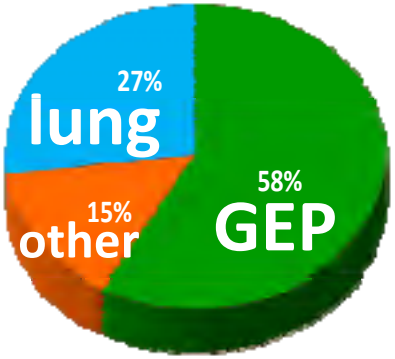
15 nov 11

GIC tumori rari: GIST & NET

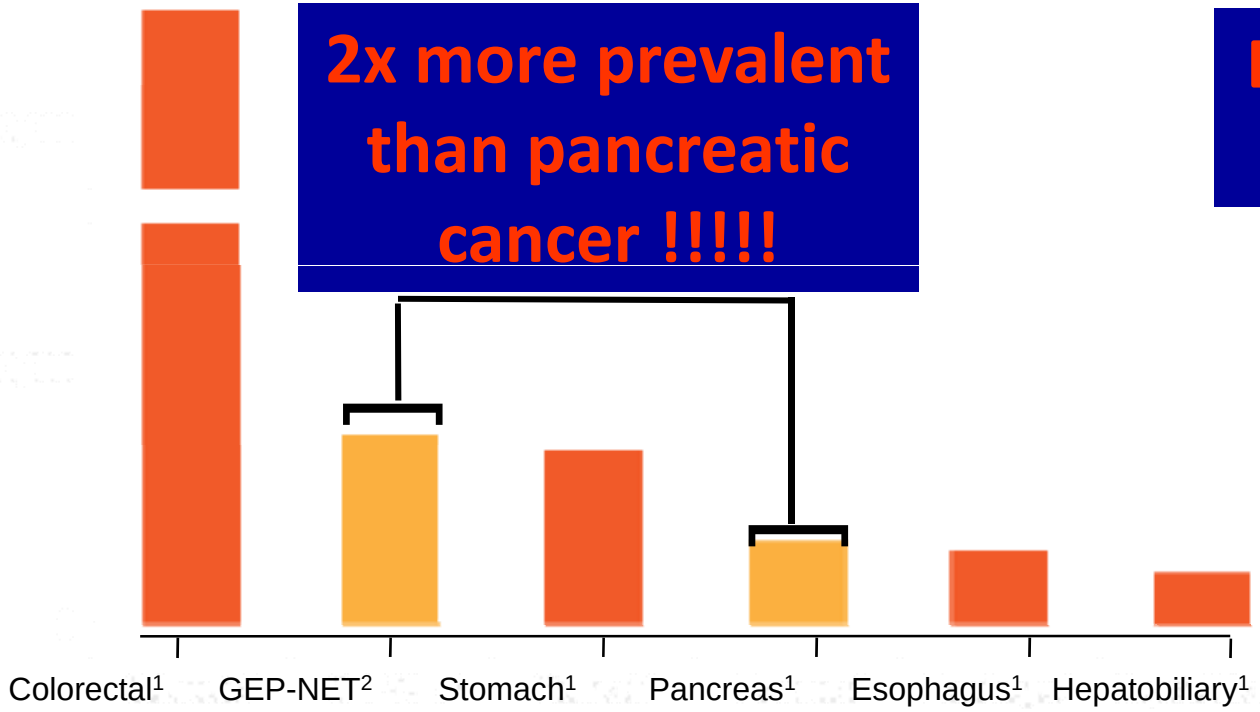
Novità in patologia dei NET

M Papotti, M Volante
Università di Torino



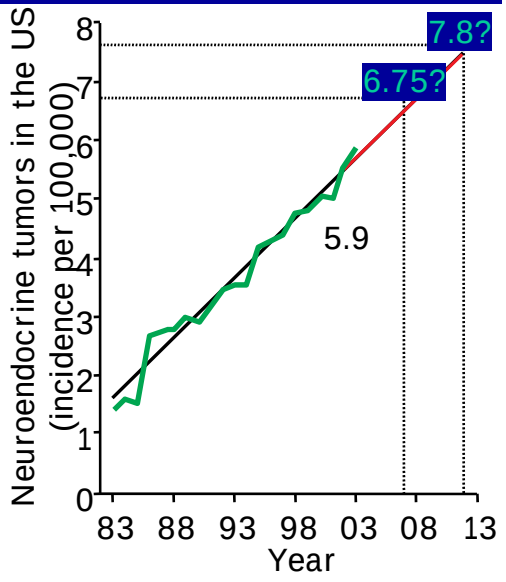
NET: RARE TUMORS, but not so much

2x more prevalent than pancreatic cancer !!!!!



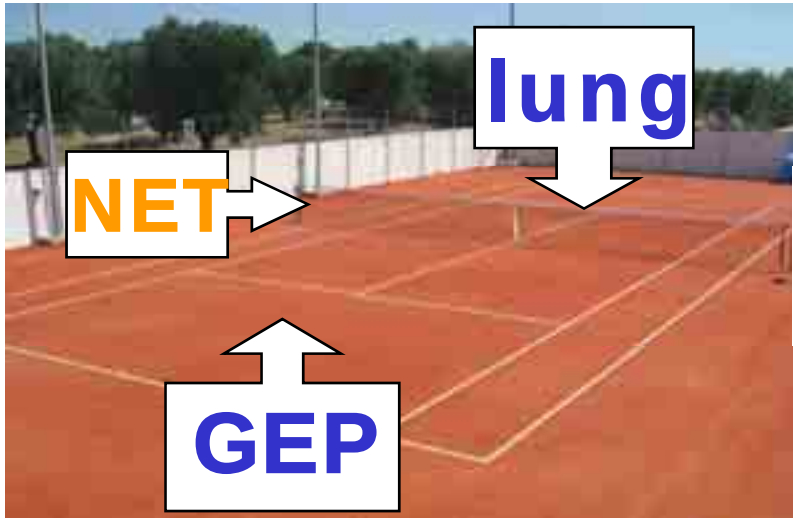
Prevalence in SEER Database

Expected increase !!!!!



Primordial concept of NET for the pathologist……

then evolved into Neuro-Endocrine Tumors (now NEN according to WHO GI 2010)



Singolo o doppio?

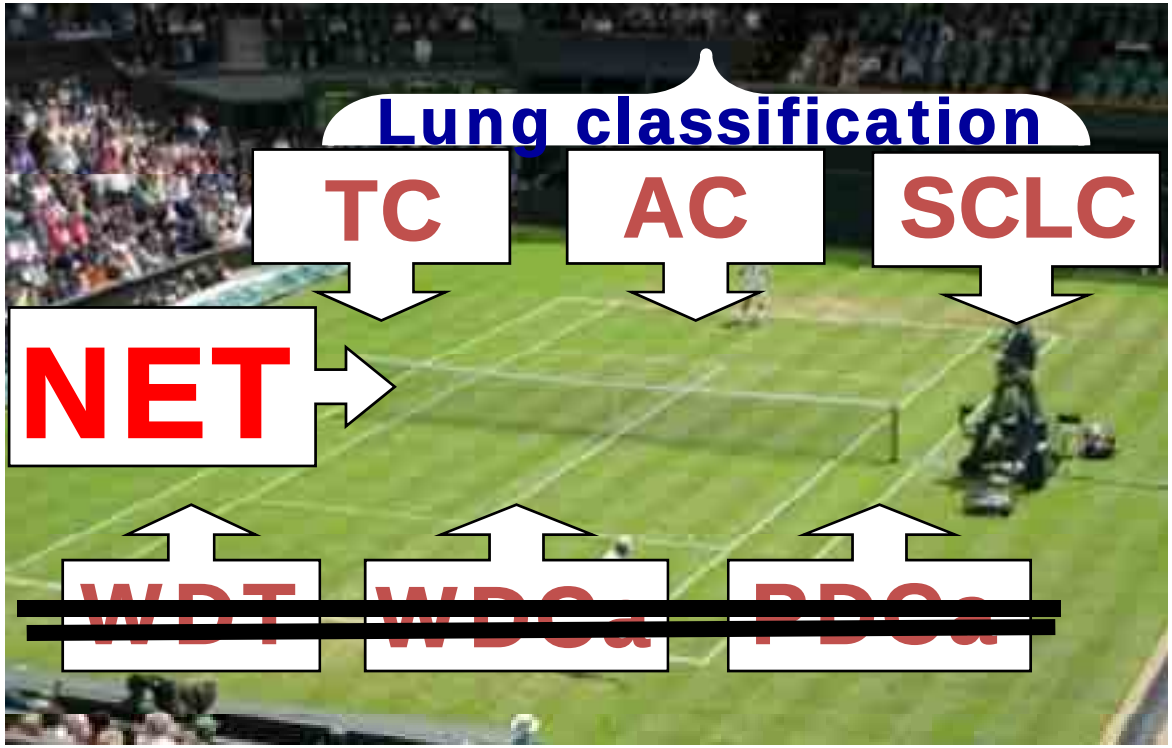
Now in GEP-NETs only:

- -NEN vs NET
- -grade & TNM

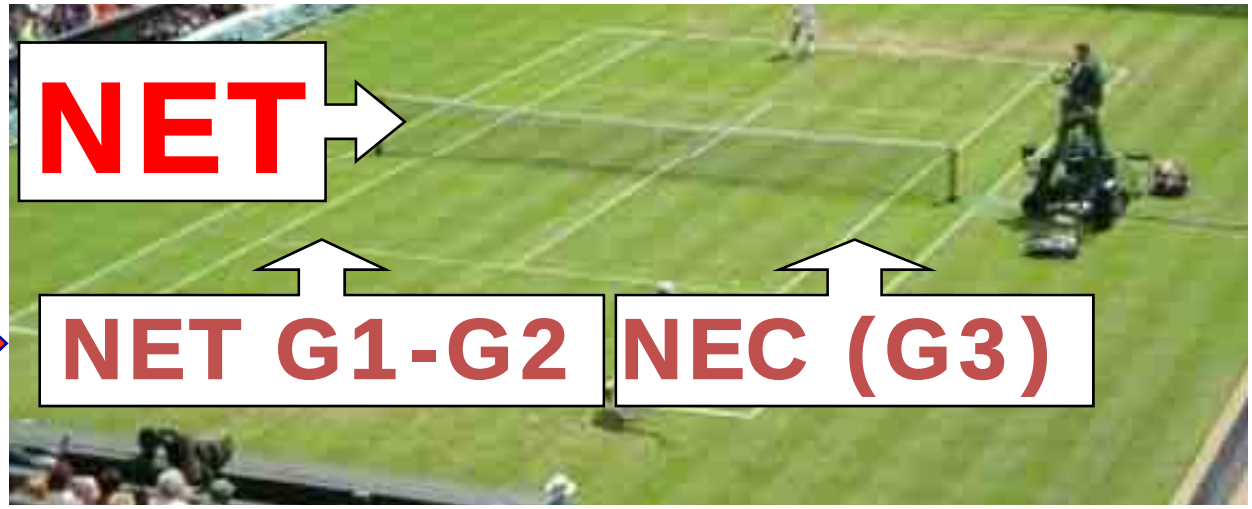
→ 2 groups

→ 3 grades

→ 4 stages



Singolo o doppio? TRIPLO



GEP NET

Confusion: which criteria for diagnosis vs grading vs staging? → needed an ordered approach, stepwise

