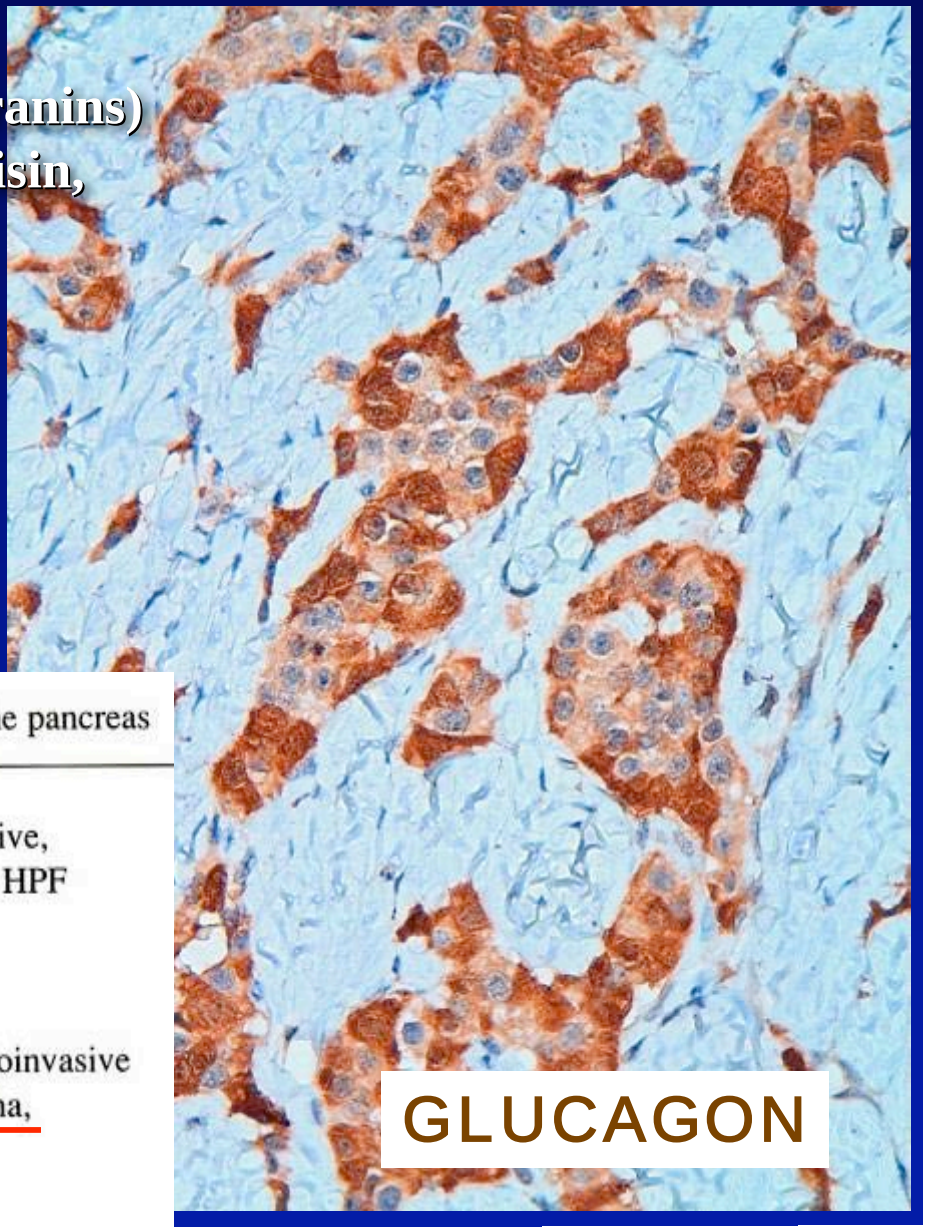
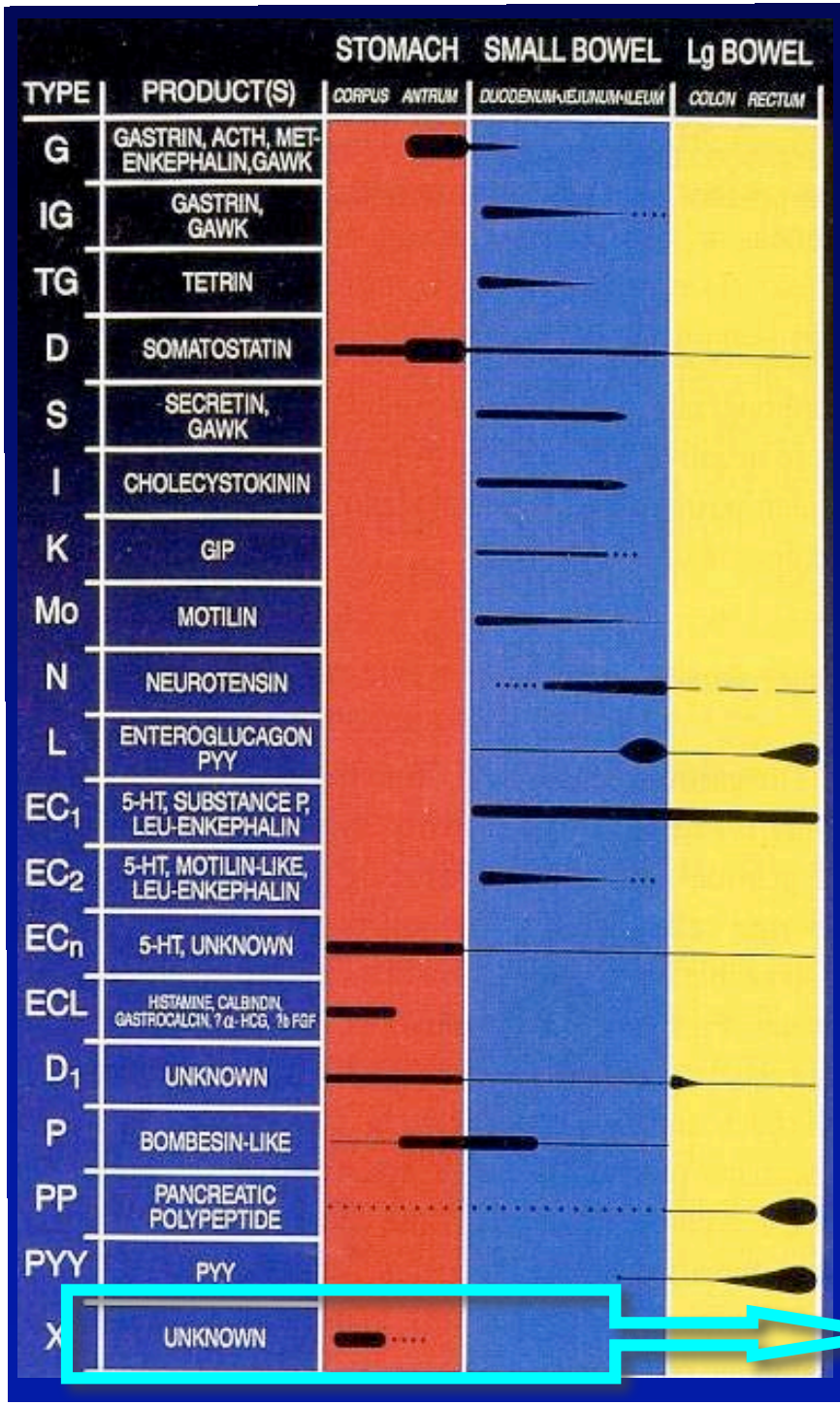
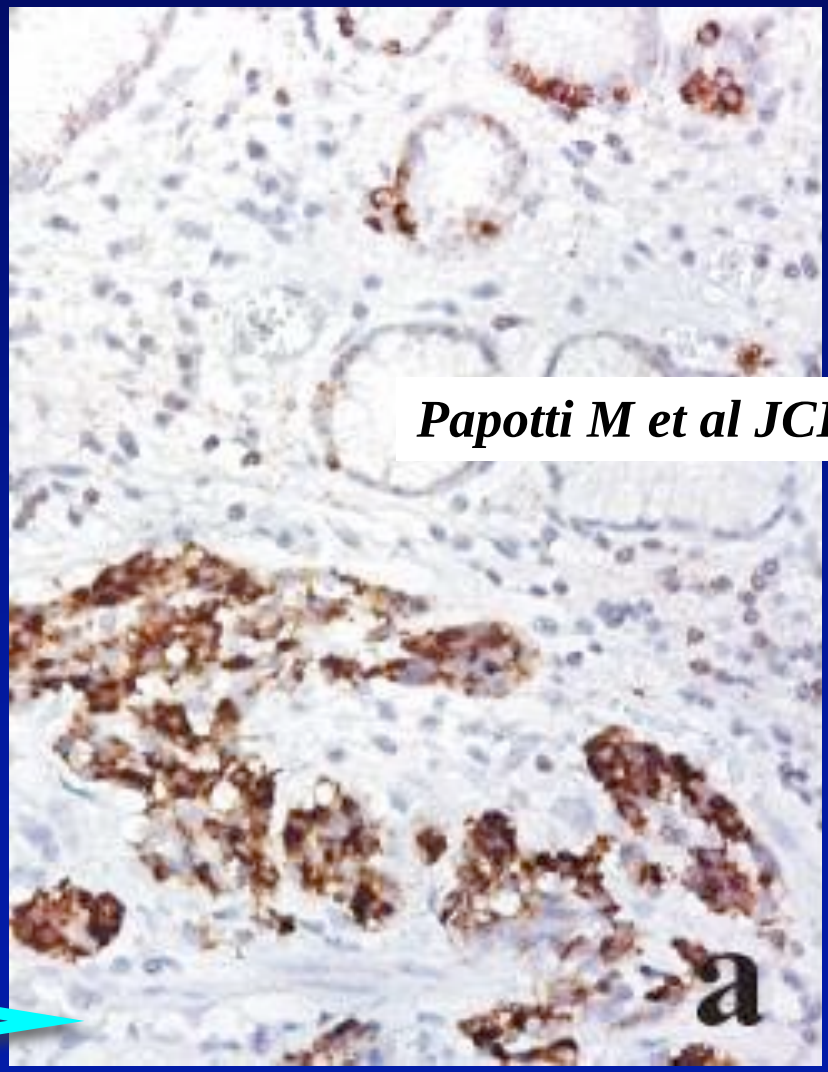


Table 10. Clinicopathological correlations of endocrine tumours of the pancreas

1	Well-differentiated endocrine tumour
1.1	Benign behaviour: confined to the pancreas, nonangioinvasive, <2 cm in size[a], ≤2 mitoses and ≤2% Ki67 positive cells/10 HPF
1.1.1	Functioning - insulinoma
1.1.2	Nonfunctioning
1.2	Uncertain behaviour: confined to the pancreas, ≥2 cm in size, >2 mitoses, >2% Ki67 cells/10 HPF, or angioinvasive
1.2.1	Functioning - gastrinoma, insulinoma, vipoma, glucagonoma, somatostatinoma, or inappropriate syndrome[b] tumour
1.2.2	Nonfunctioning



Gastric X/A like cells and GI endocrine tumors: *GHRELIN*



Papotti M et al JCEM 2001

Circulating Ghrelin Levels in Patients with Pancreatic and Gastrointestinal Neuroendocrine Tumors: Identification of One Pancreatic Ghrelinoma

