

Corso Residenziale
di Formazione
per Giovani Medici

13-15 Febbraio 2014
Hotel Europa Bologna

AME-FADOL



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Santa Maria
della Misericordia
di Udine

SOC di Endocrinologia e
Malattie del Metabolismo

Direttore Dr. Franco Grimaldi

Tumori neuroendocrini

Gruppo A - Gruppo B - Sabato 15 febbraio (ore 8.30-10.30)

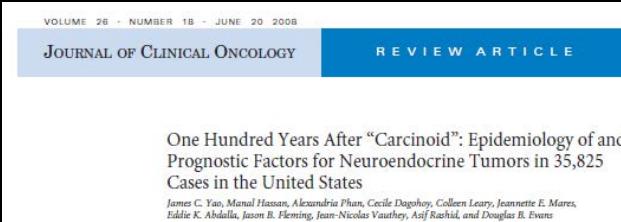
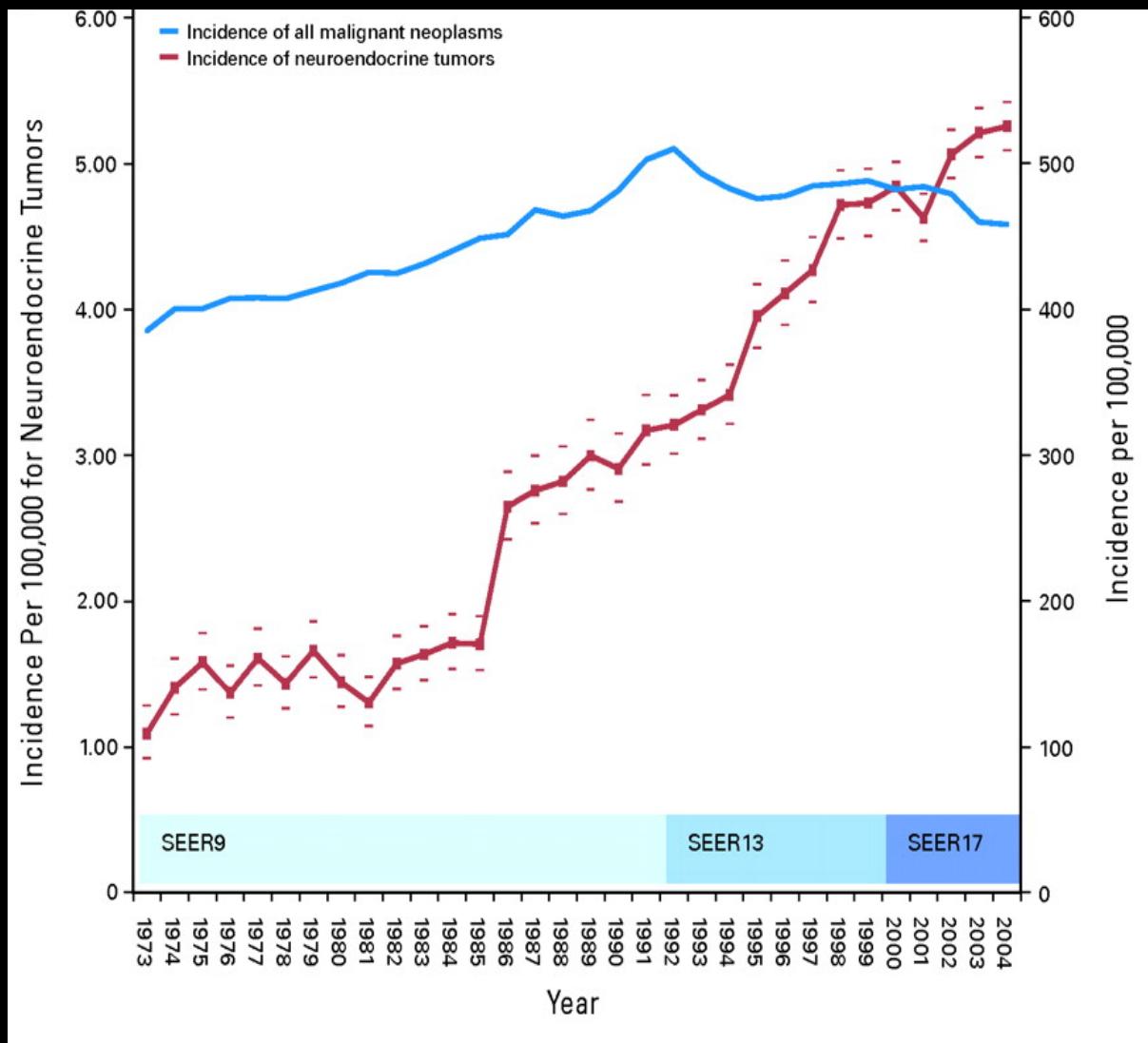
Tumori neuroendocrini Inquadramento e classificazione

Franco Grimaldi

Ai sensi dell'art. 3.3 del Regolamento applicativo dell'Accordo Stato-Regioni 05.11.2009, dichiaro che negli ultimi due anni ho avuto i seguenti rapporti anche di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