Big house: two stairs, three floors, four flats

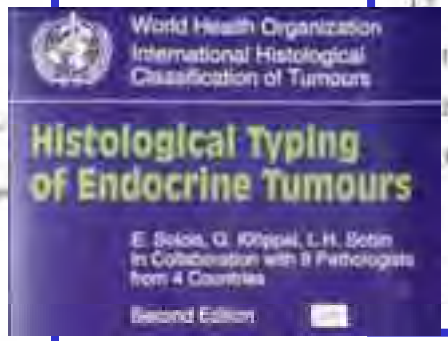
NET pathology

- **Pathological classification, grading and TNM staging guidelines**
- **Diagnostic markers**
- **Prognostic & predictive markers**
- **Conclusion**

WHO classification 2000: GI NETs

stomach

duodenum



2000

appendix

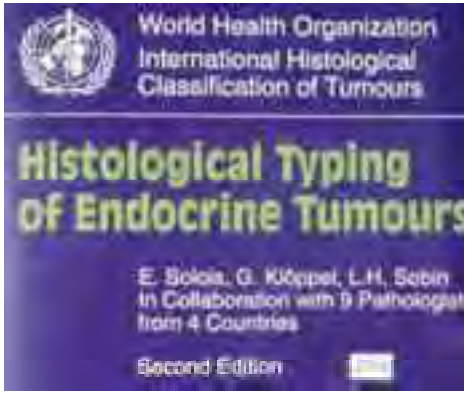
ileum/rectum

Table 14. Clinicopathological correlations of endocrine tumours of the appendix

1	Well-differentiated endocrine tumour - carcinoid, benign behaviour, nonfunctioning, confined to appendiceal wall, ≤2 cm in size
1.1.1	Serotonin-producing tumour
1.1.2	Enteroglucagon-produ… nonfunctioning, confi… or angioinvasive tu…
2	Well-differe…
2.1	Low grade … and/or with metastasis
2.2	Serotonin-producing c…
3	Mixed exocrine-endoc…
3.1	Low grade malignant …

2000 WHO classification

3-TIER SYSTEM for NETs of the GI tract pancreas



Well-differentiated endocrine tumor – Carcinoid

Well-differentiated endocrine tumor - Confined to pancreas

Well-differentiated endocrine carcinoma (malignant carcinoid) - Low grade malignant

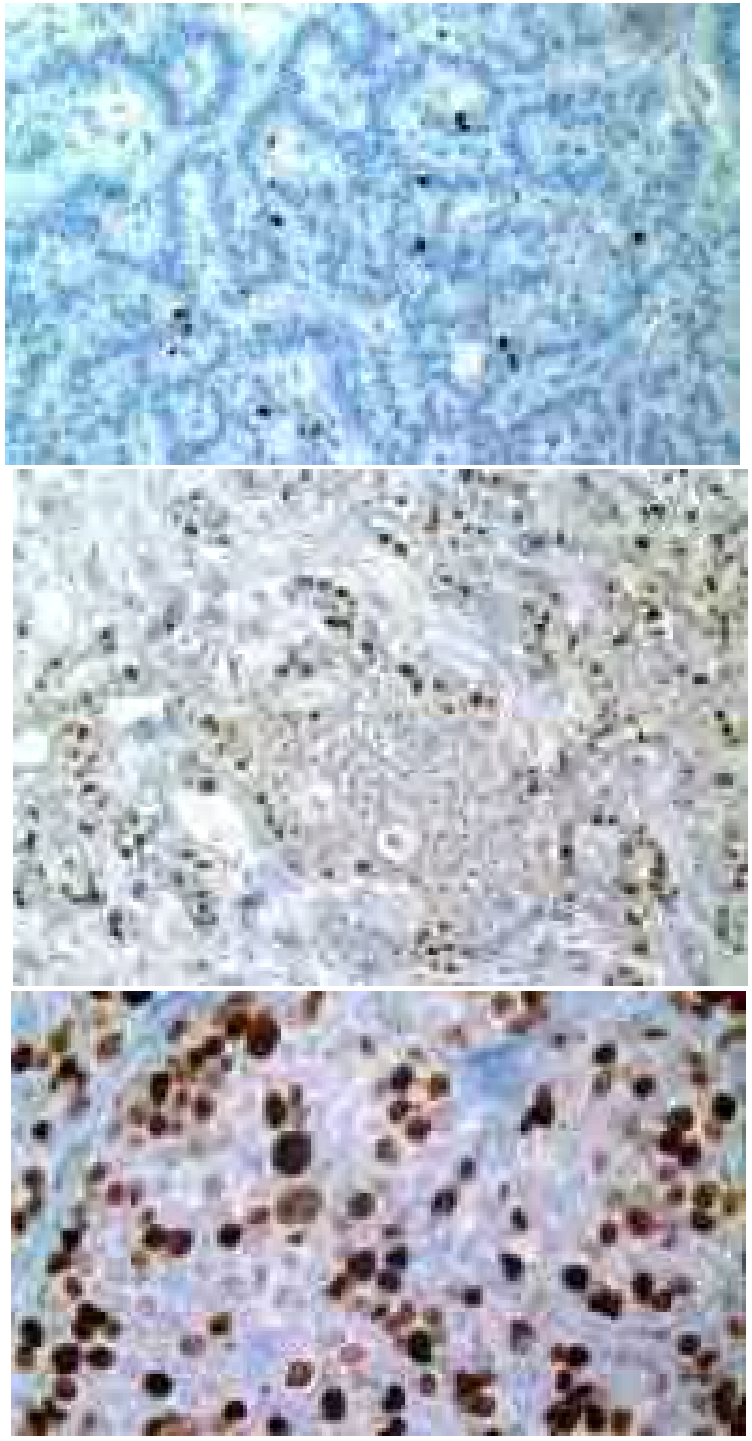
Poorly differentiated endocrine carcinoma - High grade malignant

NET GRADING

Improvement of grading system using mitoses + Ki-67

	Grading proposal for foregut NET	
Grade	Mitotic count (10 HPF)	Ki-67 index (%)
G1	<2	≤2
G2	2-20	3-20
G3	>20	>20

Rindi et al Virchows Arch 2006;449:395



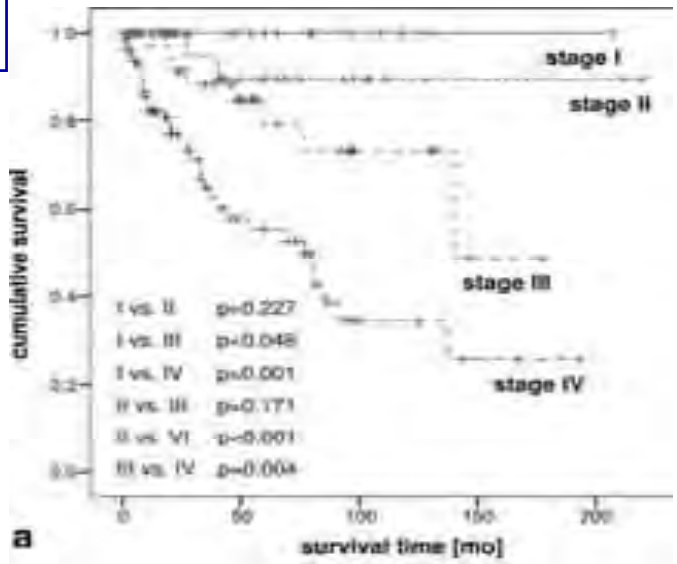
Staging system for GEP NETs and ....

Rindi G, et al. TNM staging of midgut and hindgut NETs: a consensus proposal including a grading system. Virchows Arch 2007;451:757

Couvelard A, Scoazec JY. A TNM classification for digestive NETs of midgut and hindgut: proposals from the ENETS. Ann Pathol 2007;27:426

Prognostic Relevance of a Novel TNM Classification System for Upper Gastroenteropancreatic Neuroendocrine Tumors

CANCER July 15, 2008 / Volume 113



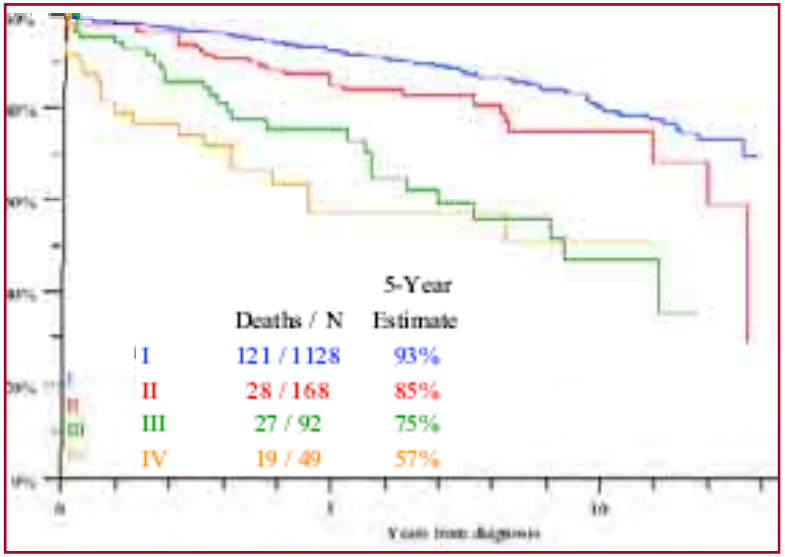
.... also for lung NETs

The IASLC Lung Cancer Staging Project

Proposals for the Inclusion of Broncho-Pulmonary Carcinoid Tumors in the Forthcoming (Seventh) Edition of the TNM Classification for Lung Cancer