S. CORBETTA, M. PERACCHI, V. CAPPIELLO, A. LANIA, E. LAURI, L. VAGO, P. BECK-PECCOZ, AND A. SPADA

(*J Clin Endocrinol Metab* 88: 3117–3120, 2003)

Malignant Gastric Ghrelinoma with Hyperghrelinemia

APOSTOLOS V. TSOLAKIS, GUIDA M. PORTELA-GOMES, MATS STRIDSBERG, LARS GRIMELIUS, ANDERS SUNDIN, BARBRO K. ERIKSSON, KJELL E. ÖBERG, AND EVA T. JANSON

(*J Clin Endocrinol Metab* 89: 3739–3744, 2004)

Immunohistochemical NE markers

pan-endocrine marker

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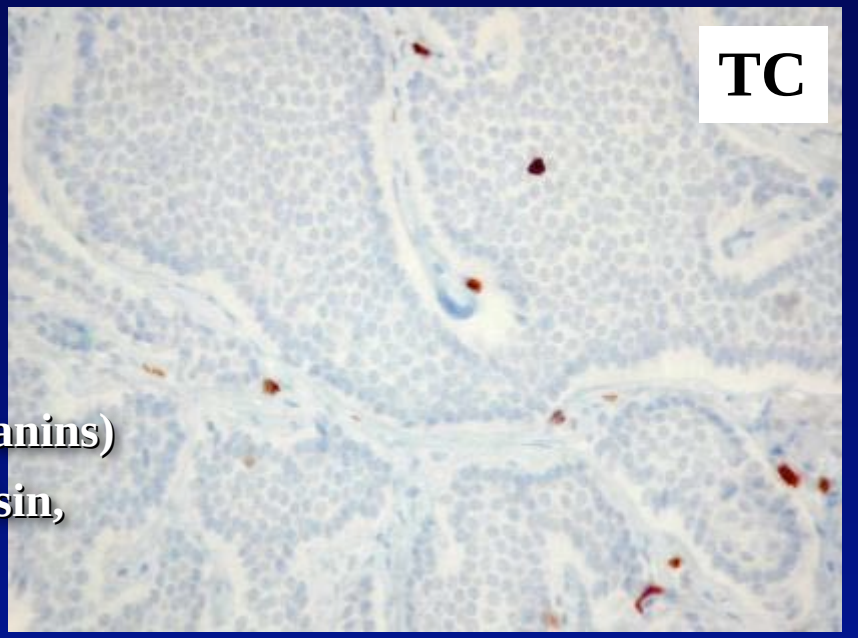
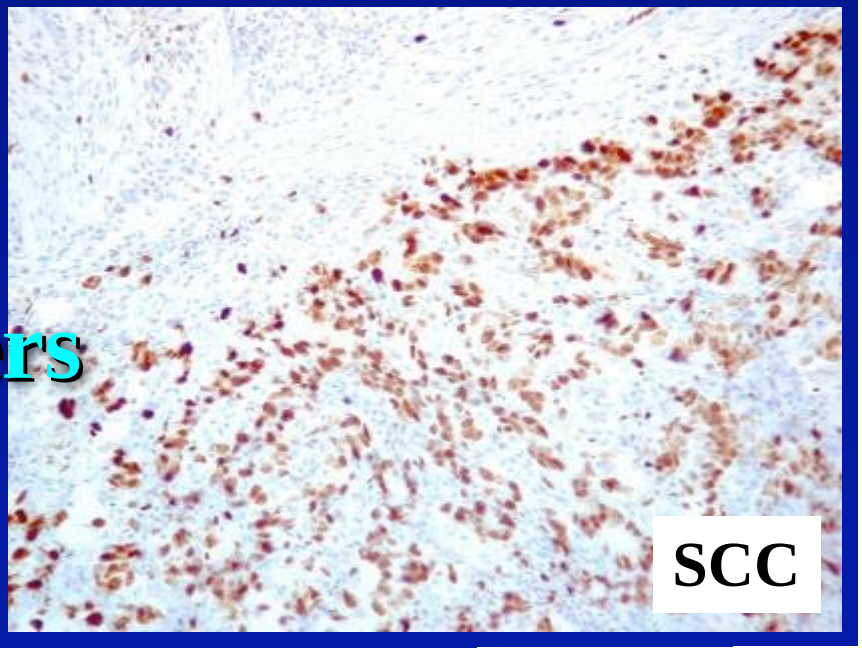
- related to secretory granules (chromogranins)
- related to synaptic vescicles (synaptophisin, VMAT)
- intermediate filaments (NF, CK HMW)
- adhesion molecules (N-CAM)

hormone markers

→ proliferation markers





World Health Organization
International Histological Classification of Tumours

Histological Typing of Endocrine Tumours

E. Solcia, G. Klöppel, L.H. Sobin
In Collaboration with 9 Pathologists

KI-67: DIAGNOSTIC USE

Table 10. Clinicopathological correlations of endocrine tumours of the pancreas

1	Well-differentiated endocrine tumour
1.1	Benign behaviour: confined to the pancreas, nonangioinvasive, <2 cm in size[a], ≤2 mitoses and ≤2% Ki67 positive cells/10 HPF
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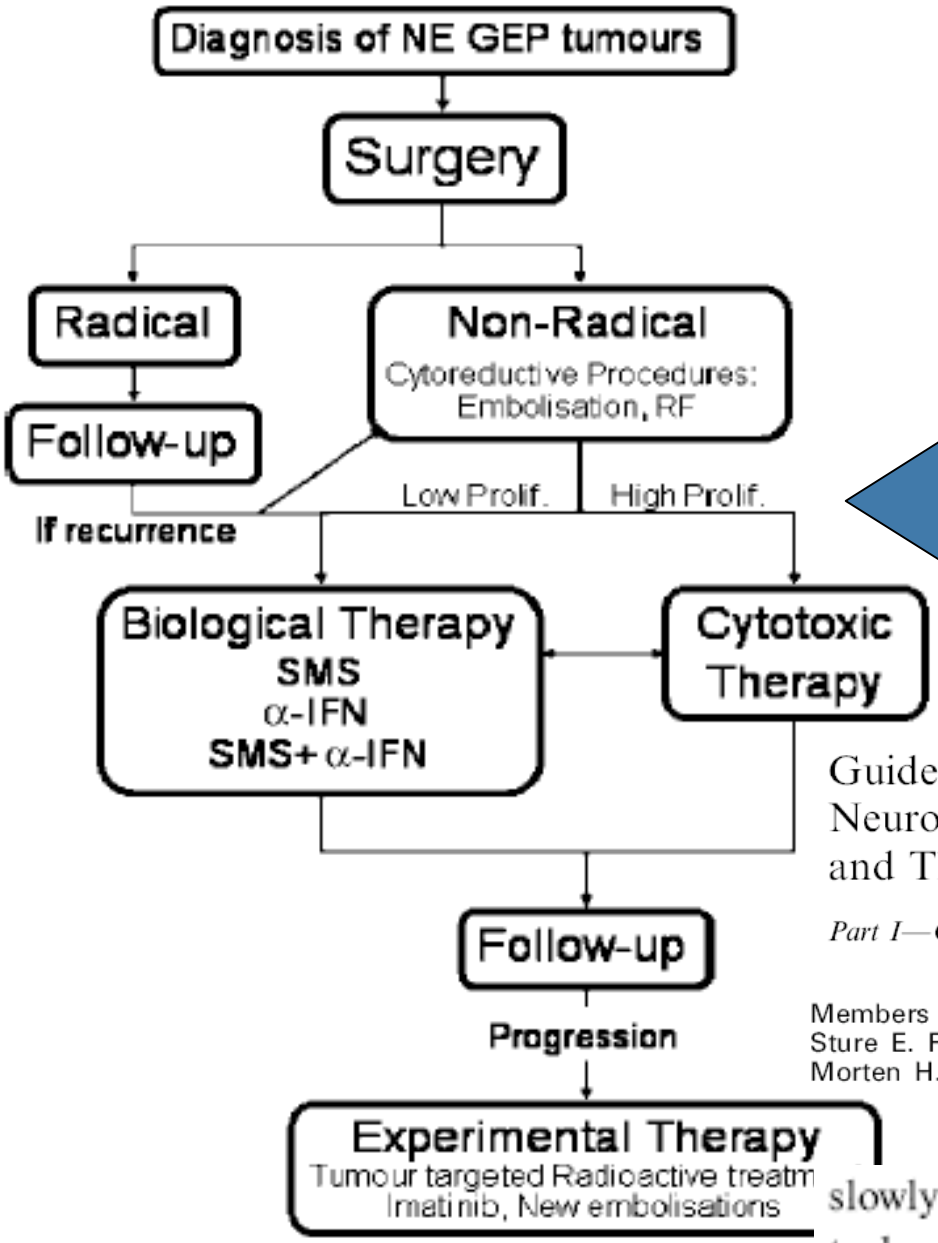
1.2	Uncertain behaviour: confined to the pancreas, ≥2 cm in size, >2 mitoses, >2% Ki67 cells/10 HPF, or angioinvasive
1.2.1	Functioning - gastrinoma, insulinoma, vipoma, glucagonoma, somatostatinoma, or inappropriate syndrome[b] tumour
1.2.2	Nonfunctioning
2	Well-differentiated endocrine carcinoma
2.1	Low grade malignant with gross local invasion and/or metastases
2.1.1	Functioning - gastrinoma, insulinoma, glucagonoma, vipoma, somatostatinoma, or inappropriate syndrome[b] tumour
2.1.2	Nonfunctioning
3	Poorly differentiated endocrine carcinoma - small cell carcinoma, high grade malignant

KI-67: Tx STRATEGY USE



10 to 15% cut-off levels according to therapy modalities

Guidelines for the Management of Gastroenteropancreatic Neuroendocrine Tumours (Including Bronchopulmonary and Thymic Neoplasms)