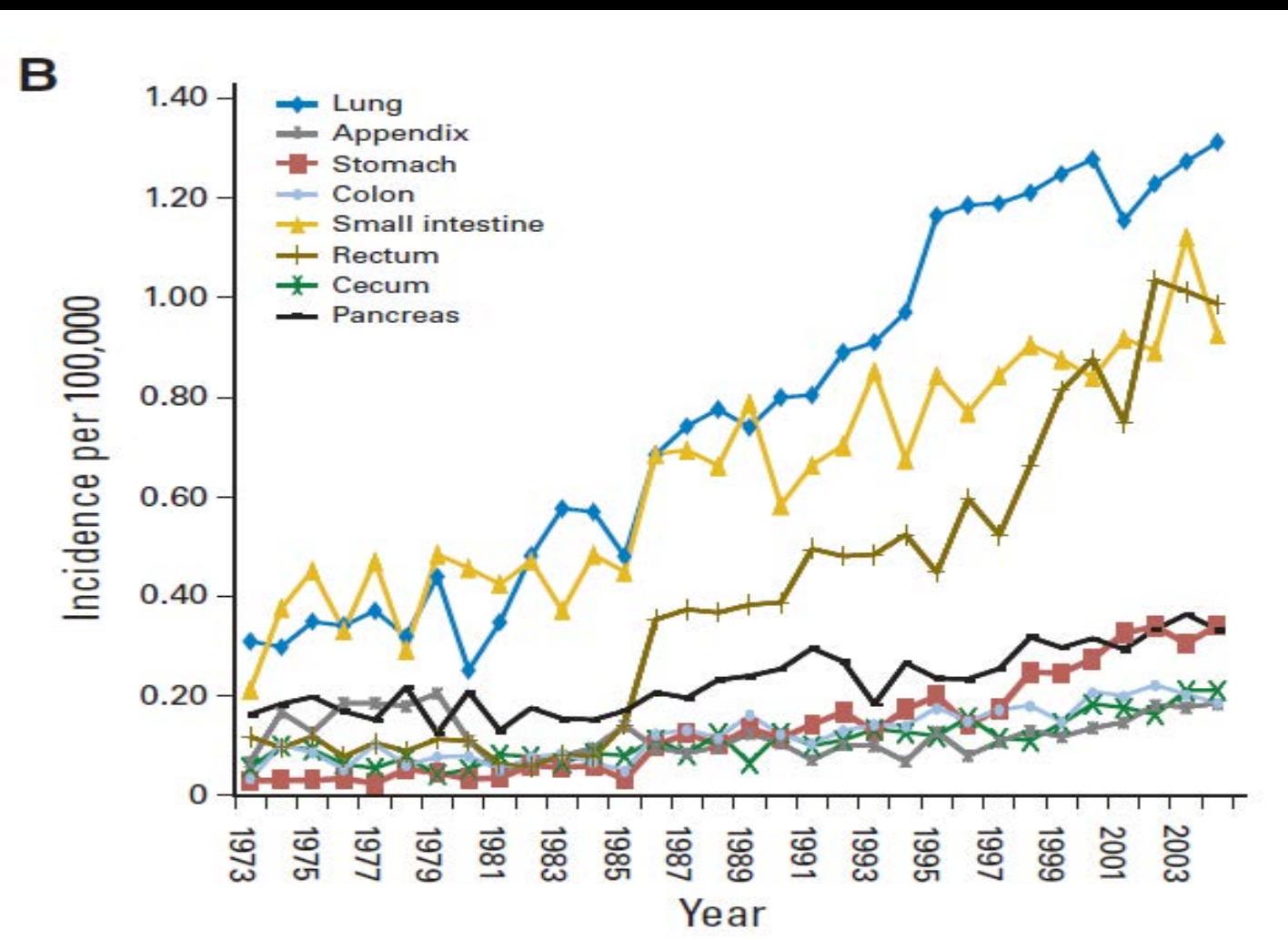
- Amge Dompe'
- Ipsen
- Italfarmaco
- Merck
- Novartis

Annual age-adjusted incidence of NETs



A 500%
increase!

Increased incidence of neuroendocrine tumors in USA (SEER 1973-2005)