William D. Travis, MD, Dorothy J. Giroux, MS,† Kari Chansky, MS,† John Crowley, PhD,† Hisao Asamura, MD,‡ Elisabeth Brambilla, MD, PhD,§ James Jett, MD,‖ Catherine Kennedy,¶ Ramon Rami-Porta, MD,# Valerie W. Rusch, MD,** and Peter Goldstraw, MB, FRCS,††*
on behalf of the International Staging Committee and Participating Institutions

J Thorac Oncol. 2008;3: 1213-



GEP-NET grading & staging

Neuroendocrine Tumors of Midgut and Hindgut Origin: Tumor-Node-Metastasis Classification Determines Clinical Outcome

Henning Jann, MD[1]; Stephanie Roll, PhD[2]; Anne Couvelard, MD[3]; Olivia Hentic, MD[4]; Marianne Pavel, MD[1]; Jacqueline Müller-Nordhorn, MD[2]; Martin Koch, MD[5]; Christoph Röcken, MD[5,6]; Guido Rindi, MD[7]; Philippe Ruszniewski, MD[4]; Bertram Wiedenmann, MD[1]; and Ulrich-Frank Pape, MD, MD[1]

BACKGROUND: Prognostic classification of neuroendocrine tumor (NET) patients is difficult due to the complexity of current classification systems. A recent proposal for a tumor-node-metastasis (TNM) classification and a grading system based on the proliferative fraction proved valid in NETs of foregut origin. The purpose of this study was to test the efficacy of a proposal for TNM staging and grading for midgut and hindgut NETs. **METHODS:** Two hundred seventy patients with histologically proven midgut and hindgut NETs were investigated. Epidemiological, clinicopathological, and tumor-specific data at initial diagnosis were recorded. Tumors were classified according to the World Health Organization (WHO) and the recent European Neuroendocrine Tumor Society-TNM staging and grading proposal. Survival analysis and statistical testing for independent prognostic factors were performed using log-rank tests and Cox regression. **RESULTS:** Of 270 NETs originating in the midgut or hindgut, 7% (5-year survival rate [YSR] 100%) were stage 1, 8% (5-YSR, 100%) were stage 2, 19% (5-YSR, 89.5%) were stage 3, and 66% (5-YSR, 83.3%) were stage 4 NETs. 62% (5-YSR 95.2%) were grade 1, 32% (5-YSR 82.0%) were grade 2, and 6% (5-YSR, 51.4%) were grade 3 NETs. WHO classification significantly separated poorly from [illegible] ther discriminate. TNM staging significantly separated stages 1, [illegible] to proliferative capacity for all grades. Multivariate analysis [illegible] **CONCLUSIONS:** The acquired data confirmed the prognostic [illegible] system and demonstrated the applicability of these classifica[illegible] therapeutic stratification and comparison of data from different

Cancer August 1, 2011

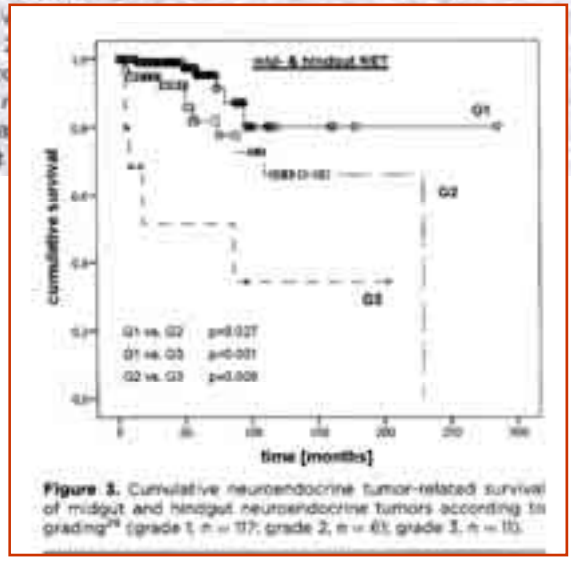


Figure 3. Cumulative neuroendocrine tumor-related survival of midgut and hindgut neuroendocrine tumors according to grading[29] (grade 1, n = 117; grade 2, n = 61; grade 3, n = 10).

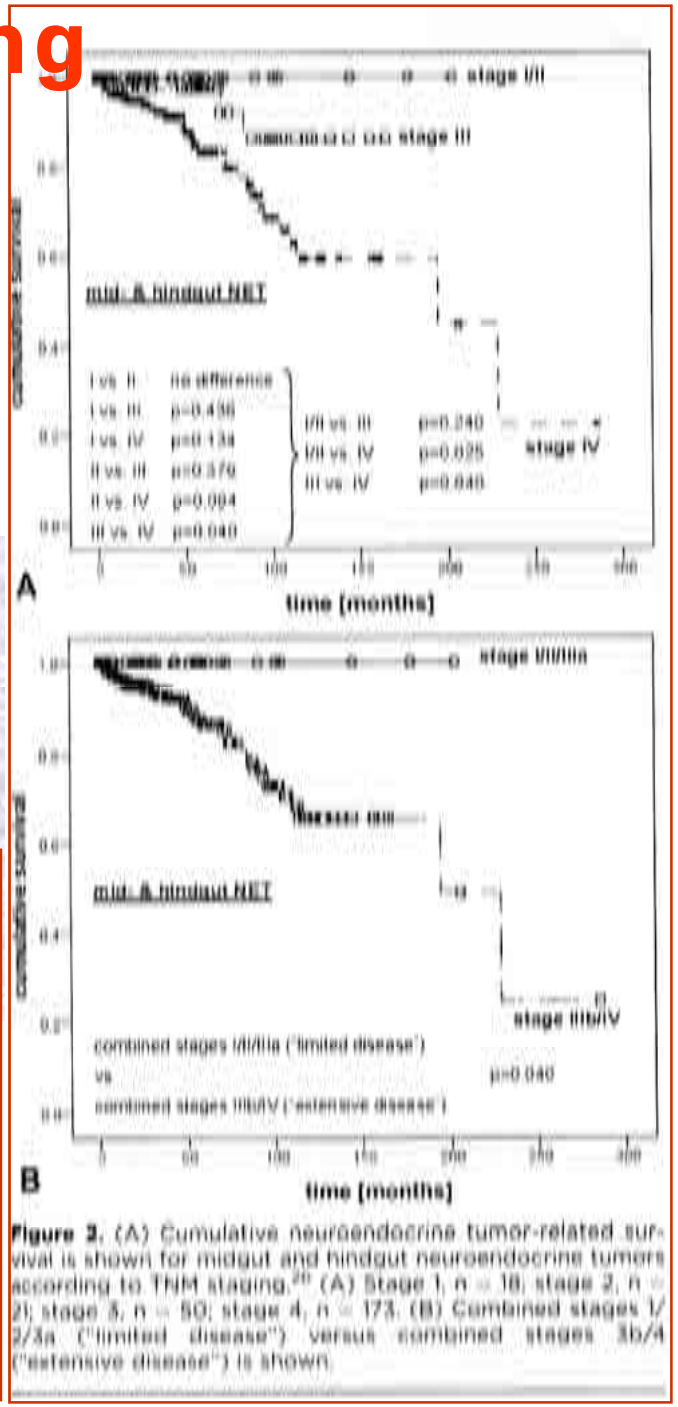
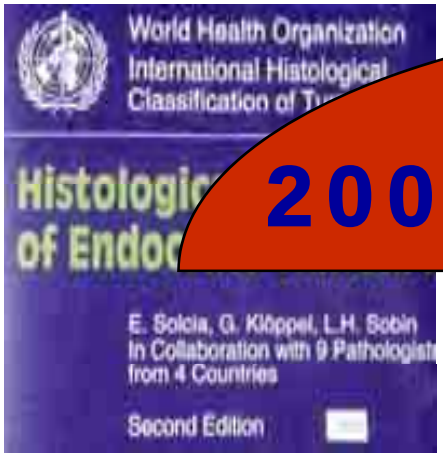


Figure 2. (A) Cumulative neuroendocrine tumor-related survival is shown for midgut and hindgut neuroendocrine tumors according to TNM staging.[29] (A) Stage 1, n = 18; stage 2, n = 21; stage 3, n = 50; stage 4, n = 173. (B) Combined stages I/2/3a ("limited disease") versus combined stages 3b/4 ("extensive disease") is shown.