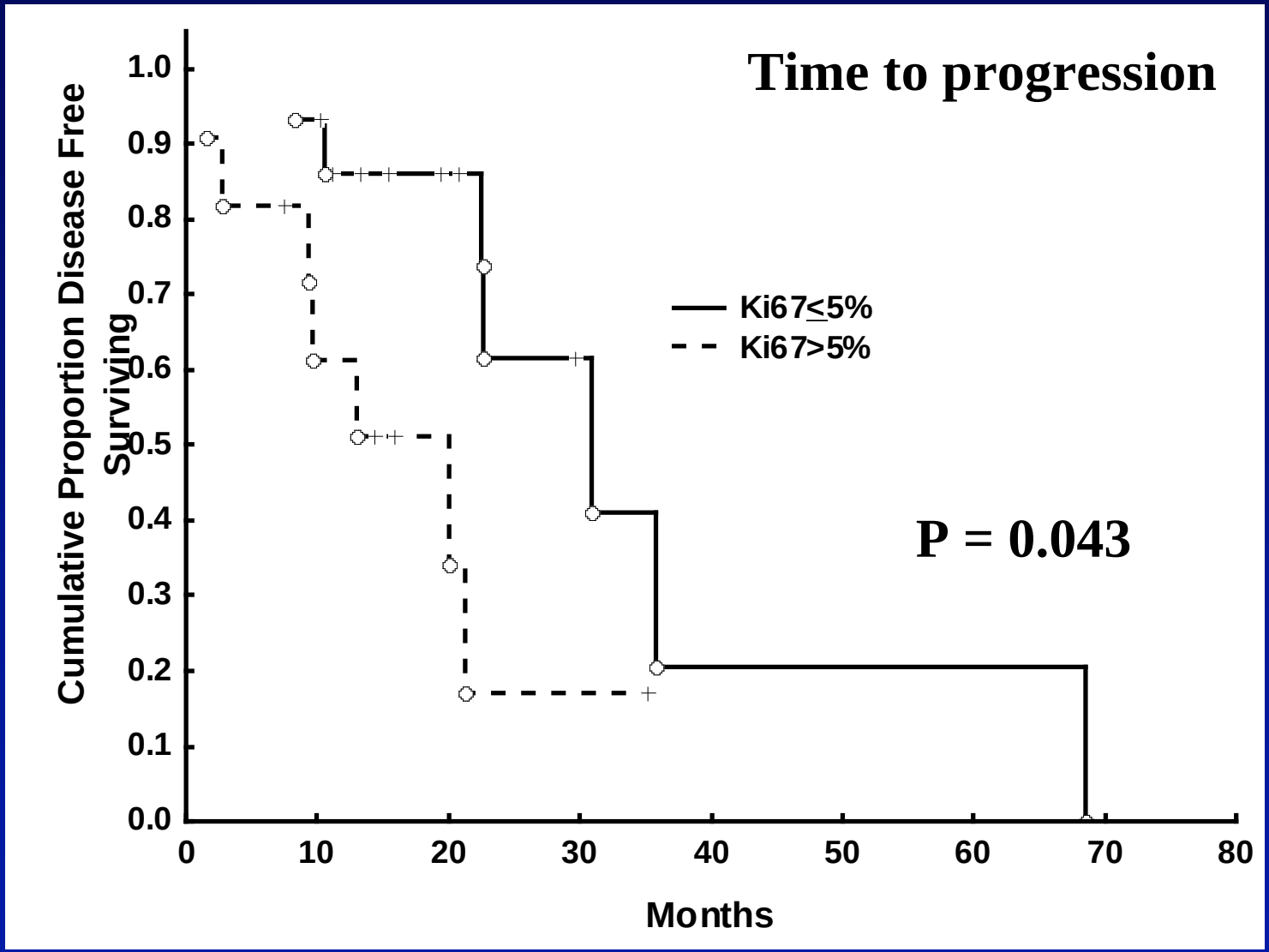
Part I—General Overview

Members of Nordic NE Tumour Group: Kjell Öberg, Lone Astrup, Barbro Eriksson, Sture E. Falkmer, Ursula G. Falkmer, Jens Gustafsen, Caj Haglund, Ulrich Knigge, Morten H. Vatn and Matti Välimäki

slowly progressing NE tumours. Cytotoxic treatment is still to be considered as first-line treatment for high-proliferating tumours, i.e. metastatic disease with angio-invasion and proliferation index above 10%. Single-agent cytotoxic

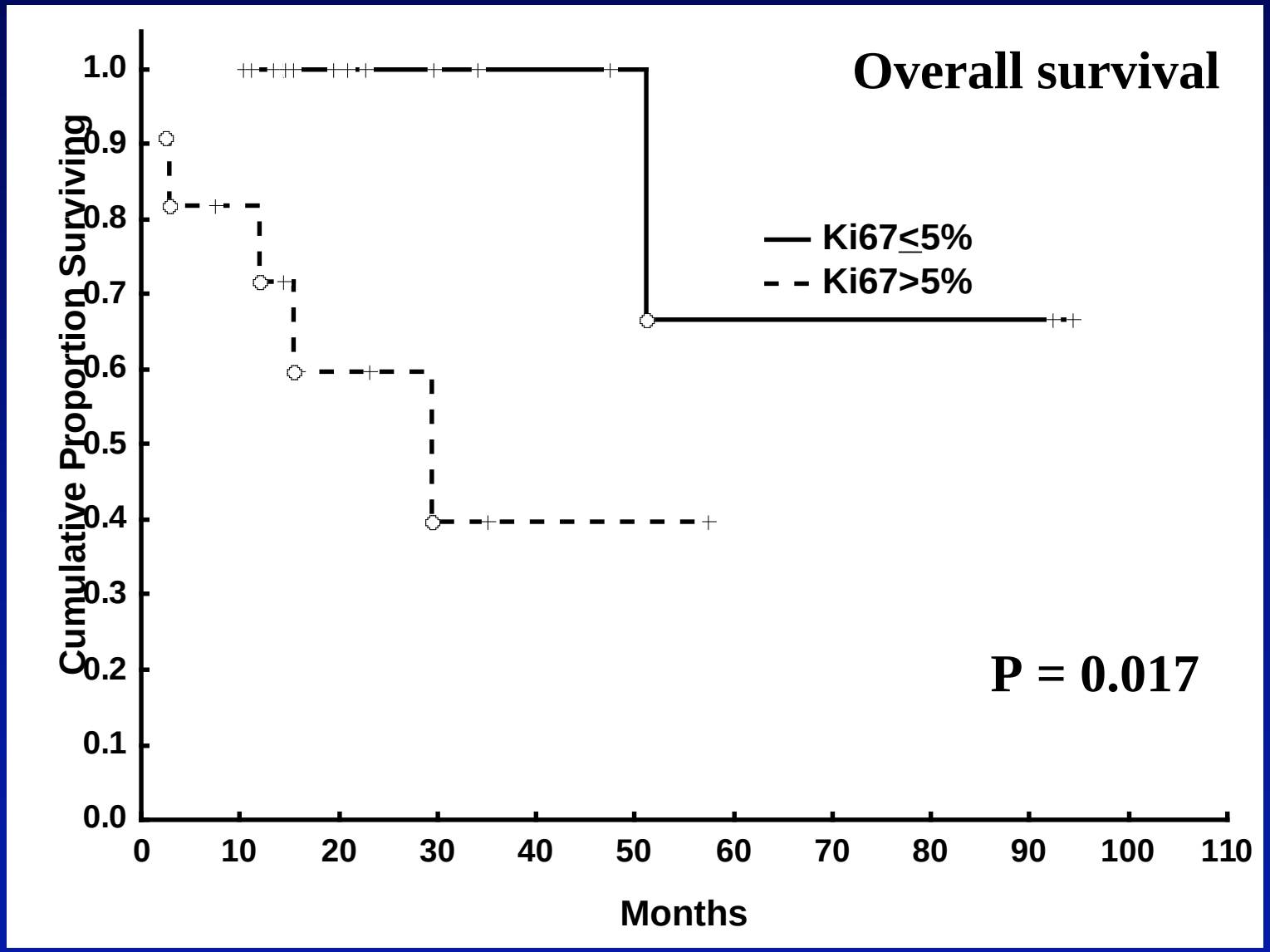
Acta Oncologica 43 (2004)

KI-67: PROGNOSTIC USE



Brizzi et al, 2007 (submitted)

KI-67: PROGNOSTIC USE



Brizzi et al, 2007 (submitted)

pure
NE tum.

….a grey zone

pure
non-NE
ca.

WDET - TC

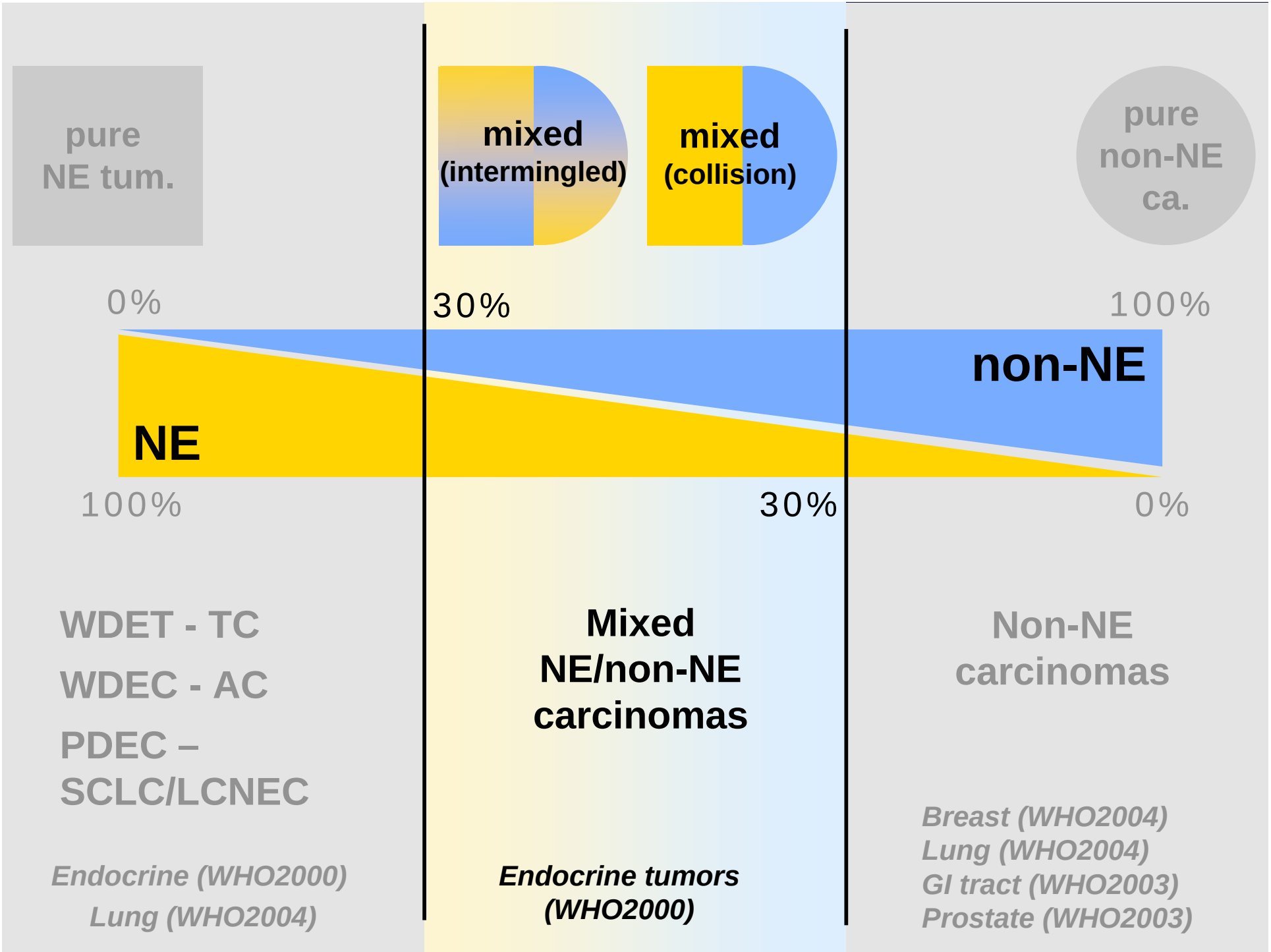
WDEC - AC

PDEC –
SCLC/LCNEC

Endocrine (WHO2000)
Lung (WHO2004)

Non-NE
carcinomas

Breast (WHO2004)
Lung (WHO2004)
GI tract (WHO2003)
Prostate (WHO2003)


pure
NE tum.
mixed
(intermingled)
mixed
(collision)
pure
non-NE
ca.
0%
30%
100%
non-NE
NE
100%
30%
0%
WDET - TC
WDEC - AC
PDEC –
SCLC/LCNEC
Endocrine (WHO2000)
Lung (WHO2004)
Mixed
NE/non-NE
carcinomas
Endocrine tumors
(WHO2000)
Non-NE
carcinomas
Breast (WHO2004)
Lung (WHO2004)
GI tract (WHO2003)
Prostate (WHO2003)

Mixed NE/non-NE carcinomas

Endocrine tumors (WHO2000)

LUNG (COMBINED)
GI TRACT & PANCREAS
THYROID
SKIN
UROGENITAL TRACT
…..