Steprise increase of GEP-NETs: possible causes

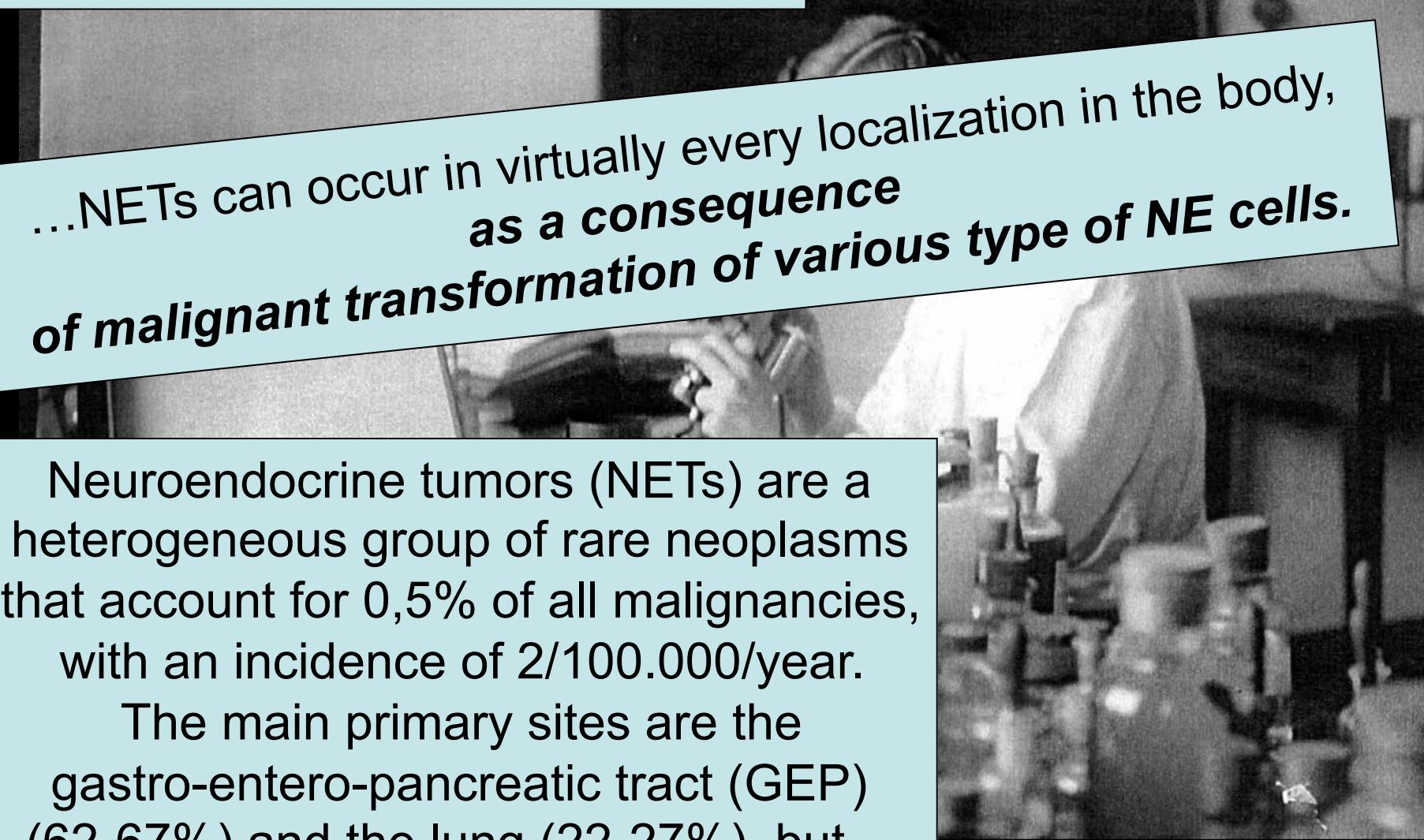
- Diffusion of endoscopic techniques
- Screening campaigns against GUT malignancies
- Progress in cyto-histological diagnosis
- Increased awareness of the existence of this group of neoplasms
- Specific and accurate high-resolution imaging techniques.