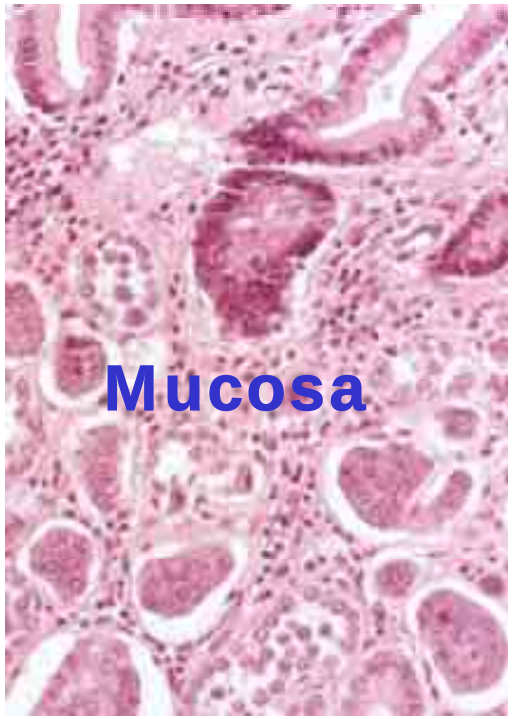


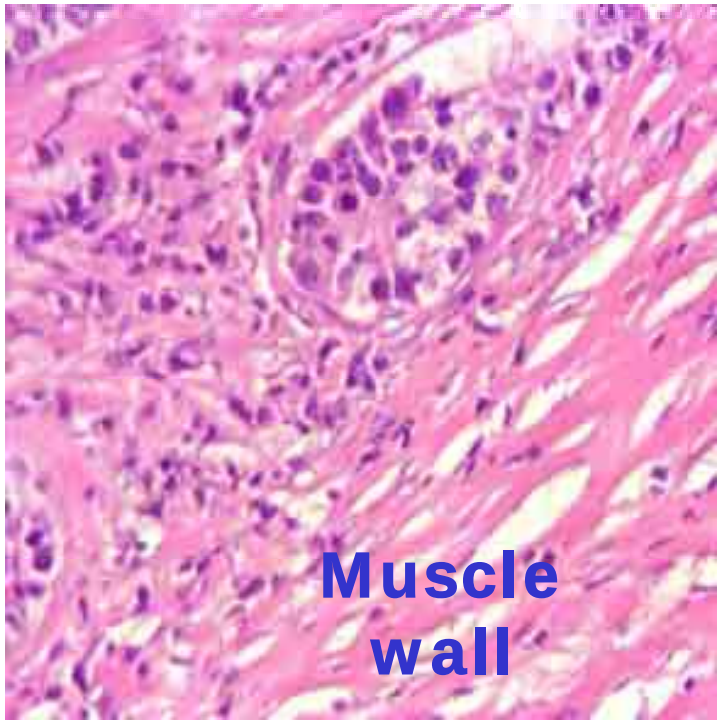
2000

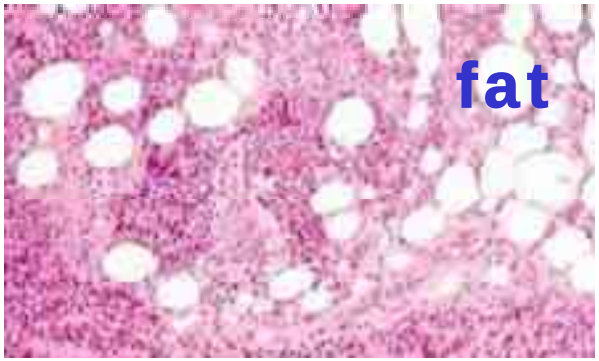
2010

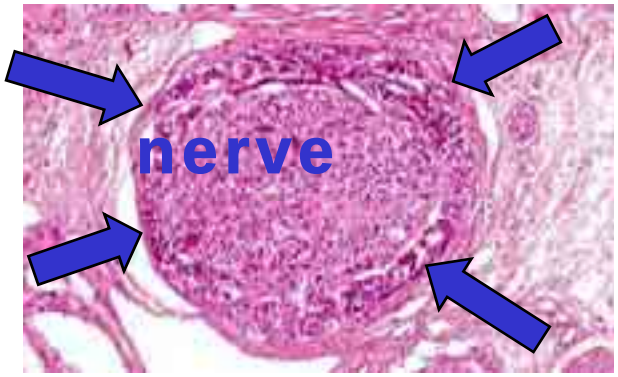
Same parameters

used for histotype (NET, WD/PDNEC)
now used for TNM stage









Neuroendocrine Neoplasms 2010 WHO Classification of the digestive System

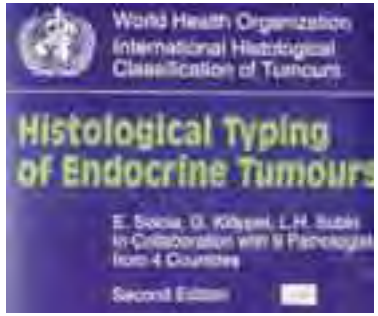
- **Working principles**
  - –"Neuroendocrine" defines peptide hormone-producing cells/tumours, sharing neural-endocrine markers
  - –"Neuroendocrine neoplasm" includes well and poorly differentiated tumours [NEN= NET + NEC]
- **Basic concept: All NENs have a malignant potential**

- Initially, NENs that were regarded as benign were not considered in the incidence data (eg, SEERS data).

- Now, all NENs have to be included because they are known to have malignant potential

OLD

3-TIER SYSTEM for NETs of the GI tract pancreas

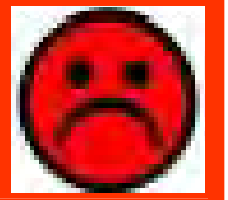


Well-differentiated endocrine tumor – Carcinoid

Well-differentiated endocrine tumor - Confined to pancreas

Well-differentiated endocrine carcinoma (malignant carcinoid) - Low grade malignant

Poorly differentiated endocrine carcinoma - High grade malignant



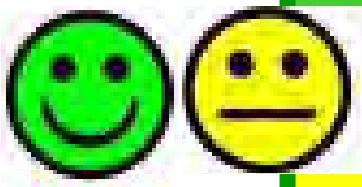
Mixed Exocrine-Endocrine carcinoma / MEEC

NEW

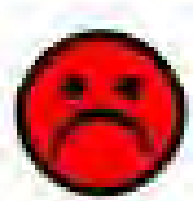
2-TIER SYSTEM for GEP-NENs [3 grades & 4 stages]

Neuroendocrine neoplasm (NEN) =

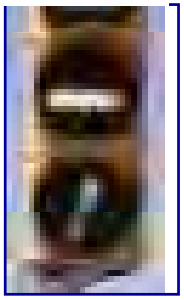
NE tumor + NE carcinoma + mixed tumors



Neuroendocrine tumor/NET (Carcinoid)
G1 or G2 TNM stage....

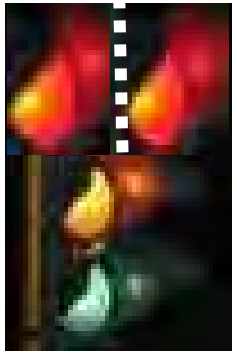


Neuroendocrine carcinoma / NEC (poorly differentiated, high grade malignant)
G3 TNM stage....



Mixed Adeno-Neuroendocrine carcinoma / MANEC

Bosman FT et al. WHO classification of tumors of the GI tract. IARC, Lyon, 2010.



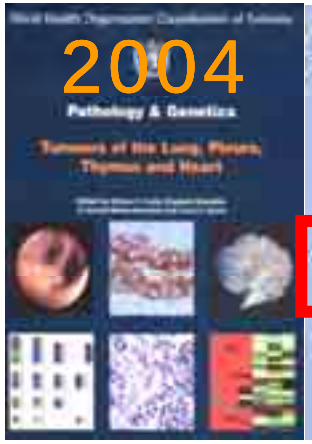
SPECTRUM OF LUNG NETs

typical carcinoid — rare

atypical carcinoid — very rare

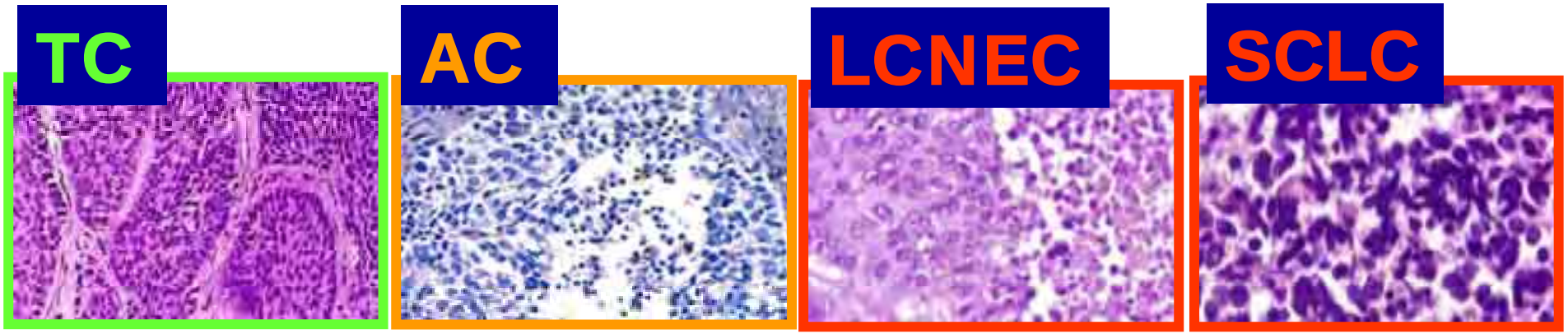
Small or Large cell NE carcinoma — common / rare

Most benign → Malignant

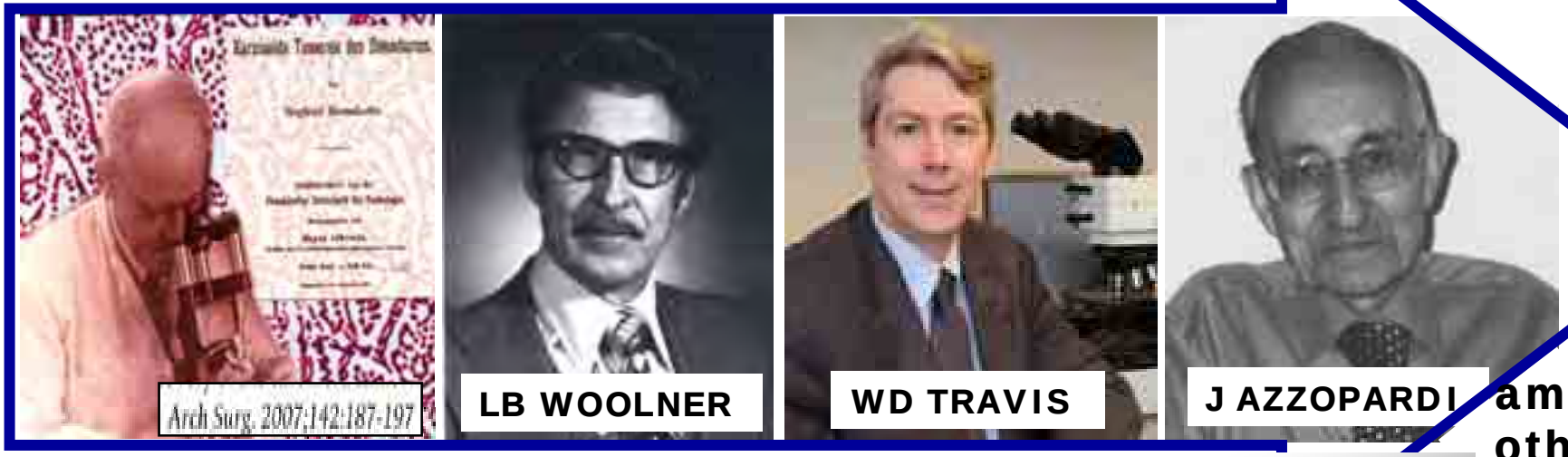


Malignant epithelial tumours

Squamous cell carcinoma	8070/3
Papillary	8052/3
Clear cell	8084/3
Small cell	8073/3
Basaloid	8083/3
Small cell carcinoma	8041/3
Combined small cell carcinoma	8045/3
Adenocarcinoma	8140/3
Adenocarcinoma, mixed subtype	8255/3
Acinar adenocarcinoma	8550/3
Papillary adenocarcinoma	8260/3
Large cell carcinoma	8012/3
Large cell neuroendocrine carcinoma	8013/3
Combined large cell neuroendocrine carcinoma	8013/3
Basaloid carcinoma	8123/3
Lymphoepithelioma-like carcinoma	8082/3
Clear cell carcinoma	8310/3
Large cell carcinoma with rhabdoid phenotype	8014/3
Pulmonary blastoma	8972/3
Carcinoid tumour	8240/3
Typical carcinoid	8240/3
Atypical carcinoid	8249/3



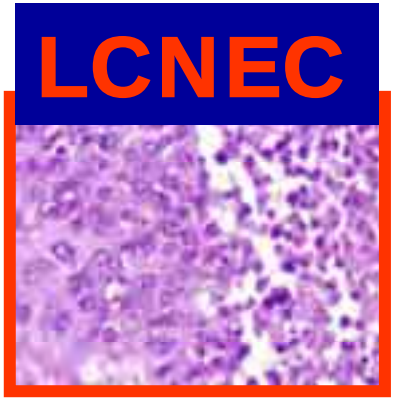
- Different & separate subtypes in the WHO
- Different epidemiology and pathology
- Different therapy & clinical behavior
- Different Authors.....