Mixed NE/non-NE carcinomas

Endocrine tumors (WHO2000)

DEFINITION(S)

LUNG (COMBINED) classified as variants of LCNEC and SCC (10%?)

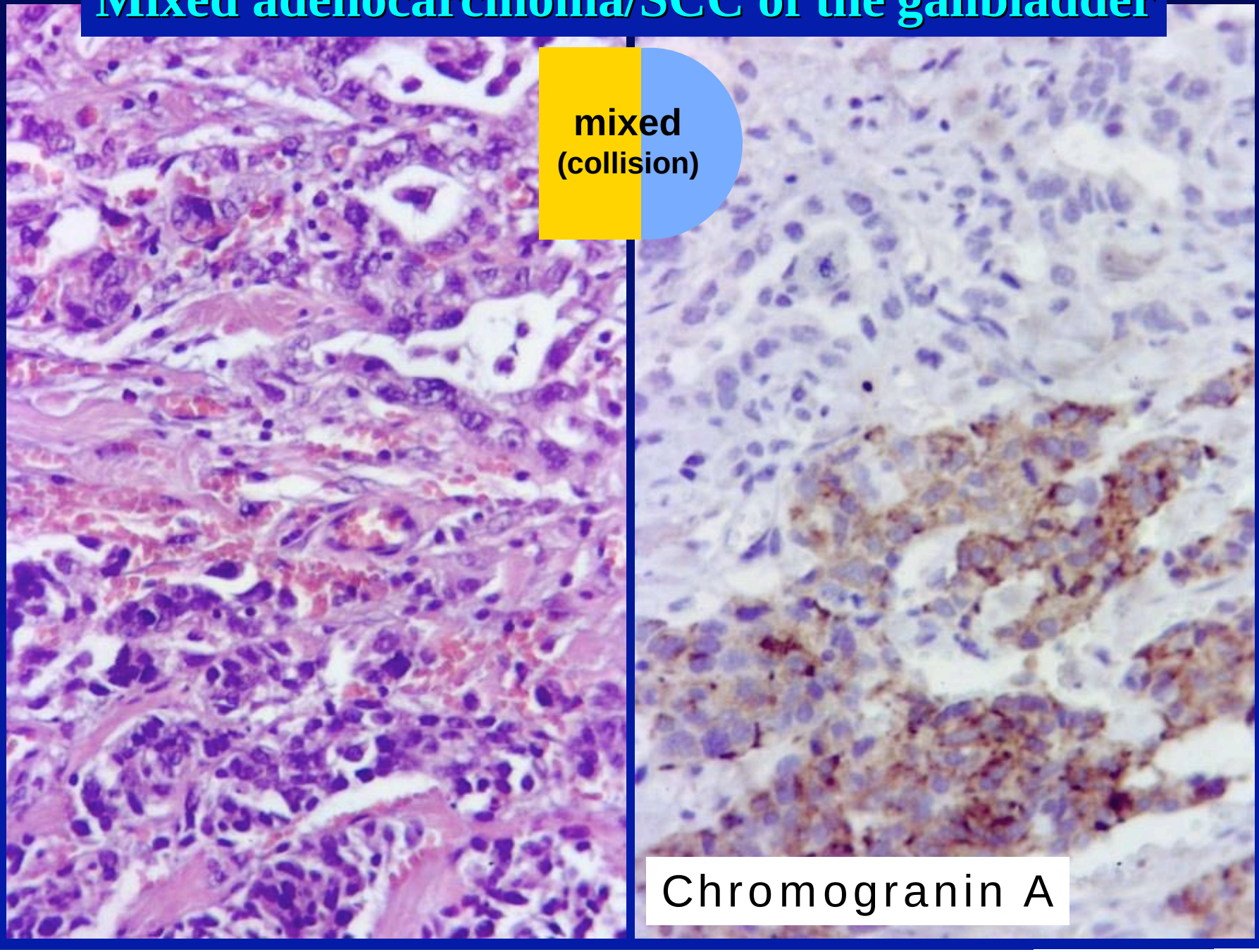
GI TRACT & PANCREAS
"at least one third"

THYROID

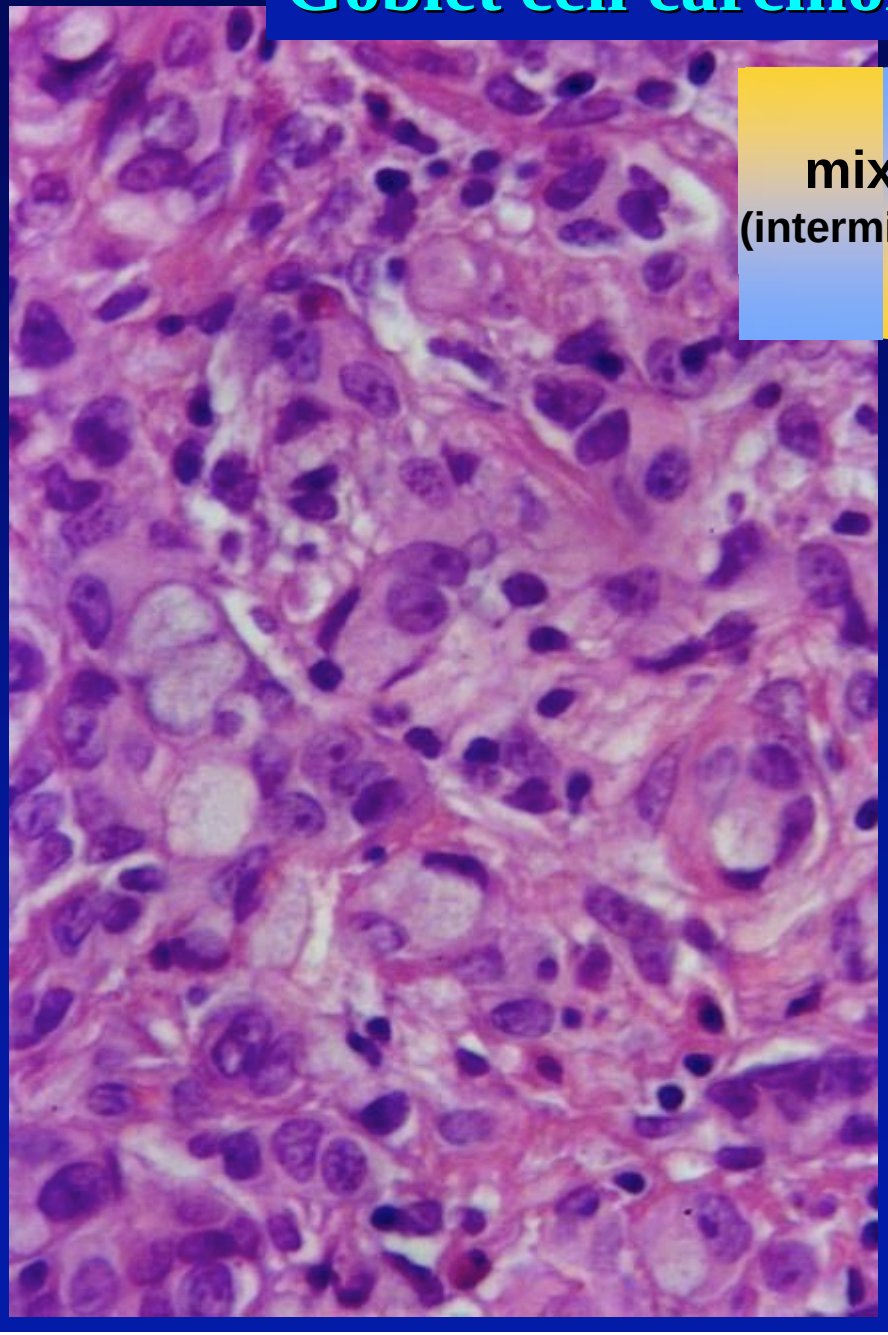
SKIN

UROGENITAL TRACT

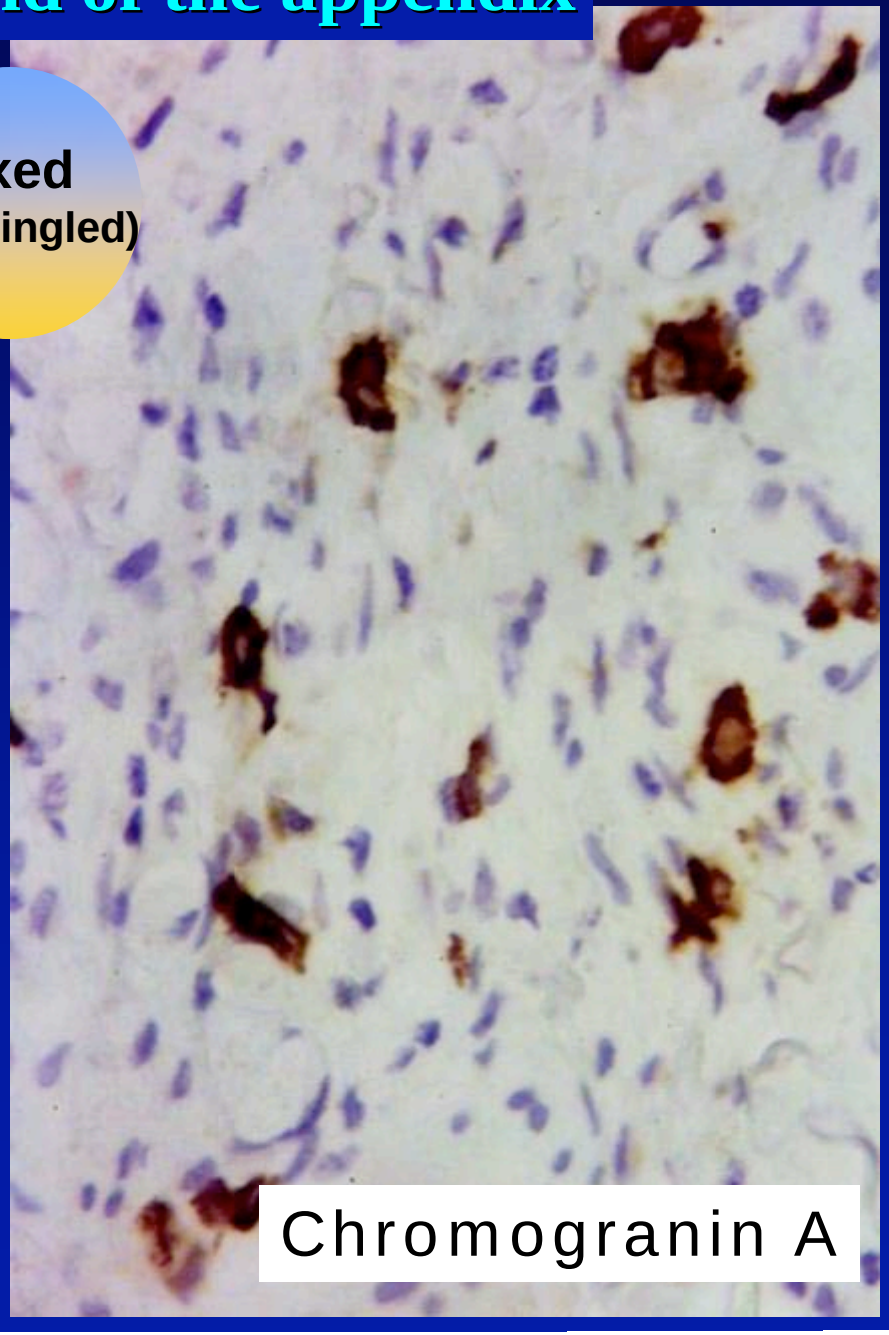
Mixed adenocarcinoma/SCC of the gallbladder