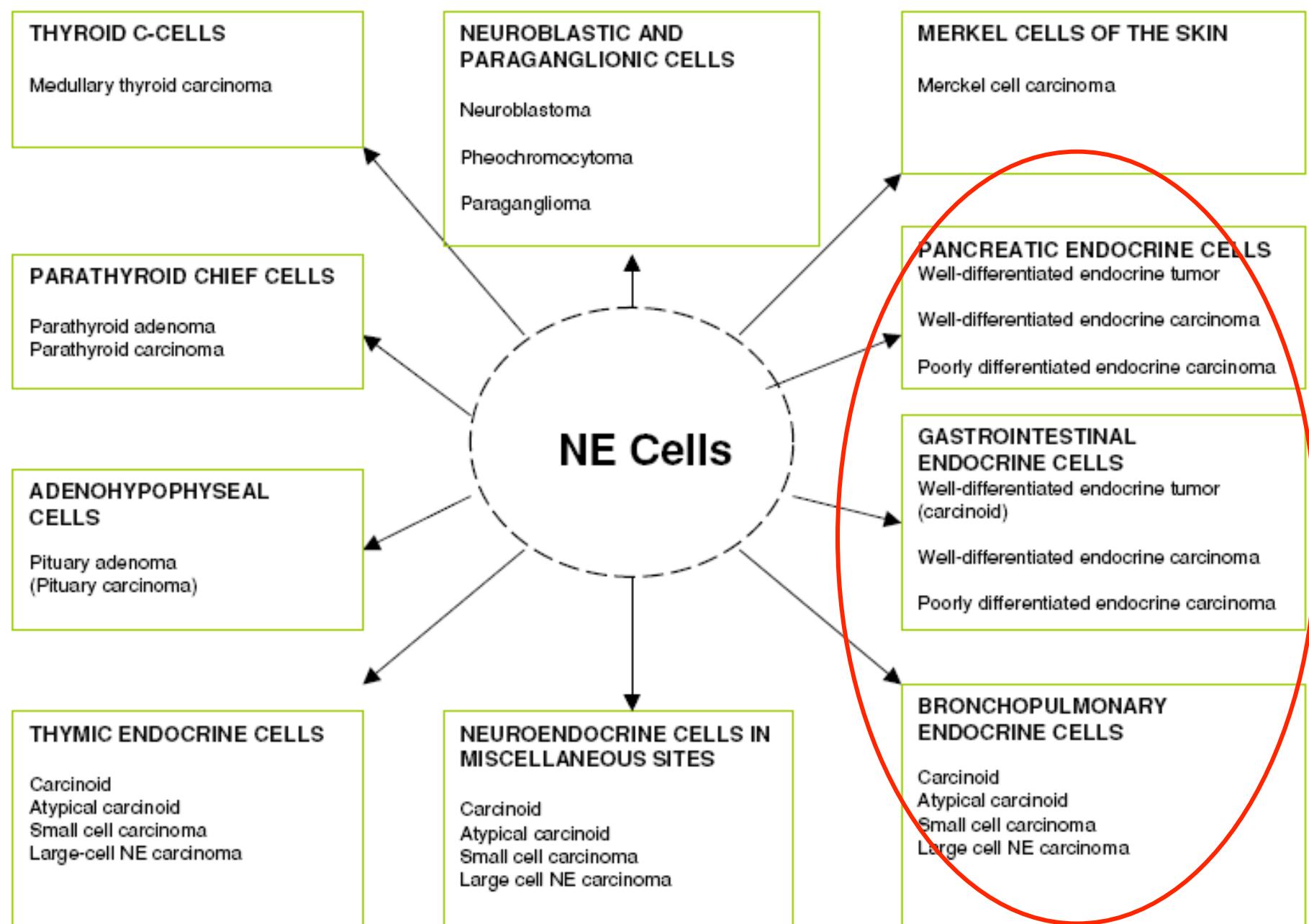
Definition

...NETs can occur in virtually every localization in the body,
*as a consequence
of malignant transformation of various type of NE cells.*

Neuroendocrine tumors (NETs) are a heterogeneous group of rare neoplasms that account for 0,5% of all malignancies, with an incidence of 2/100.000/year.

The main primary sites are the gastro-entero-pancreatic tract (GEP) (62-67%) and the lung (22-27%), but...





Tumori neuroendocrini: gruppo eterogeneo di neoplasie in termini di:

- ✓ Classificazione/nomenclatura
- ✓ Sede
- ✓ Presentazione clinica
- ✓ Aspetti macroscopici
- ✓ Aspetti microscopici
- ✓ Comportamento biologico

Neuroendocrine Tumors: the scaring nomenclature

neuroendocrine

GEP-NET

Oat cell carcinoma

Intermediate grade NET

Malignant carcinoid

APUDoma

High grade neuroendocrine carcinoma

Pancreatic endocrine neoplasm

Carcinoid tumor

Well differentiated neuroendocrine carcinoma

Neuroendocrine carcinoma

Poorly differentiated endocrine carcinoma

Islet cell tumor

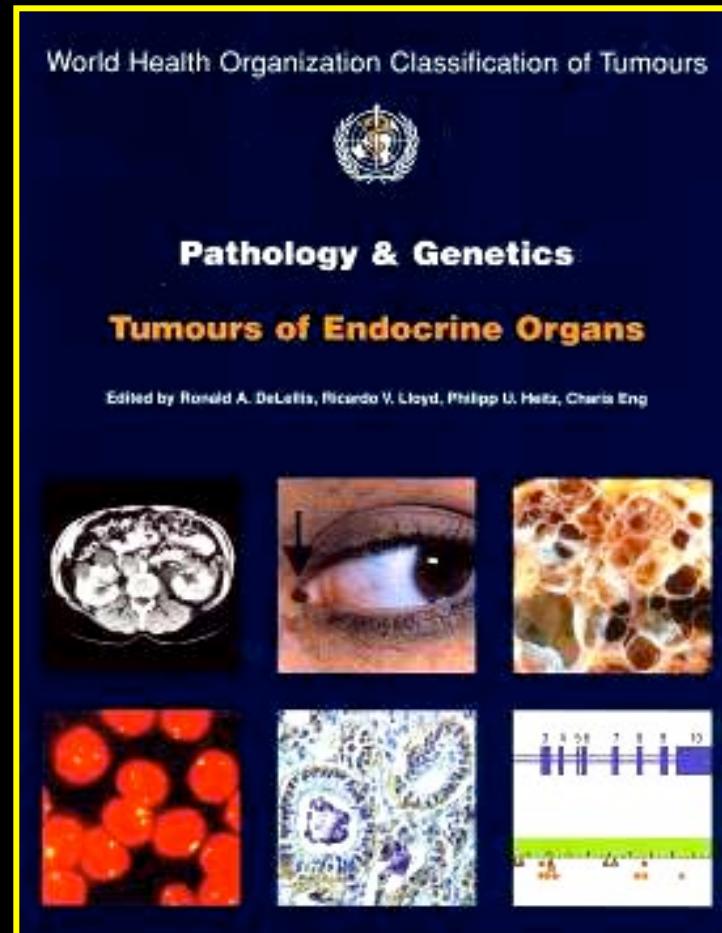
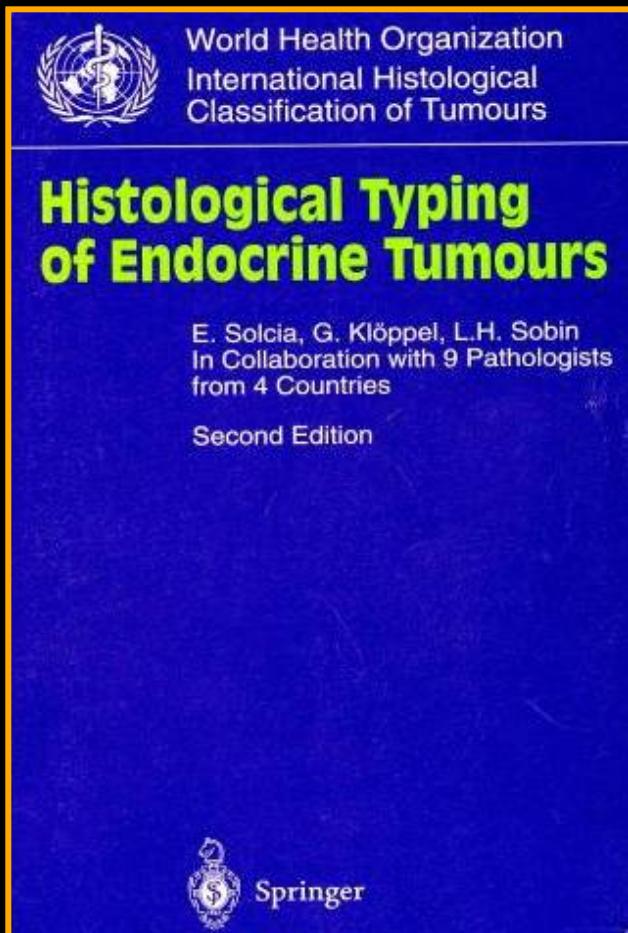
Small cell carcinoma
Atypical carcinoid tumor