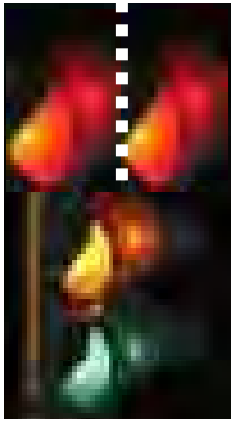


TC AC LCNEC SCLC

Small cell carcinoma
Combined small cell carcinoma

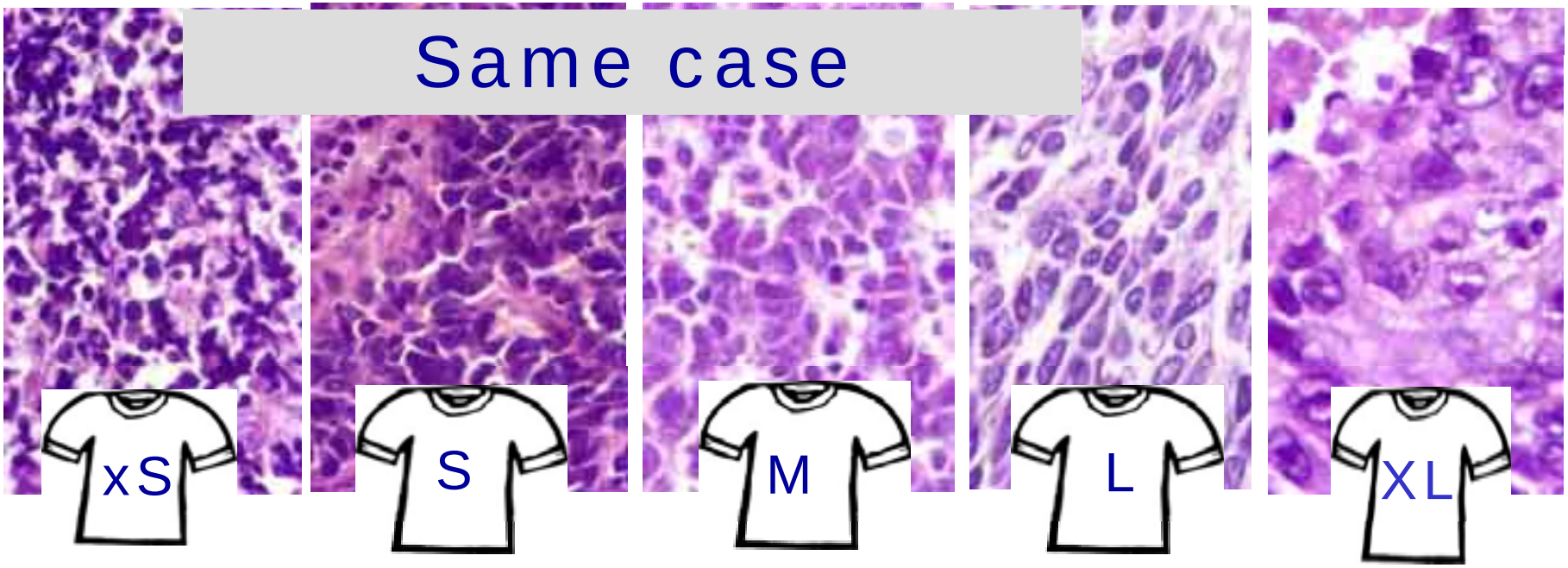
LCNEC





SCLC

Same case



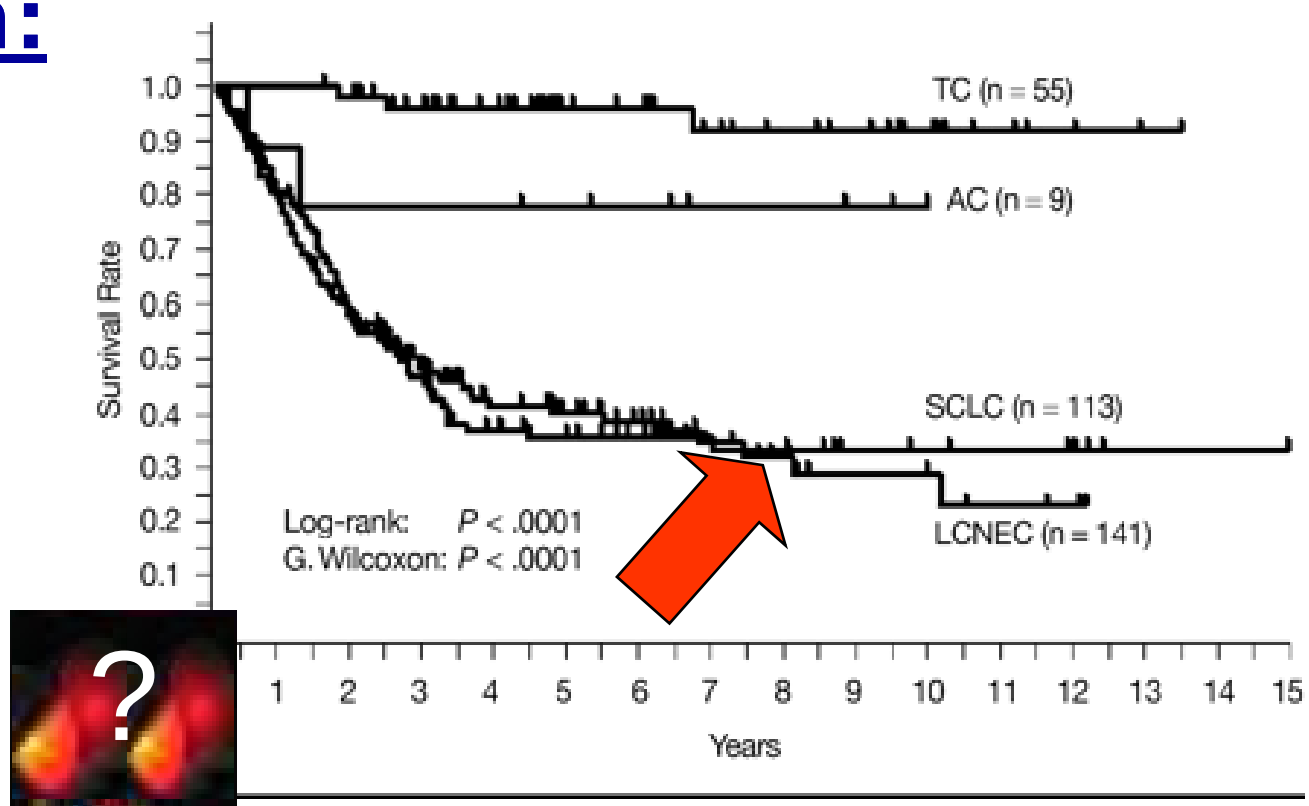
MIXED SMALL AND LARGE CELL CAs: does it matter?

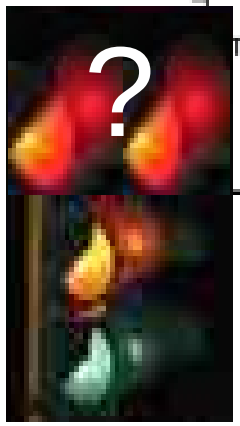
DISTINGUISHING SCLC FROM LCNEC: does it matter? NO !!!!!!!!!!

In addition:

- Similar behavior & survival.

- Similar therapy of LCNEC and SCLC





Asamura et al JCO 24, 70-76, 2006

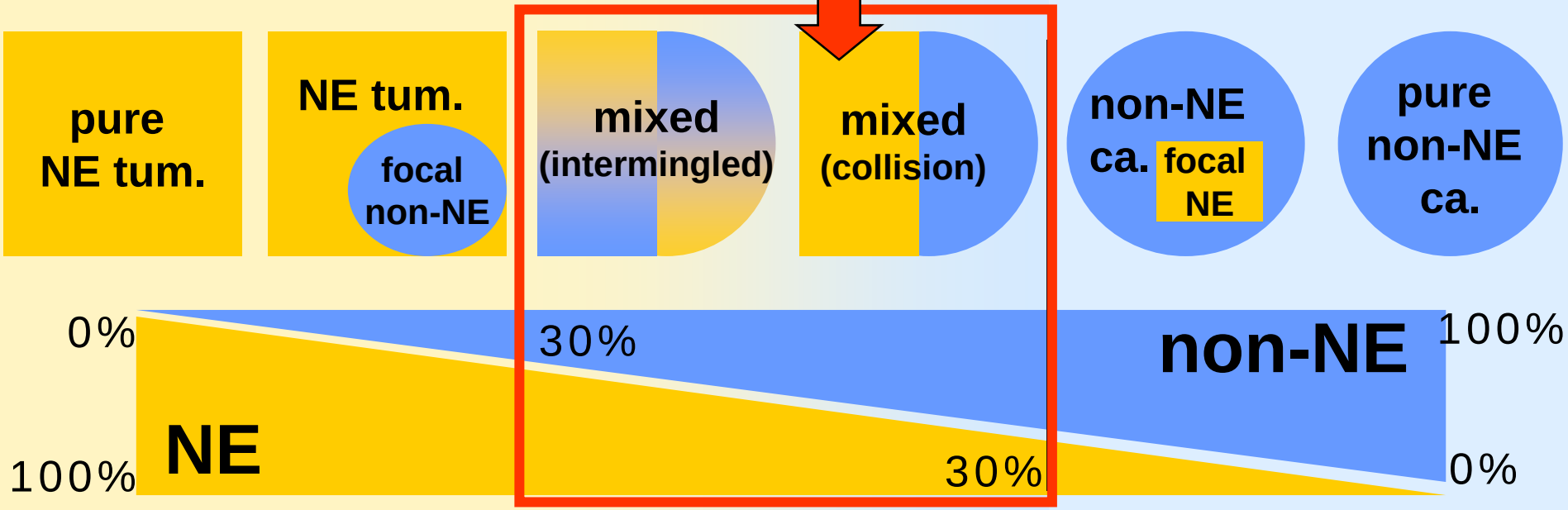
NEW 2010 WHO CLASSIFICATION

GEP-NENs CATEGORIES RECOGNIZED

1 NET G1-G2

2 NEC (G3)

3 mixed adeno-neuroendocrine carcinoma (MANEC)



Evolution of the concept of goblet cell carcinoid in the spectrum of mixed exocrine / NE carcinomas (MANEC)

1974 GCC: carcinoid with mucin production

<2010 GCC: Mixed exocrine / NE carcinoma

>2010 GCC: mucinous adenocarcino-ma (focal NE)

pure NE tum.