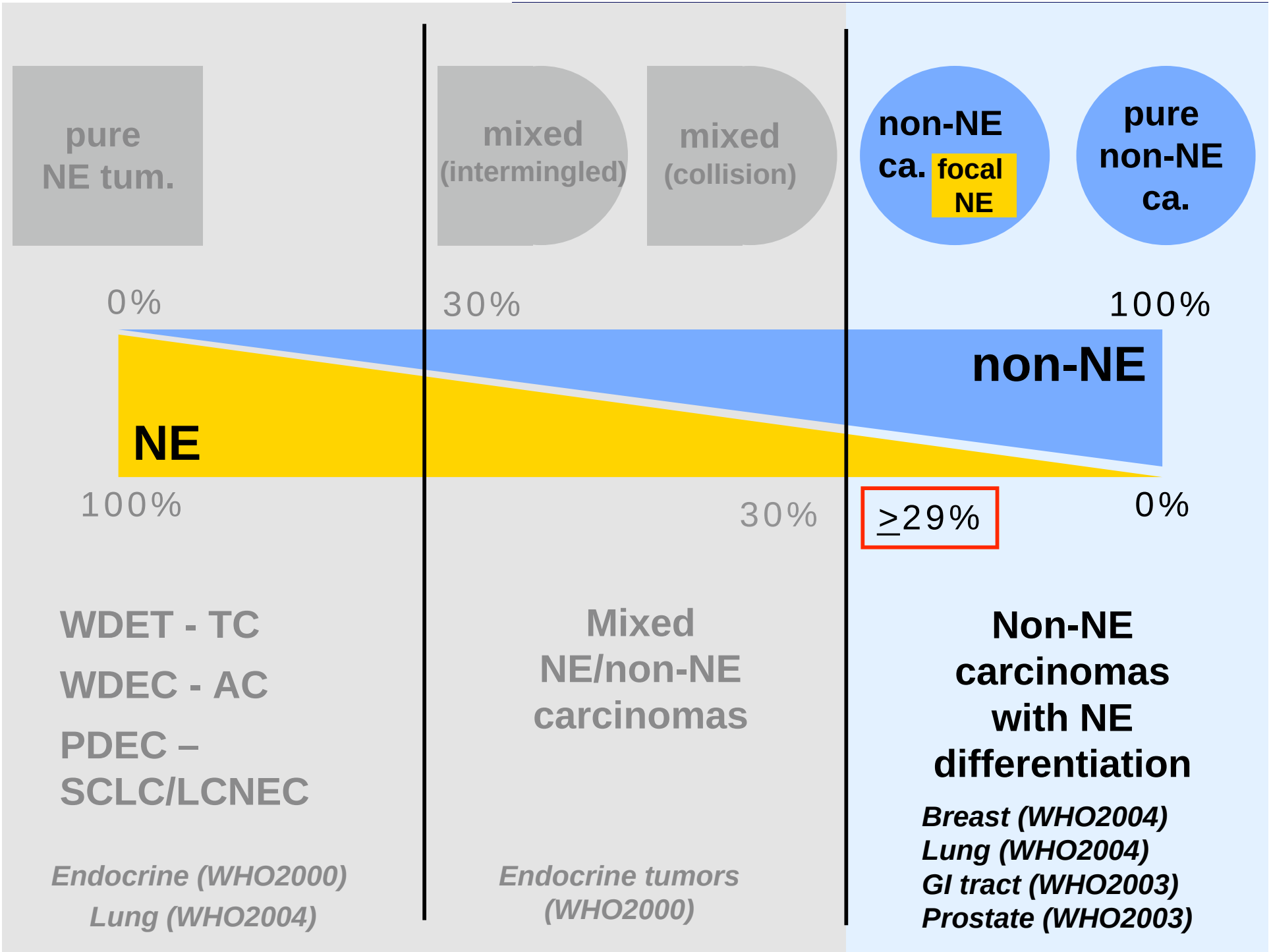
Goblet cell carcinoid of the appendix



mixed
(intermingled)



Chromogranin A


pure
NE tum.
mixed
(intermingled)
mixed
(collision)
non-NE
ca.
focal
NE
pure
non-NE
ca.
0%
30%
100%
non-NE
NE
100%
30%
≥29%
0%
WDET - TC
WDEC - AC
PDEC –
SCLC/LCNEC
Endocrine (WHO2000)
Lung (WHO2004)
Mixed
NE/non-NE
carcinomas
Endocrine tumors
(WHO2000)
Non-NE
carcinomas
with NE
differentiation
Breast (WHO2004)
Lung (WHO2004)
GI tract (WHO2003)
Prostate (WHO2003)

LUNG
BREAST
GI TRACT & PANCREAS
UROGENITAL TRACT
(PROSTATE)
…..

non-NE ca. focal NE

pure non-NE ca.

Non-NE carcinomas with NE differentiation

Breast (WHO2004)
Lung (WHO2004)
GI tract (WHO2003)
Prostate (WHO2003)

non-NE ca. focal NE

pure non-NE ca.

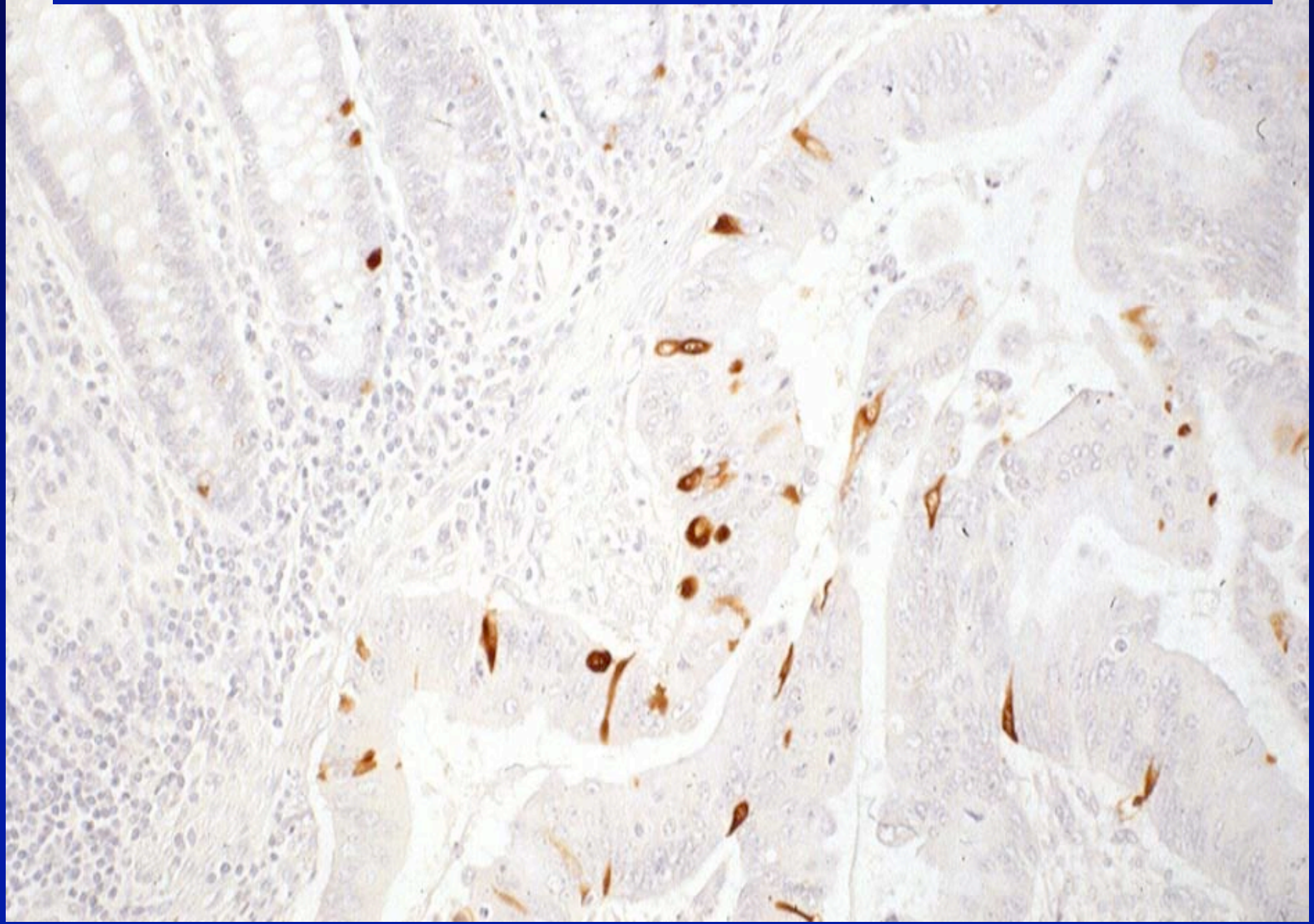
NO CLEAR DEFINITION(S)

… should be less than one third?

Non-NE carcinomas with NE differentiation

Breast (WHO2004)
Lung (WHO2004)
GI tract (WHO2003)
Prostate (WHO2003)

Colon adenocarcinoma with focal NE differentiation



…..ANY BIOLOGICAL/CLINICAL MEANING??

non-NE ca. focal NE

pure non-NE ca.