Large cell neuroendocrine carcinoma

Ruolo della istologia

- ✓ riconoscere le diverse condizioni secondo criteri riproducibili
- ✓ fornire informazioni a carattere prognostico
- ✓ fornire informazioni a carattere predittivo

Classificazione Istologica dei NET



Classificazione WHO 2000 dei Tumori Endocrini GEP

Well-differentiated endocrine tumor
- benign/uncertain behavior



Well-differentiated endocrine carcinoma
- Low grade malignant



Poorly differentiated endocrine carcinoma
- High grade malignant



Mixed Exocrine-Endocrine carcinoma / MEEC

WHO 2000: Criticisms

- Stage-related information mixed with grading system
- Complicated clinical-pathological classification schemes
- The category “uncertain behaviour” may puzzle clinicians
- Use of the term “carcinoid” with its incorrect benign connotation.

WHO 2000: what need to be clarified

- **Differentiation:** extent to which neoplastic cells resemble their non-neoplastic counterparts
- **Grade:** defines the inherent biologic aggressiveness of the tumor
- **Staging:** defines tumor progression (organ confined, locally advanced, nodal or distant metastases).

Grade vs. Stage in NETs

- Both are prognostically relevant
- May be independent

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. Scoazec · B. Wiedenmann ·
and all other Frascati Consensus Conference
participants

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ORIGINAL ARTICLE

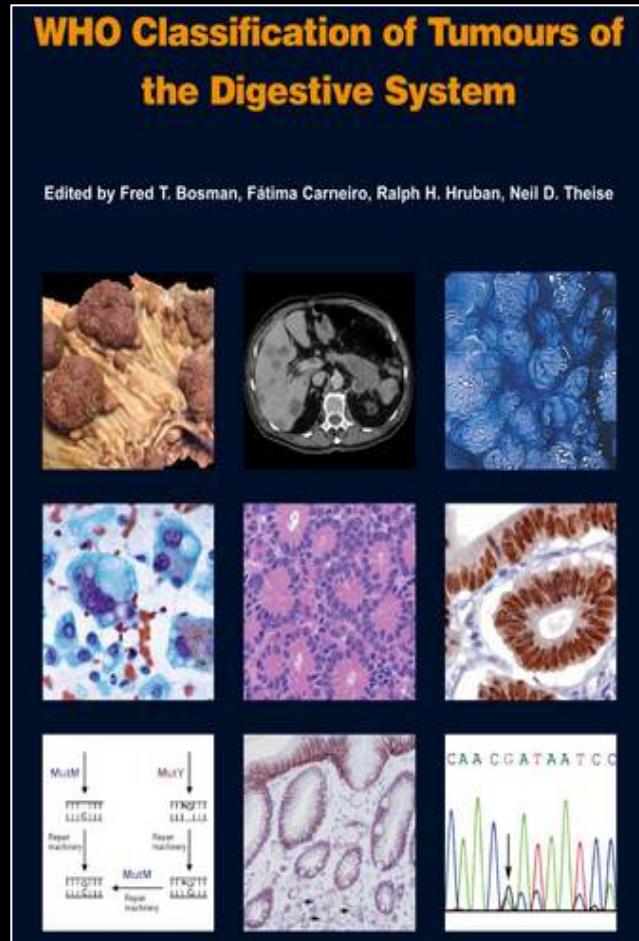
TNM staging of midgut and hindgut (neuro) endocrine tumors: a consensus proposal including a grading system

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

WHO 2010

- The term *neuroendocrine* is adopted to indicate the expression of neural markers in neoplastic cells (>30%) with otherwise exquisitely endocrine properties and phenotype.
- Neuroendocrine tumor and neuroendocrine neoplasia are synonymous

Classificazione WHO 2010 dei tumori del sistema digestivo

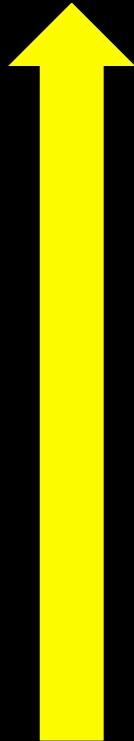


✓ Principi generali

- “**Neuroendocrine**”: termine che definisce la produzione di peptidi ormonali e la co-espressione di marcatori neurali ed endocrini
- “**Neuroendocrine neoplasm**” include lesioni sia bene sia scarsamente differenziate.