NE tum.

focal non-NE

mixed (intermingled)

mixed (collision)

non-NE ca.

focal NE

pure non-NE ca.

0%

100%

NE

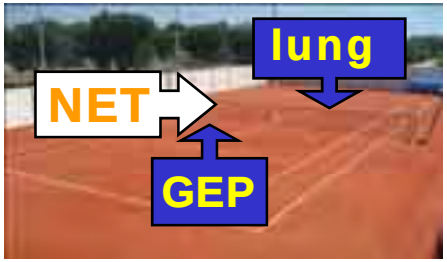
30%

30%

non-NE

100%

0%



SUMMARY

Differentiation

++ + -

LUNG

TYPICAL CARCINOID

ATYPICAL CARCINOID

SMALL CELL / LARGE CELL NE CARCINOMA

Combined carcinoma

GEP

NEUROENDOCRINE TUMOR G1 or G2

POORLY DIFF. NE CARCINOMA (small / large cell)

MANEC

Good Intermediate Poor

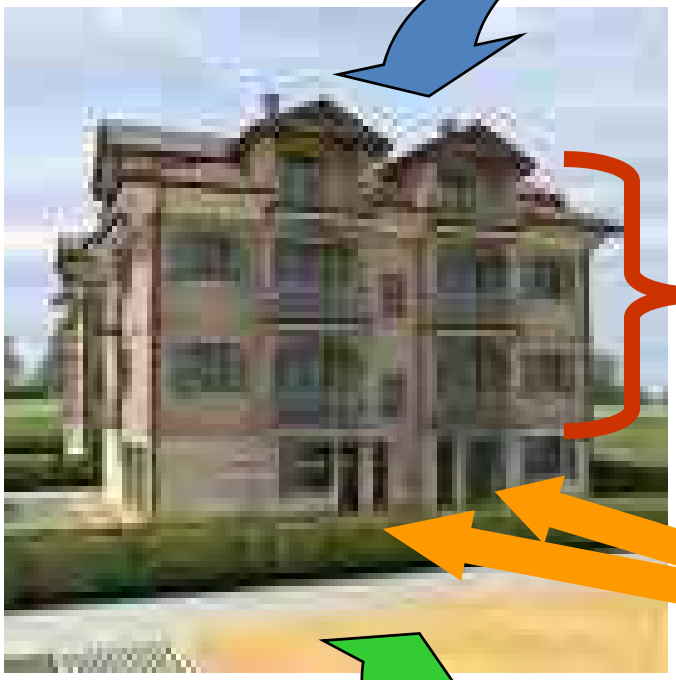
Prognosis

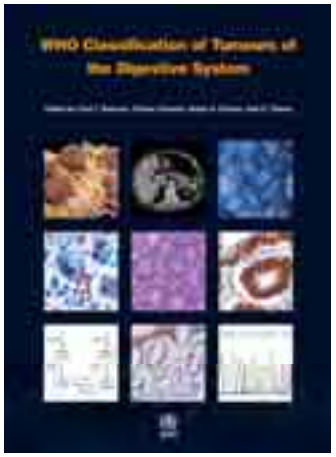
Big NEN house built step by step

4 Stages
3 Grades
2 Dx

GEP NENs

The model of a big "neuroendocrine" house





4 flats= Stage I-II-III-IV
→ TNM: size & invasion

3 floors= Grade 1-2-3 → mitoses & Ki67

2 stairs= NET vs NEC → structure + grade

1 court= NEN vs nonNEN
→ morphology & NE markers

NET pathology

- **Pathological classification, grading and TNM staging guidelines**
- **Diagnostic markers**
- **Prognostic & predictive markers**
- **Conclusion**

BIO-MARKERS

NO RELEVANT NEWS

romogranins
aptophysin
M (CD56)
NSE, VMAT
PGP9.5
Neurofilaments
HMW Cytokeratin

mones: calcitonin,
bombesin, insulin, glucagon,
somatostatin, gastrin, PP,
VIP, ACTH, serotonin,
ghrelin, cortistatin,
obestatin, secretagogin,...

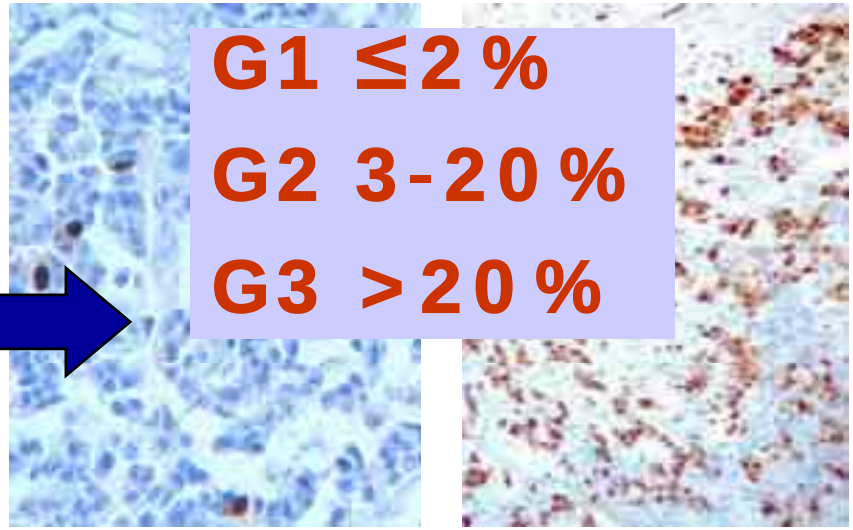
NET pathology

- **Pathological classification, grading and TNM staging guidelines**
- **Diagnostic markers**
- **Prognostic & predictive markers**
- **Conclusion**