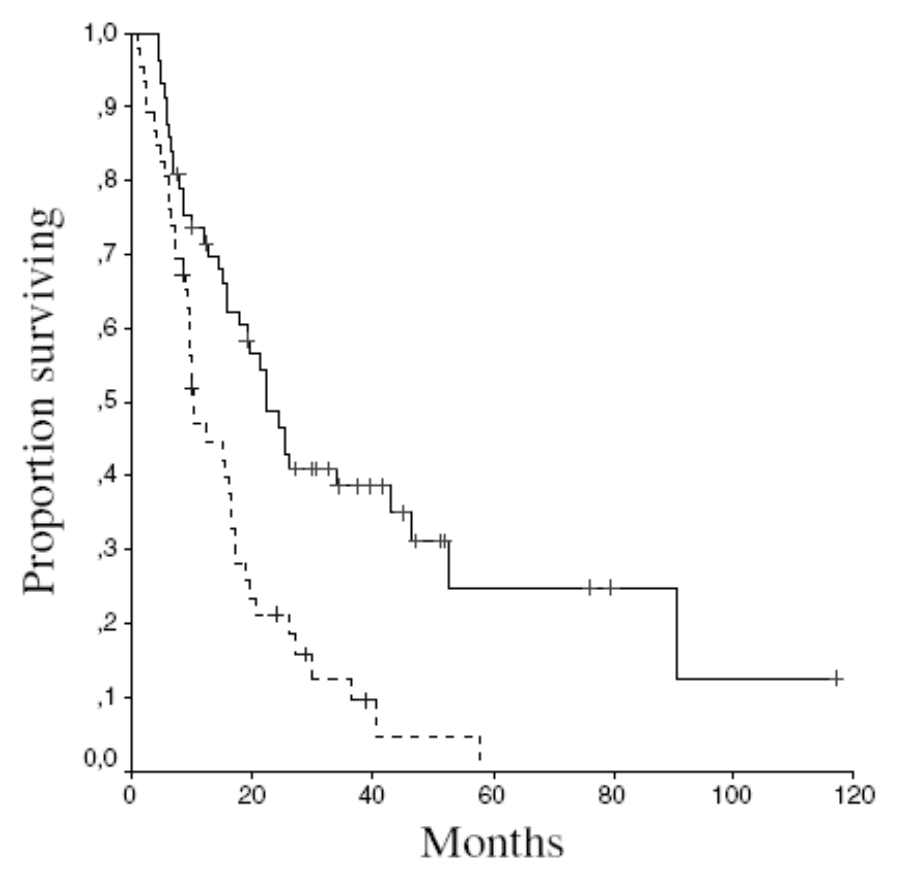
Non-NE carcinomas with NE differentiation

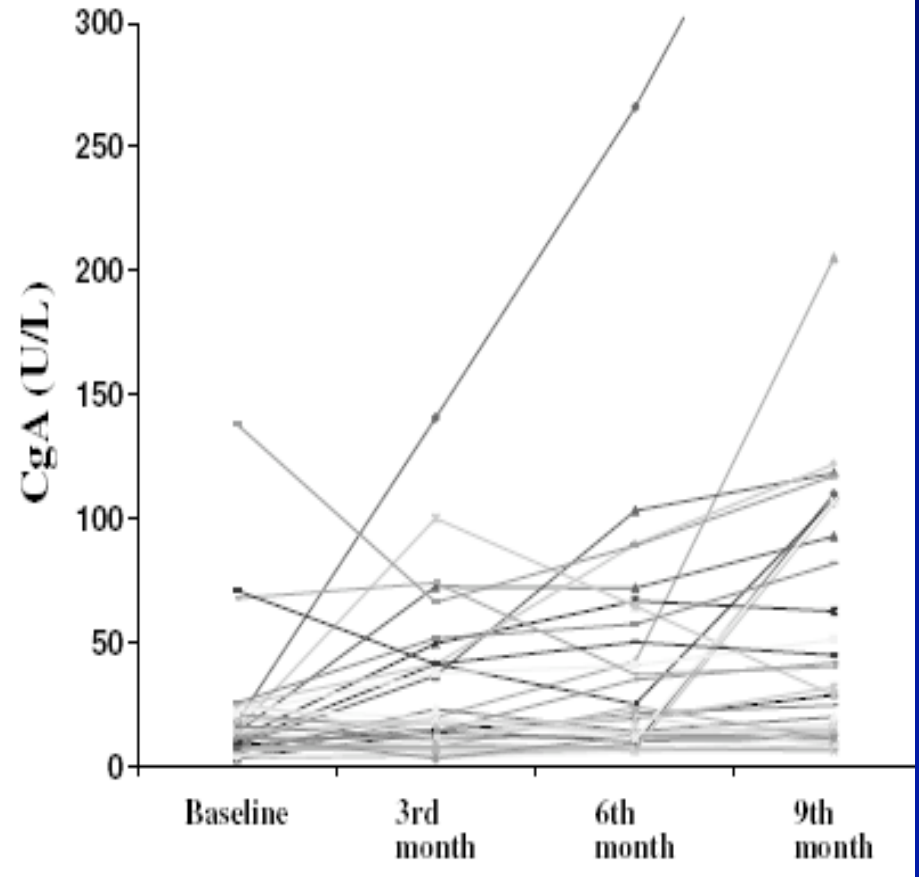
Breast (WHO2004)
Lung (WHO2004)
GI tract (WHO2003)
Prostate (WHO2003)

Independent prognostic role of circulating chromogranin A in prostate cancer patients with hormone-refractory disease

A Berruti[1], A Mosca[1], M Tucci[1], C Terrone[2], M Torta[1], R Tarabuzzi[2], L Russo[1], C Cracco[2], E Bollito[3], R M Scarpa[2], A Angeli[4] and L Dogliotti[1]

Endocrine-Related Cancer (2005) **12** 109–117





WHO CLASSIFICATION(S)

aims…..

WHO CLASSIFICATION(S):

REPRODUCIBILITY

Feasibility of the new WHO classification of pulmonary neuroendocrine tumours

Alain B. Younossian, Marie-Ann Bründler, Martin Tötsch

Division of Clinical Pathology, Department of Pathology, University Hospital of Geneva, Switzerland

SWISS MED WKLY 2002;132:535–540

Prognostic and immunohistochemical validation of the Capella classification of pancreatic neuroendocrine tumours: an analysis of 82 sporadic cases

M F Heymann, M Joubert, J Nemeth,[1] B Franc,[2] J Visset,[3] A Hamy,[3] J le Borgne,[3] J C le Neel,[3] A Murat,[4] S Cordel[5] & M F le Bodic

Department of Pathology, University Hospital; [1]Paris Lariboisière; [2]Paris Ambroise Paré; Departments of [3]Surgery and [4]Endocrinology; and [5]Institute of Biology, Inserm U. 419, University Hospital, Nantes, France

Histopathology 2000, **36**, 421–432

WHO CLASSIFICATION(S):

CLINICAL RELEVANCE

SPECTRUM of NE TUMORS of THE LUNG

TC	AC	LCNEC	SCLC
<2 mitoses no necrosis	2-9 mitoses or necrosis	≥10 mitoses (necrosis)	small cells (necrosis)

Significantly different survival p<0.0001

Significantly different survival p<0.0001

NO significantly different survival

Travis et al

Am J Surg Pathol 22:934, 1998

SPECTRUM of NE TUMORS of THE LUNG

~~TC~~ ~~AC~~ ~~LCNEC~~ ~~SCLC~~

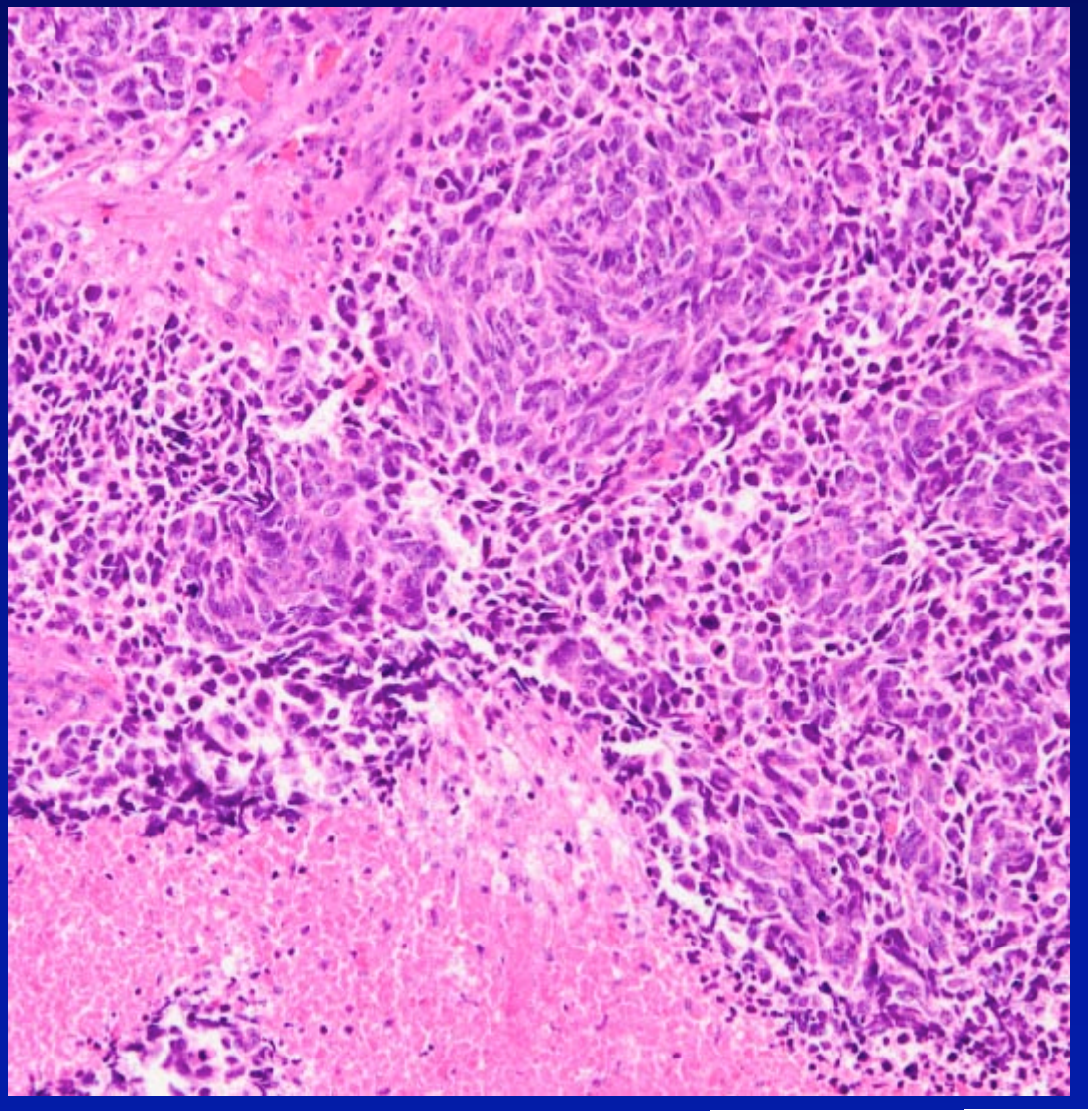
TC

AC

LCNEC

SCLC

NO significantly different survival



Assessment of Outcomes in Typical and Atypical Carcinoids According to Latest WHO Classification

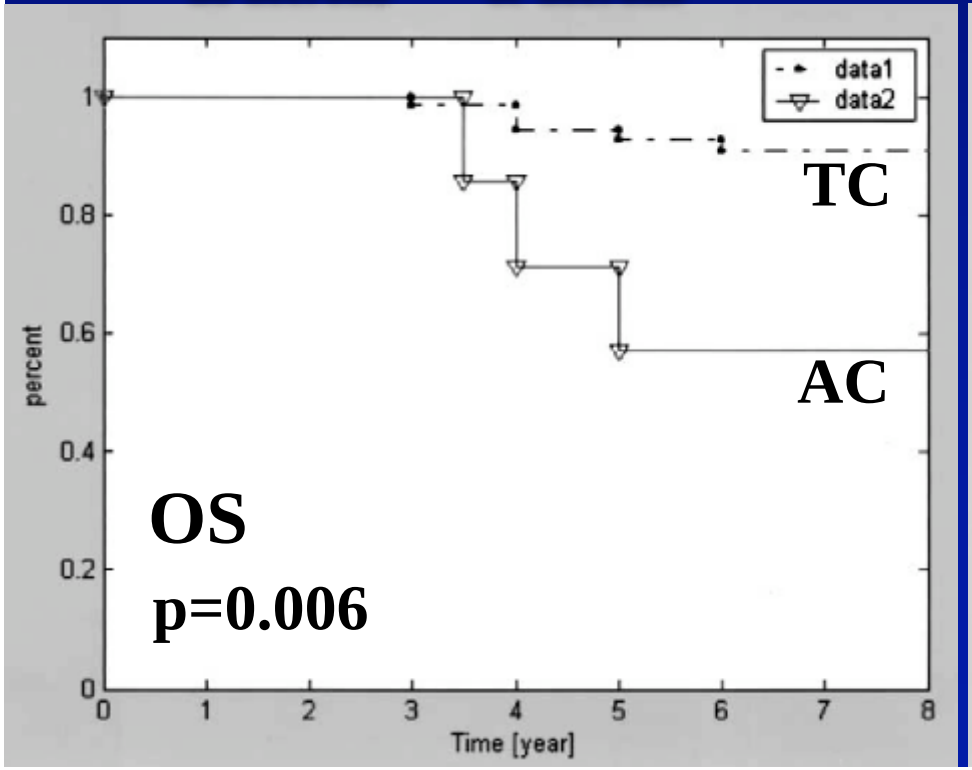
Maurizio Mezzetti, MD, Federico Raveglia, MD, Tiziana Panigalli, MD, Luigi Giuliani, MD, Fabio Lo Giudice, MD, Stefano Meda, MD, and Serena Conforti, MD