✓ **Tutte le neoplasie neuroendocrine (NEN) sono potenzialmente maligne**

Neoplasie Neuroendocrine (NEN): approccio diagnostico “a step”

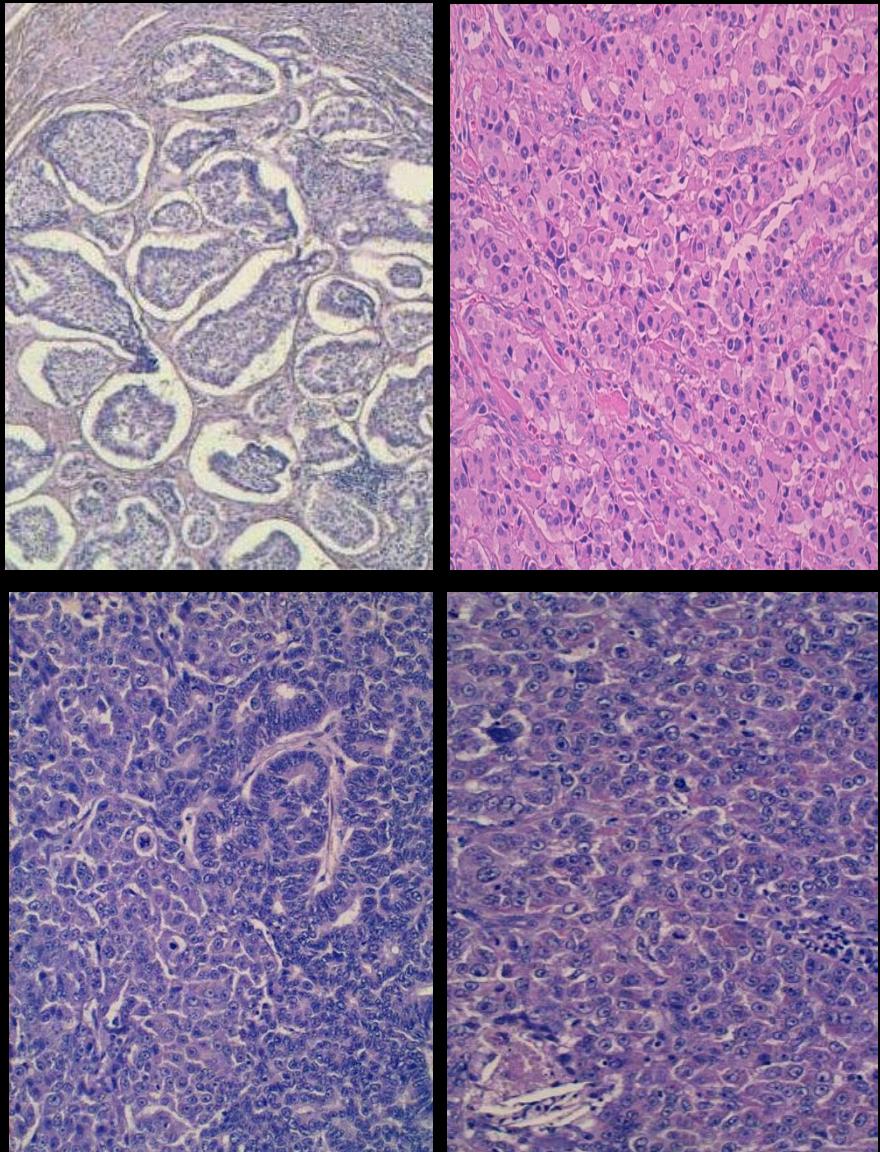


- 1) Diagnosi di NEN**
- 2) NET vs NEC → struttura**
- 3) Grading 1-2-3 → indice mitotico & Ki67**
- 4) Stadio TNM I-II-III-IV → dimensioni e invasività**

Diagnosi di NEN → morfologia & NE markers

Aspetti morfologici dei NEN:

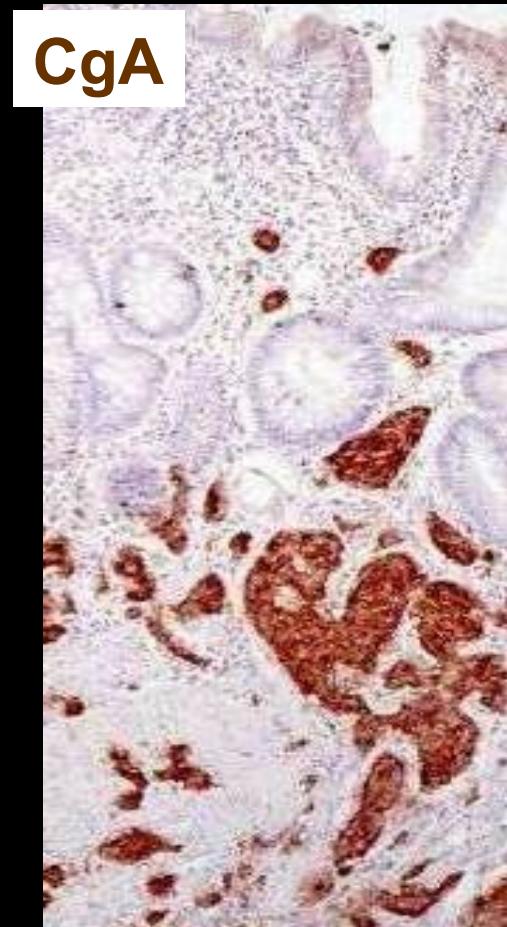
- ✓ Insulare
- ✓ Trabecolare
- ✓ Ghiandolare
- ✓ Poco differenziato