Ki-67 proliferation index

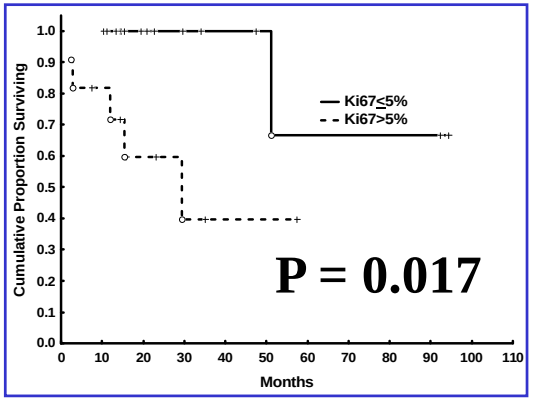
DIAGNOSTIC USE

→ Grading of GEP-NET

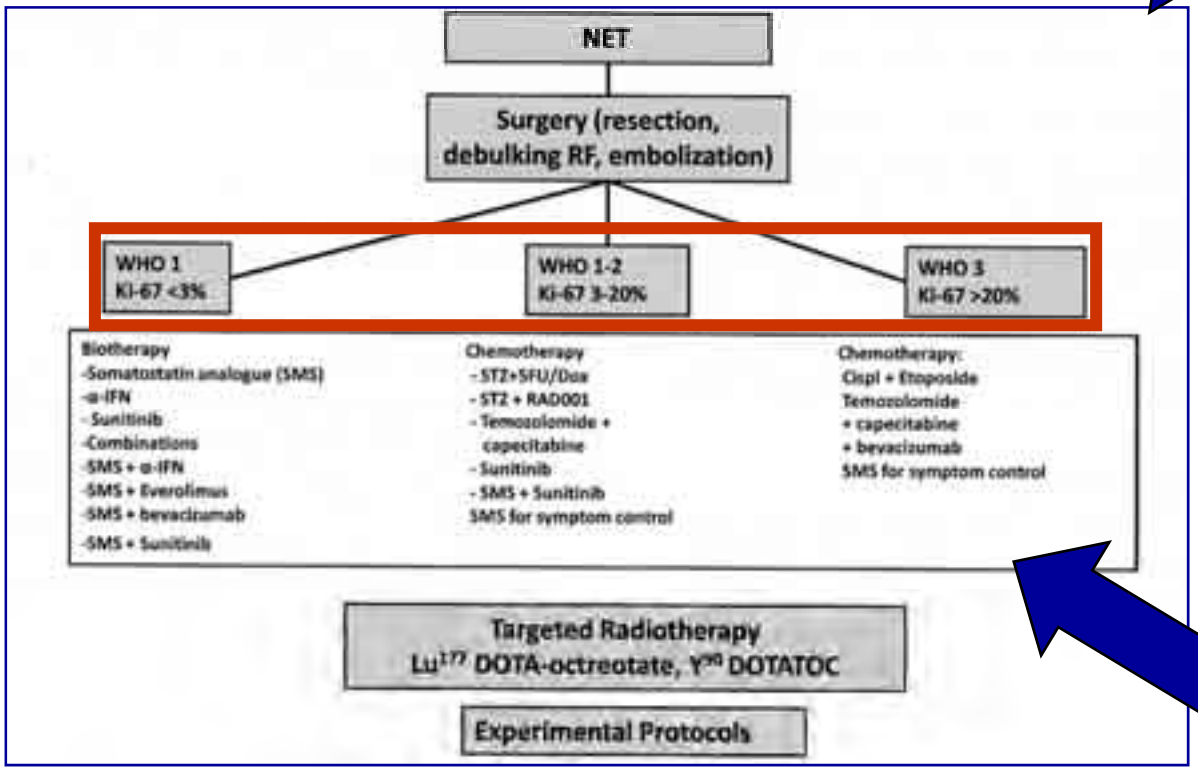


PROGNOSTIC USE

OS



Brizzi et al 2009



THERAPEUTIC ALGORITHM

EXAMPLES OF PREDICTIVE MARKERS IN NETS

1

SOMATOSTATIN RECEPTORS

2

mTOR PATHWAY MOLECULES

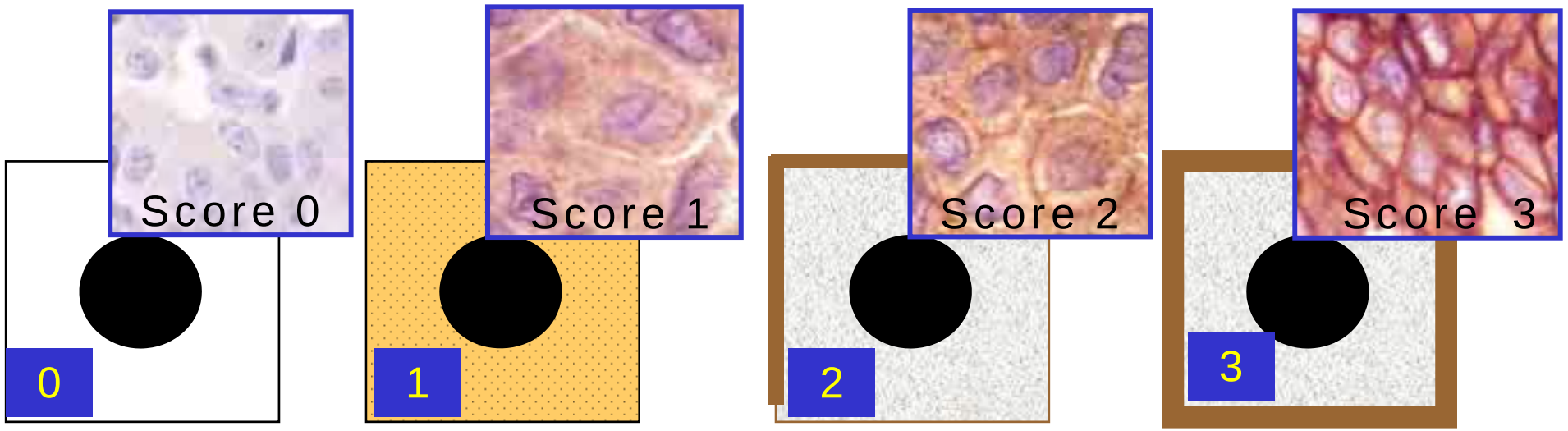
1

Proposed score for SSTR2 IHC interpretation

Somatostatin receptor type 2A immunohistochemistry in neuroendocrine tumors: a proposal of scoring system correlated with somatostatin receptor scintigraphy

Marco Volante[1], Maria Pia Brizzi[1], Annagiulia Faggiano[2], Stefano La Rosa[3], Ida Kaps[1], Anna Ferrero[1], Gelsomina Mansueto[4], Luisella Righi[1], Silvana Gascoini[5], Carlo Capella[3], Gaetano De Rosa[2], Luigi Dogliotti[1], Annamaria Colao[2] and Mauro Papotti[1]

Mod Pathol 2007;20:1172-82

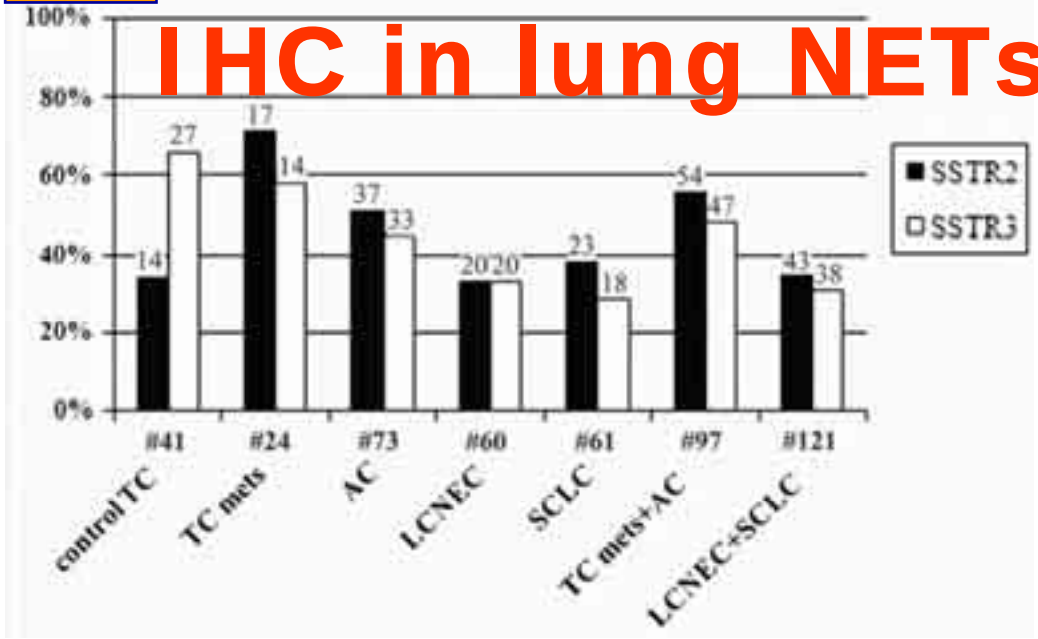


50% 54% 87% 94%

CONCORDANCE WITH OCTREOSCAN DATA

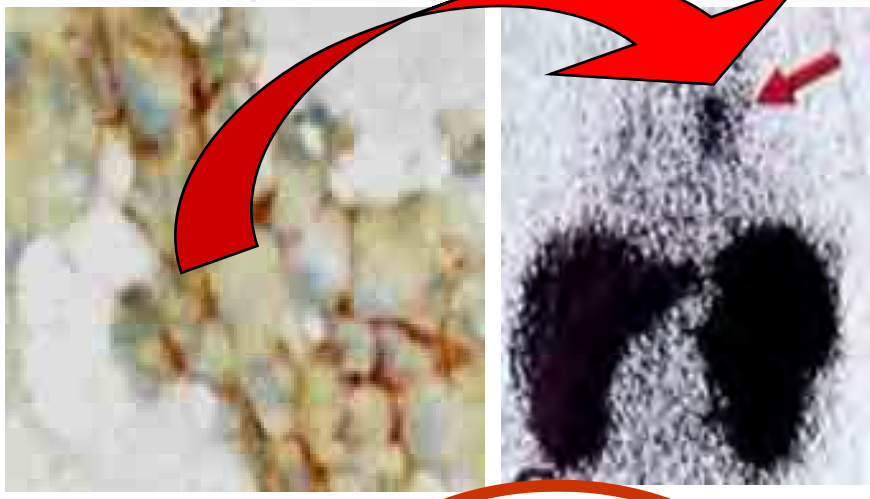
1 REPORTED NEW GOOD ANTIBODIES

IHC in lung NETs



original article **Ann Oncol 2010;21:548-55.**

Somatostatin receptor tissue distribution in lung neuroendocrine tumours: a clinicopathologic and immunohistochemical study of 218 'clinically aggressive' cases



	SSTR2A	SSTR3	2A + 3
Concordance	64% (18/28)	50% (14/28)	71% (20/28)
"sensitivity"	70%	48%	80%
"specificity"	71%	57%	42%

2 Targeting mTOR

Clinical data

Octreotide and the mTOR Inhibitor RAD001 (Everolimus) Block Proliferation and Interact with the Akt-mTOR-p70S6K Pathway in a Neuro-Endocrine Tumour Cell Line

Neuroendocrinology 2008;87:168–181

Simona Gr… Chrysanthia A. Leontiou[a] Antônio Ribeiro de Oliveira Jr.[a, e] Paolo Dalino[a] Nabila Salahuddin[a] Márta Korbonits[a] Ashley B. Grossman[a]

Efficacy of RAD001 (Everolimus) and Octreotide LAR in Advanced Low- to Intermediate-Grade Neuroendocrine Tumors: Results of a Phase II Study

James C. Yao, Alexandria T. Phan, David Z. Chang, Robert A. Wolff, Kenneth Hess, Sanjay Gupta, Carmen Jacobs, Jeannette E. Mares, Andrea N. Landgraf, Asif Rashid, and Funda Meric-Bernstam

VOLUME 26 · NUMBER 26 · SEPTEMBER 10 2008

JOURNAL OF CLINICAL ONCOLOGY

Everolimus for Advanced Pancreatic Neuroendocrine Tumors

James C. Yao, M.D., Manisha H. Shah, M.D., Tetsuhide Ito, M.D., Ph.D., Catherine Lombard Bohas, M.D., Edward M. Wolin, M.D., … M.D., … M.D., Tomas Hans, Ph.D., Jaromir Lincy, M.Sc., David Lebwohl, M.D., and Kjell Öberg, M.D., Ph.D., for the RADIANT-3 Study Group

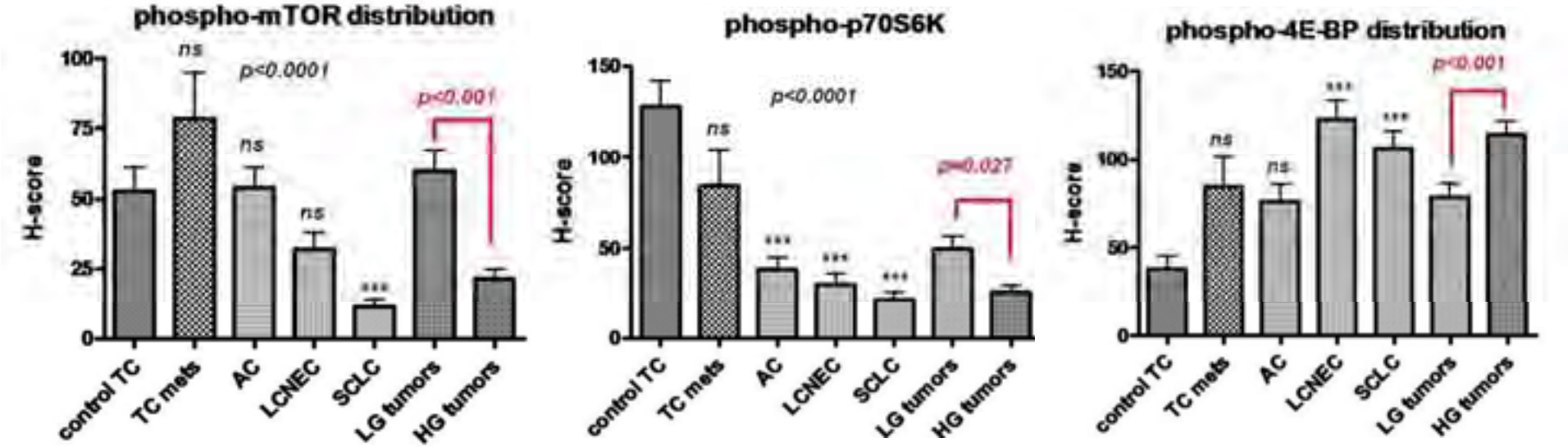
N ENGL J MED 364;6 NEJM.ORG FEBRUARY 10, 2011