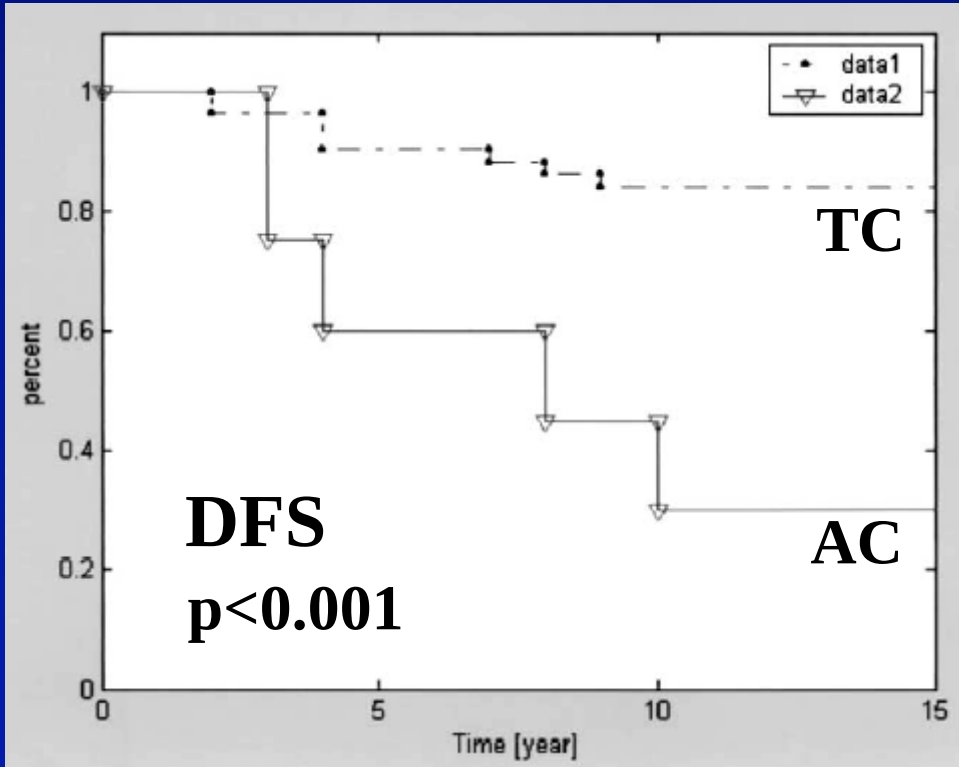
School of Specialization of Thoracic Surgery, S. Paolo Hospital, Milan, Italy

Ann Thorac Surg 2003;76:1838–42

TC <2 mitoses no necrosis

AC 2-9 mitoses or necrosis





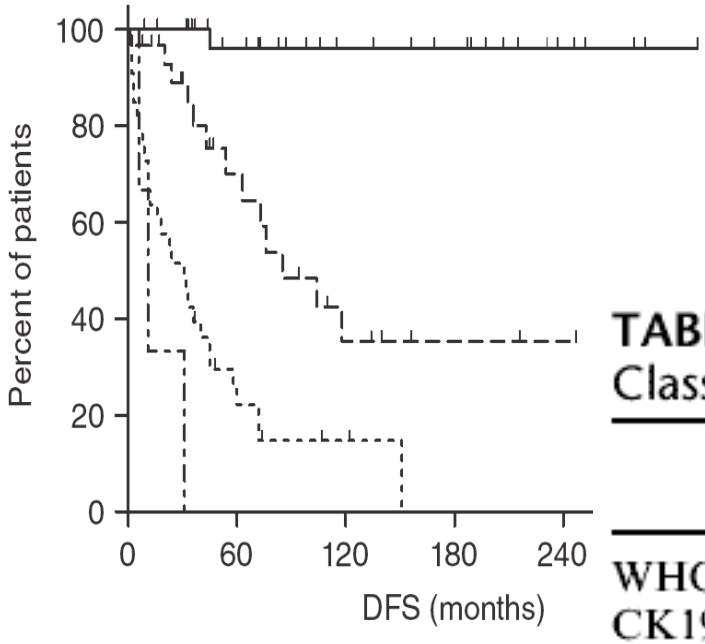
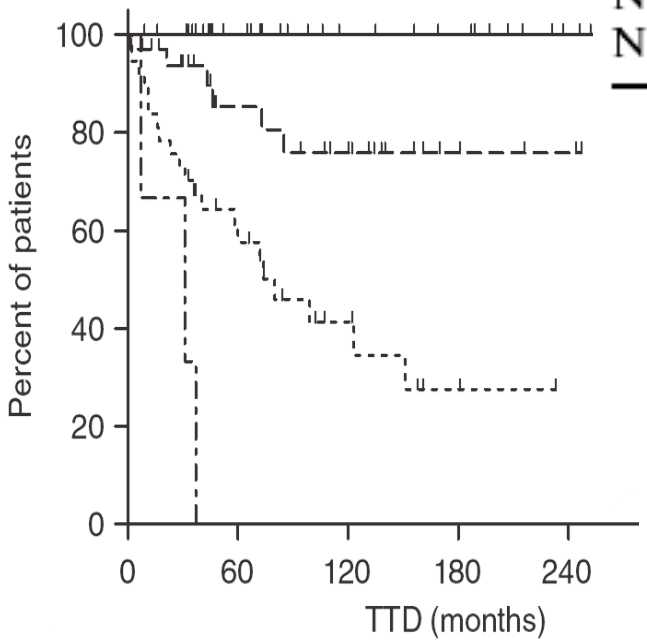


TABLE 1. Multivariate Analysis Including WHO 2004 Classification

	Multivariate *P* Value DFS	Multivariate *P* Value TTD
WHO classification	0.000	0.001
CK19 (positive)	0.019	0.001
Necrosis	0.057	0.130
Nodular fibrosis	0.052	0.518

10 HPF indicates 10 high-power fields, corresponding to an area of 2 mm^2.



Am J Surg Pathol 2007;31:1677–1682

WHO 2004 Criteria and CK19 are Reliable Prognostic Markers in Pancreatic Endocrine Tumors

Anja M. Schmitt, MD, Martin Anlauf, MD,† Valentin Rousson, PhD,‡ Sonja Schmid,* Andreas Kofler, MD,* Florian Riniker,* Juliane Bauersfeld,† Andre Barghorn, MD,* Nicole M. Probst-Hensch, MD,* Holger Moch, MD,* Philipp U. Heitz, MD,* Guenter Kloeppel, MD,† Paul Komminoth, MD,§ and Aurel Perren, MD*‖*

TNM STAGING

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. Erikssson · A. Falchetti · M. Falconi · P. Komminoth · M. Körner · J. M. Lopes · A-M. McNicol · O. Nilsson · A. Perren · A. Scarpa · J-Y. Scoazec · B. Wiedenmann · and all other Frascati Consensus Conference participants

Virchows Arch (2006) 449:395–401

T0 TIS T1 size T4

invasion

N0 N1

M0 M1

Proposed TNM Staging for Foregut Neuroendocrine Tumors of the Stomach, Duodenum, and Pancreas

Stage	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
IIA	T2	N0	M0
IIB	T3	N0	M0
IIIA	T4	N0	M0
IIIB	Any T	N1	M0
IV	Any T	Any N	M1

Virchows Arch (2007) 451:757–762
DOI 10.1007/s00428-007-0452-1

ORIGINAL ARTICLE

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

T0 TIS T1* size T4

invasion

N0 N1

M0 M1

T1a and b in the colon/rectum

PROS e CONS……..

CLASSIFICATION
(diagnosis)

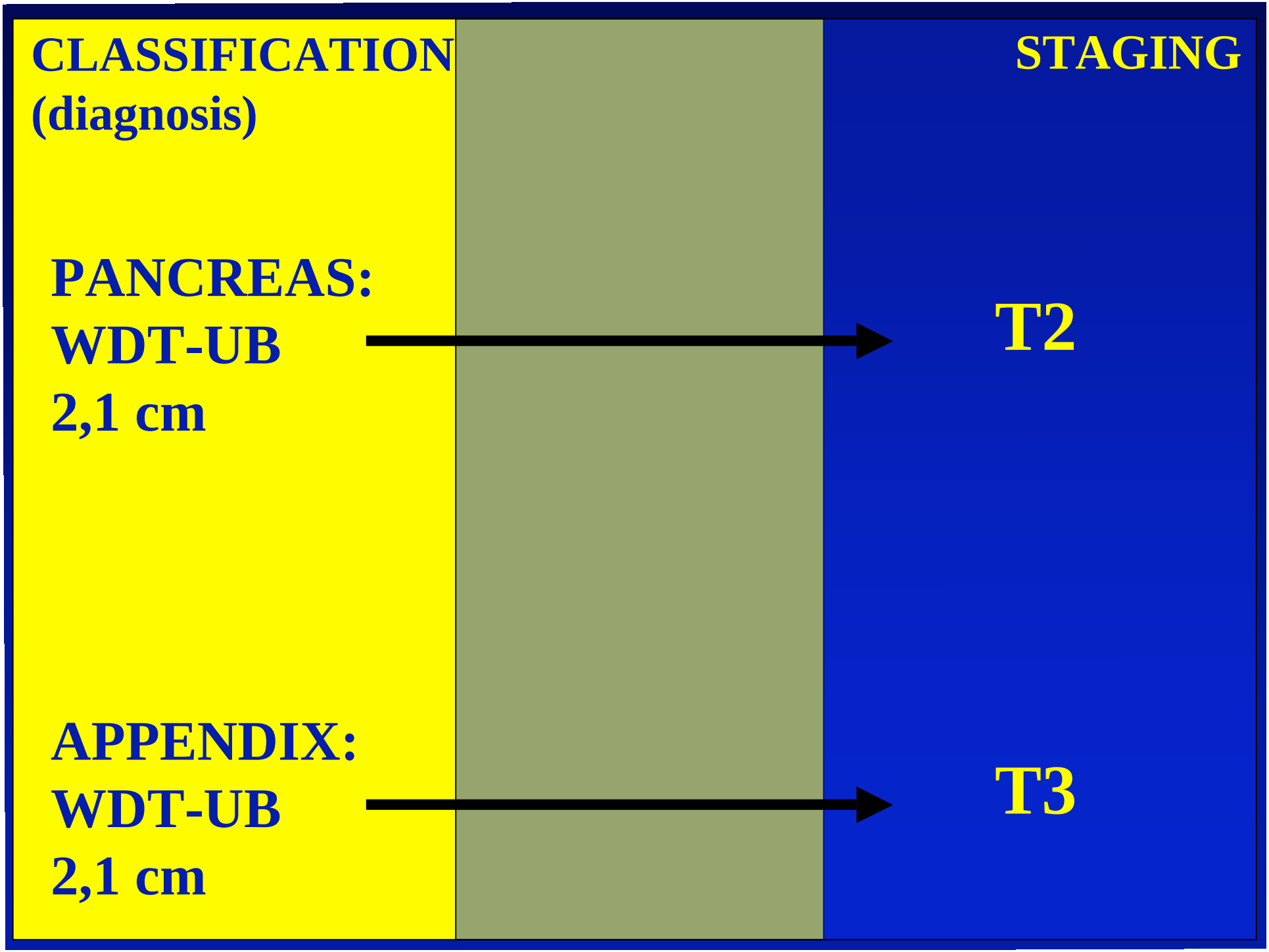
STAGING

CLASSIFICATION
(diagnosis)

size

invasion

STAGING


CLASSIFICATION
(diagnosis)
STAGING
PANCREAS:
WDT-UB
2,1 cm
T2
APPENDIX:
WDT-UB
2,1 cm
T3