Marcatori immunoistochimici nei NEN

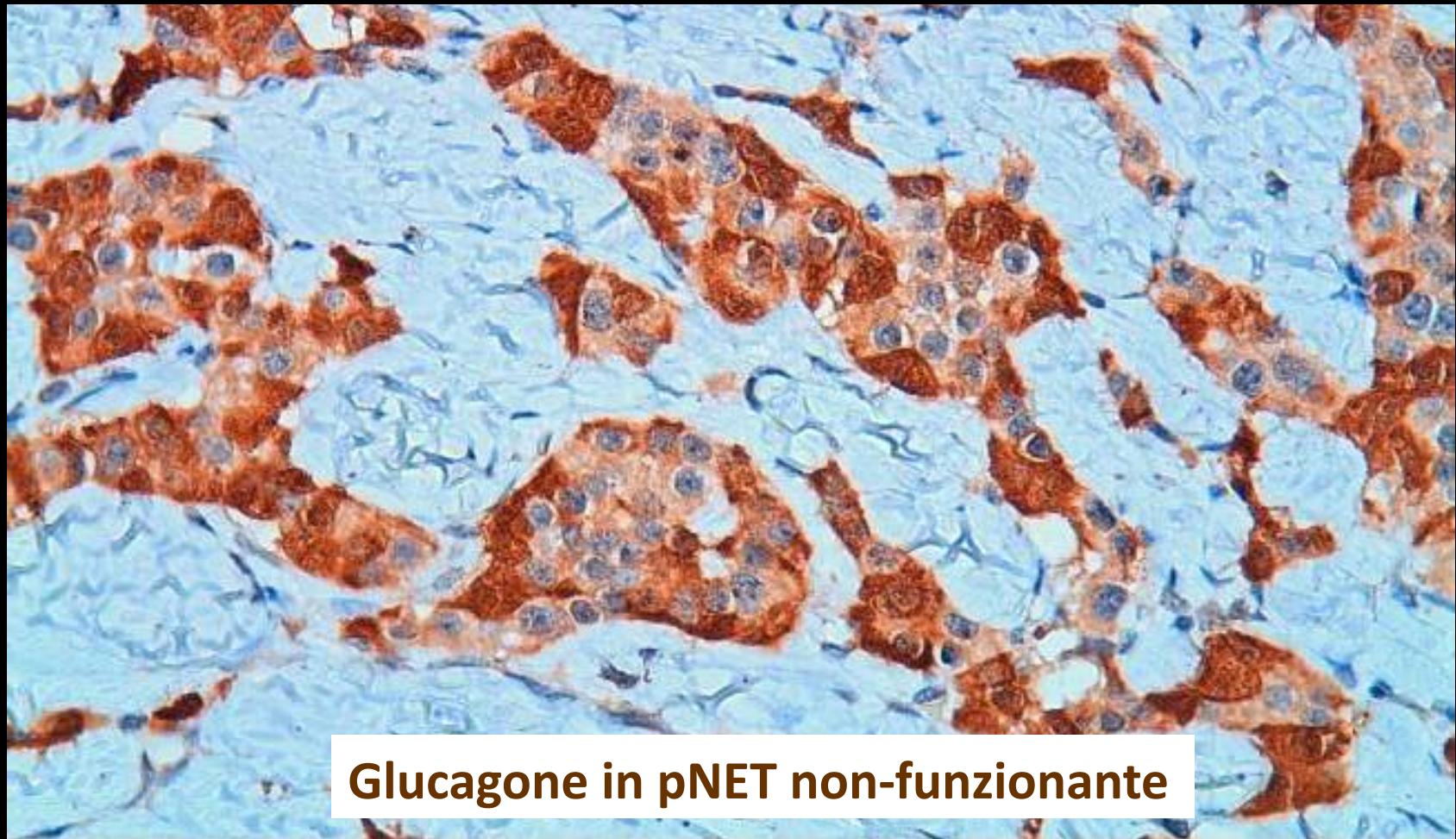
Marcatori pan-endocrini

- ✓ Citosolici: **NSE**
- ✓ Associati ai granuli secretori: **Cromogranina A**
- ✓ Associati alle vescicole sinaptiche: **Sinaptofisina**
- ✓ Filamenti intermedi (**NF, CK HMW**)
- ✓ Molecole di adesione (**N-CAM**)