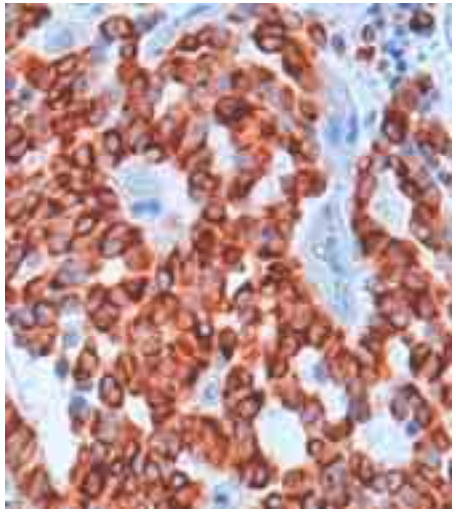
Everolimus 10 mg increases median PFS from 4.6 to 11 mos in advanced PanNET

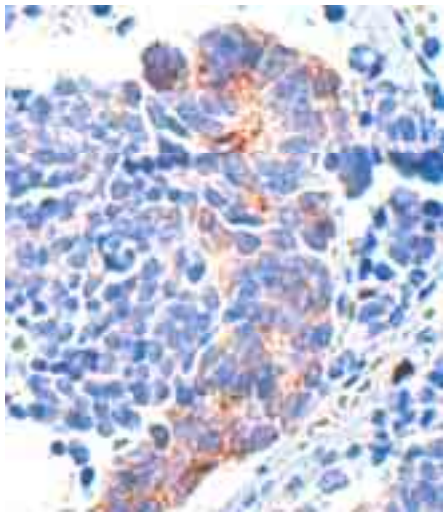
QUESTION 1: which profiles of mTor pathway activation in NETs (eg lung)?

2

IHC expression of phospho-mTOR and of p70S6K &4EBP-1 in 258 resected lung NETs (40 control TC, 24 TC with mets, 73 AC, 60 LCNEC & 61 SCLC).







*** = p <0.0001

Mammalian target of rapamycin signaling activation patterns in neuroendocrine tumors of the lung

Luisella Righi, Marco Volante, Ida Rapa, Veronica Tavaglione, Frediano Inzani[1], Giuseppe Pelosi[2] and Mauro Papotti

Endocrine-Related Cancer (2010) 17 977–987

NET pathology

- **Pathological classification, grading and TNM staging guidelines**
- **Diagnostic markers**
- **Prognostic & predictive markers**
- **Conclusion**

Pathology report of NETs

When assessing individual NENs / NETs:

- Define **malignancy** based on a 2 (or 4) tier system
- Define differentiation **grade** (including Ki-67 proliferative index)
- Assess the TNM **stage**
- Define the **hormonal** production, if any
- Identify pathological parameters of aggressiveness or **prognostic factors, if relevant**
- ***Upon request***, assess **predictive factors** useful for target therapy (e.g. somatostatin receptors, mTor pathway molecules, thymidilate synthase, other target enzymes, ...)

Open issues

- Get used to the new 2010 classification and terminology of WD GEP-NETs
- Mixed endocrine – exocrine tumors (MANEC)
- Apply tumor grade (mitoses & Ki-67)
- Controversial staging for appendiceal NETs
- Use of predictive markers of response to therapy

- Classification of other NETs (pheochro-mocytoma, medullary thyroid carcinoma, parathyroid, Merkel cell carcinoma)

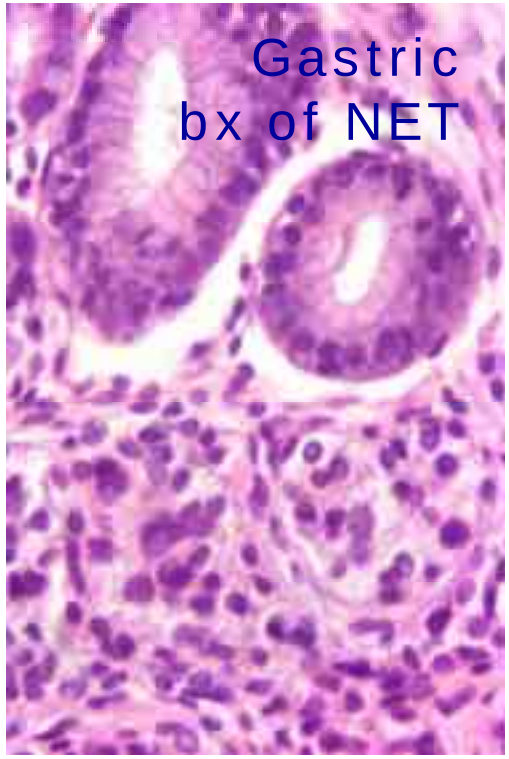
Non cerco casa ma consulto l'immobiliare "per motivi di servizio"

Thank you!!!

University of Turin
Medical School at
San Luigi Hospital,
Orbassano, Torino

Is a “preoperative” diagnosis possible?

- Yes: definition of NE phenotype.
- Often possible to distinguish WD from PD NE carcinoma.
- Pathological stage not defined.
- Difficult to define primary tumor in the presence of metastases, only.
- Prognostic factors identifiable but not 100% reliable.
- Problems on scant material. Which tissue?



Mitotic index evaluation

-Count mitoses in 50 fields

-Express mitotic rate as number per 10 high power fields (2 mm^2)

Options to quantify Ki67 index

–**Manual** count of a 500-2000 tumors cells and calculate the percentage of positive nuclei

–**Digital** image analysis system to measure the percentage of positive nuclei

–Approximate **“eyeballed” estimate** of the percentage of positive nuclei

-The result should be reported as a single percentage reflecting the ***average of the regions counted*** (not a range of values).

TNM staging of GEP-NENs

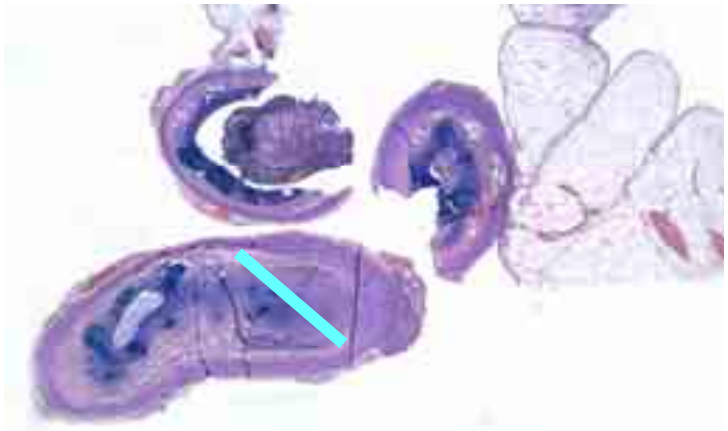
- **SITE-specific**
- **Based on depth of invasion and size**

ENETS: 2006/2007
Rindi, Klöppel, Ahlman,Wiedenmann. TNM staging of foregut, midgut and hindgut (neuro)endocrine tumours: A consensus proposal including a grading system. *Virchows Archiv.* 2006;449:395-401, and 2007;451:757-762.

UICC/AJCC: 2009
Sobin, Gospdarowicz, Wittekind. *TNM Classification of Malignant Tumours*. Wiley-Blackwell. 7th Edition; 2009.

- *Similar TNM classifications:*
  - Stomach
  - Duodenum
  - Jejunum/ileum
  - Colon/rectum
- *Different TNM classification*
  - Appendix
  - Pancreas

Staging of appendiceal NETs



	ENETS TNM	UICC/AJCC TNM
T1	<1 cm; invasion of muscularis propria	T1a: ≤1cm T1b: >1– 2 cm
T2	**≤2 cm; and <3 mm invasion of subserosa/ mesoappendix**	**>2–4 cm; or invasion of cecum**
T3	**>2 cm; or >3 mm invasion of subserosa/ mesoappendix**	**>4 cm; or invasion of ileum**
T4	invasion of peritoneum/ other organs	invasion of peritoneum/ other organs

Grading & staging of PanNETs

Pancreatic endocrine tumors: improved TNM staging and histopathological grading permit a clinically efficient prognostic stratification of patients

Aldo Scarpa[1,2], William Mantovani[3], Paola Capelli[1], Stefania Beghelli[1,2], Letizia Boninsegna[4], Rossella Bettini[4], Francesco Panzuto[5], Paolo Pederzoli[4], Gianfranco delle Fave[5] and Massimo Falconi[4]

MODERN PATHOLOGY (2010), 1–10

Pancreatic endocrine tumors are rare diseases and devising a clinically effective prognostic stratification of patients is a major clinical challenge. This study aimed at assessing whether the tumor-node-metastasis (TNM)-based staging and proliferative activity-based grading recently proposed by the European NeuroEndocrine Tumors Society (ENETS) have clinical value. TNM was applied to 274 patients with histologically diagnosed pancreatic endocrine tumors operated from 1991 to 2005, with last follow-up at December 2007. According to World Health Organization (WHO) classification, 246 were well-differentiated neoplasms (51 benign, 56 uncertain behavior, 139 carcinomas) and 28 poorly differentiated carcinomas. Grading was based on Ki67 immunohistochemistry. Survival analysis not only ascertained the prognostic value of the TNM system but also highlighted that in the absence of nodal and distant metastasis, infiltration and tumor dimensions over 4 cm had prognostic significance. T parameters were then appropriately modified to reflect this weakness. The 5-year survival for modified TNM stages I, II, III and IV were 100, 93, 65 and 35%, respectively. Multivariate analysis identified TNM stages as independent predictors of death, in which stages II, III and IV showed a risk of death of 7, 29 and 58 times higher than stage I tumors ($P<0.0001$). Ki67-based grading resulted an independent predictor of survival with cut-offs at 5 and 20%. In conclusion, WHO classification assigns clinically significant diagnostic categories to pancreatic endocrine tumors that need prognostic stratification by applying a staging system. The ENETS–TNM provides the best option, but it requires some modifications to be fully functional. The modified TNM described in this study ameliorates the clinical applicability and prediction of outcome of the ENETS–TNM; it (i) assigns a risk of death proportional to the stage at the time of diagnosis, and (ii) allows a clinically based staging of patients, as the T parameters as modified permit their clinical-radiological recognition. Ki67-based grading discerns prognosis of patients with same stage diseases.

NEN house

4 stages …

3 Grades ….

2 Diagnoses …

START

1 NE neoplasia

Example of an ileal tumor

T3 N0

G2

NET

NEN