Proposed Grading System

Virchows Arch (2006) 449:395–401

Virchows Arch (2007) 451:757–762

Grade	Mitotic count (10 HPF)[a]	Ki-67 index (%)[b]
G1	<2	≤2
G2	2–20	3–20
G3	>20	>20

Proposed Grading System

Virchows Arch (2006) 449:395–401

Virchows Arch (2007) 451:757–762

Grade	Mitotic count (10 HPF)[a]		Ki-67 index (%)[b]
G1	<2	WD NEC	≤2
G2	2–20		3–20
G3	>20	PD NEC	>20

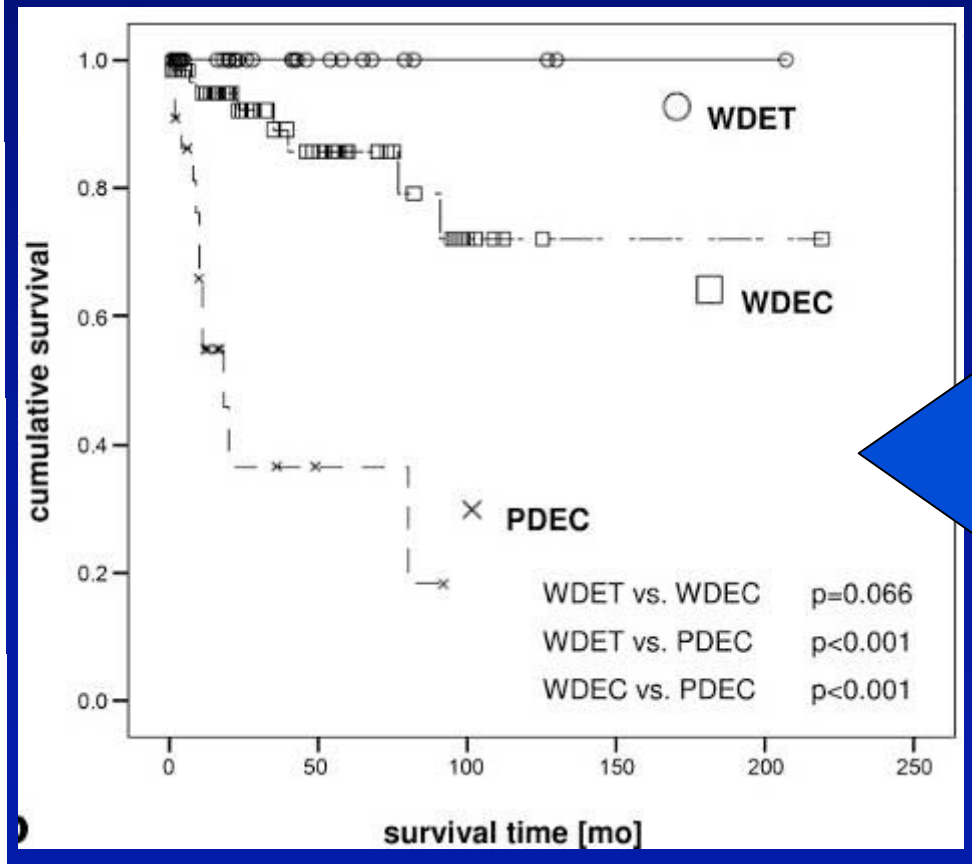
TNM STAGING:

REPRODUCIBILITY
and/or
CLINICAL RELEVANCE

Prognostic relevance of a novel TNM classification system for upper gastroenteropancreatic neuroendocrine tumors

Ulrich-Frank Pape, MD [1]*, Henning Jann, BSc [1], Jacqueline Müller-Nordhorn, MD [2], Angelina Bockelbrink, MD [2], Uta Berndt, MD [1], Stefan N. Willich, MD, PhD [2], Martin Koch, MD [3], Christoph Röcken, MD [3], Guido Rindi, MD [4], Bertram Wiedenmann, MD [1]

Cancer. 2008 May 27. [Epub ahead of print]

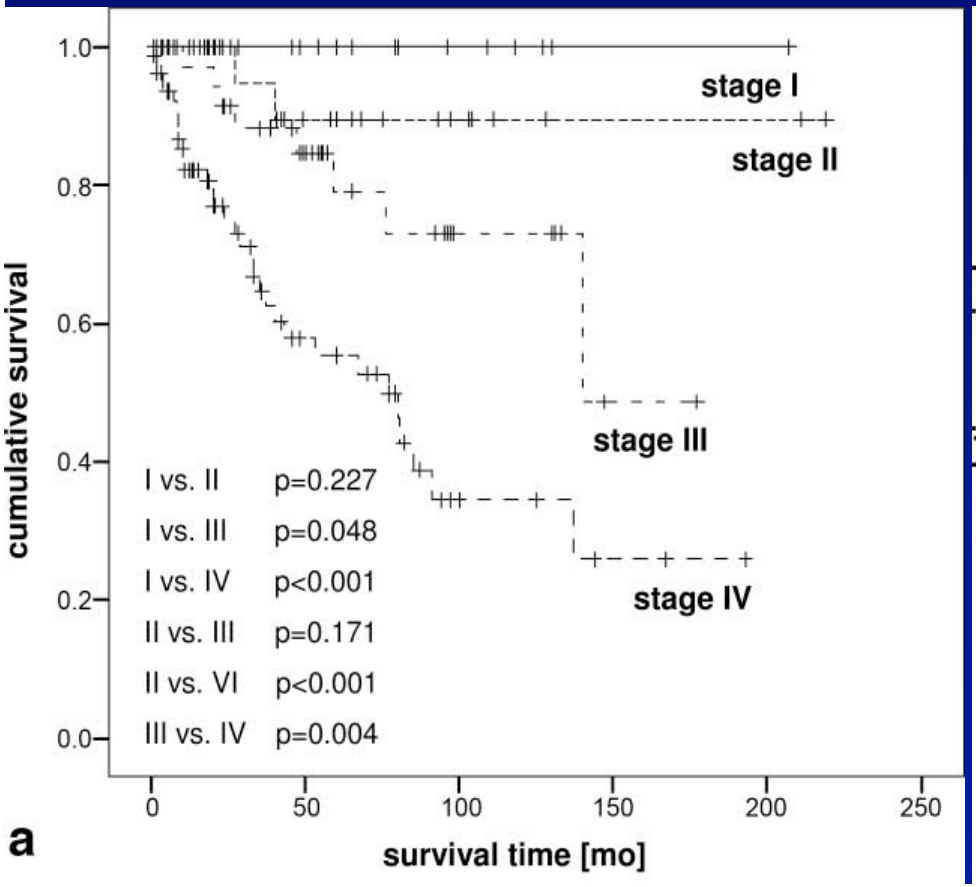


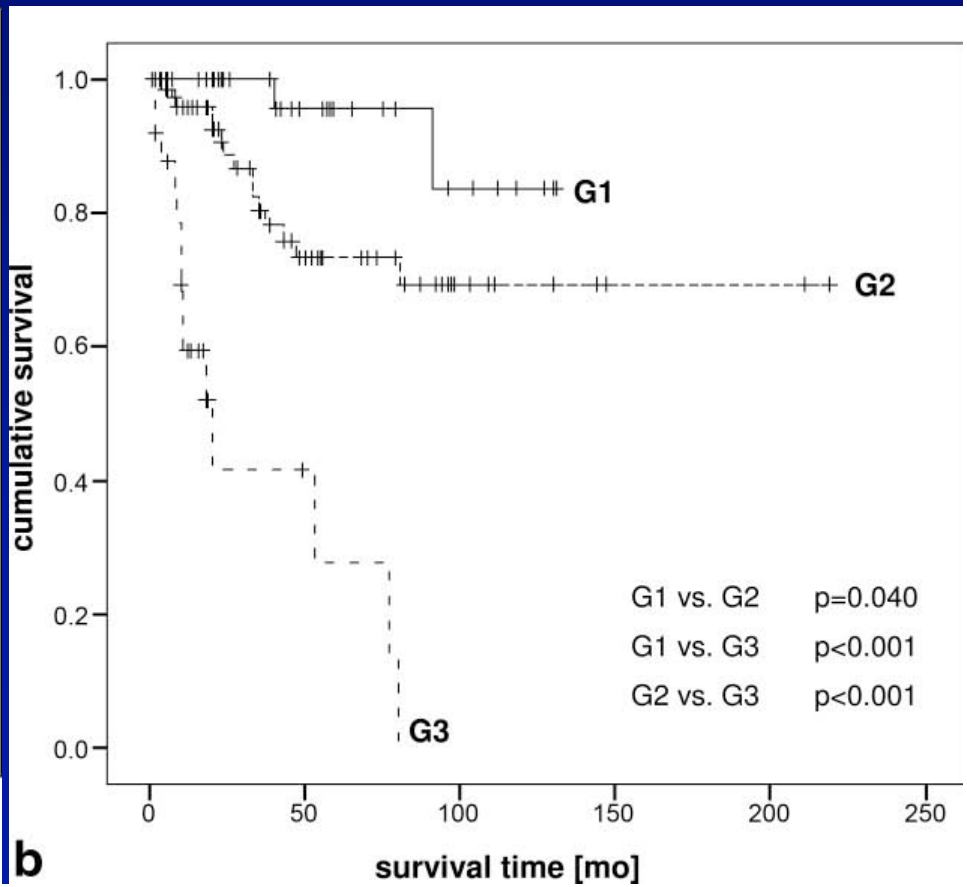
WHO Classification 2000

Prognostic relevance of a novel TNM classification system for upper gastroenteropancreatic neuroendocrine tumors

Ulrich-Frank Pape, MD [1]*, Henning Jann, BSc [1], Jacqueline Müller-Nordhorn, MD [2], Angelina Bockelbrink, MD [2], Uta Berndt, MD [1], Stefan N. Willich, MD, PhD [2], Martin Koch, MD [3], Christoph Röcken, MD [3], Guido Rindi, MD [4], Bertram Wiedenmann, MD [1]

Cancer. 2008 May 27. [Epub ahead of print]






marco.volante@unito.it