Marcatori immunoistochimici nei NEN

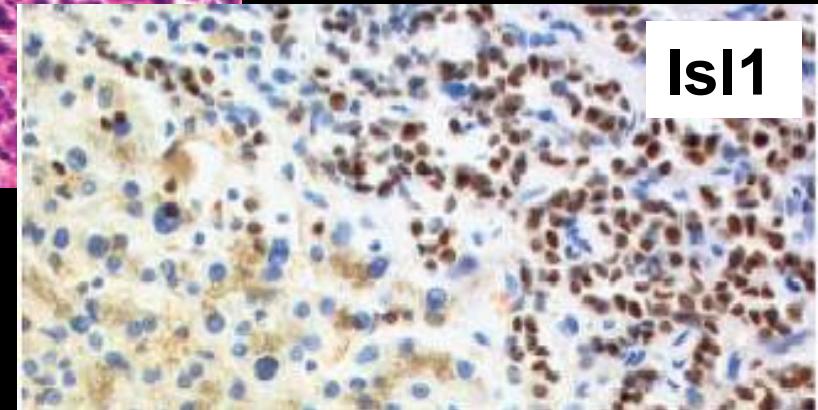
Produzione ormonale



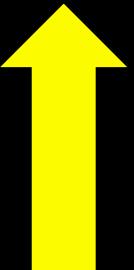
Marcatori immunoistochimici nei NEN

Definizione di origine

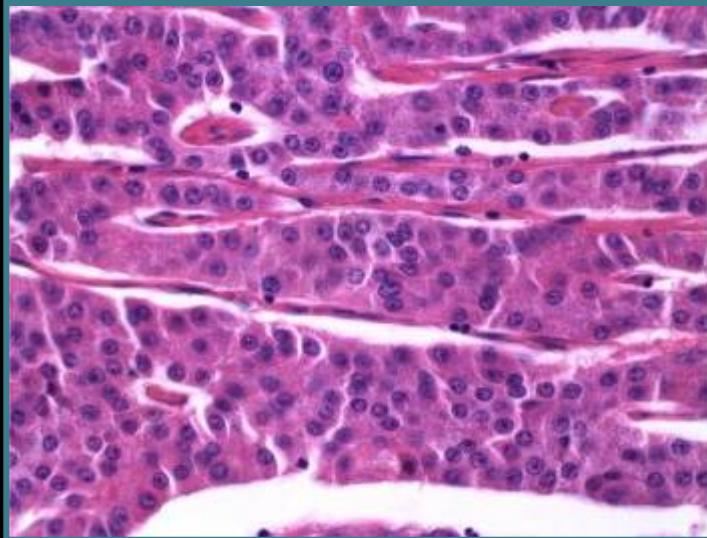
Islet 1 (Isl1)
come marcator
di origine
pancreatica



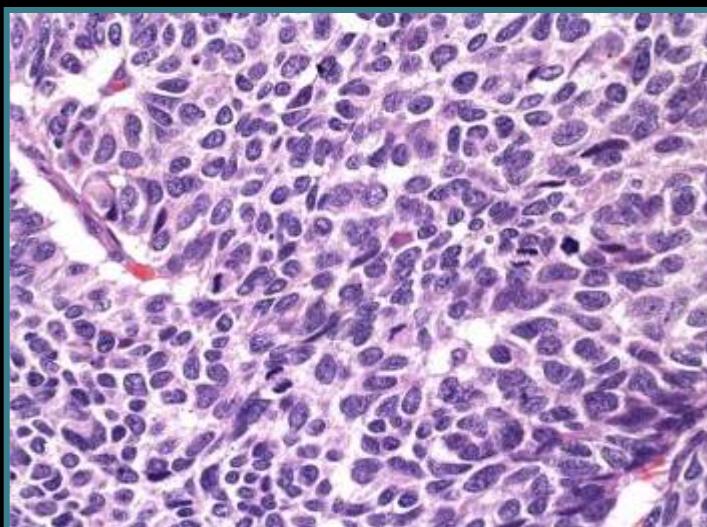
Neoplasie Neuroendocrine (NEN): Approccio diagnostico “a step”

- 1) Diagnosi di NEN**
 - 2) NET vs NEC → struttura**
 - 3) Grado 1-2-3 → mitosi & Ki67**
 - 4) Stadio TNM I-II-III-IV → dimensione ed invasività**
- 

Classificazione WHO 2010 del sistema digestivo



**Neuroendocrine tumor/
NET**



**Neuroendocrine
carcinoma / NEC**

WHO: 2000 vs 2010

WHO 2000

**Well-differentiated
endocrine tumour (WDET)**

**Well-differentiated
endocrine carcinoma
(WDEC)**

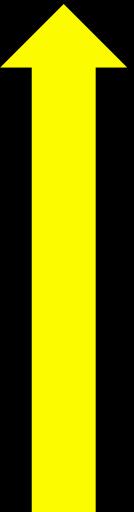
**Poorly differentiated
endocrine carcinoma/small-
cell carcinoma (PDEC)**

WHO 2010

TUMORE VS. CARCINOMA



Neoplasie Neuroendocrine (NEN): Approccio diagnostico “a step”

- 
- 1) Diagnosi di NEN**
 - 2) NET vs NEC → struttura + grado**
 - 3) Grado 1-2-3 → mitosi & Ki67**
 - 4) Stadio TNM I-II-III-IV → dimensione ed invasività**

WHO 2010

Grading



ATTIVITÀ PROLIFERATIVA



Conta
Mitotica



Frazione
proliferativa

Ki67 Labeling Index of NETs

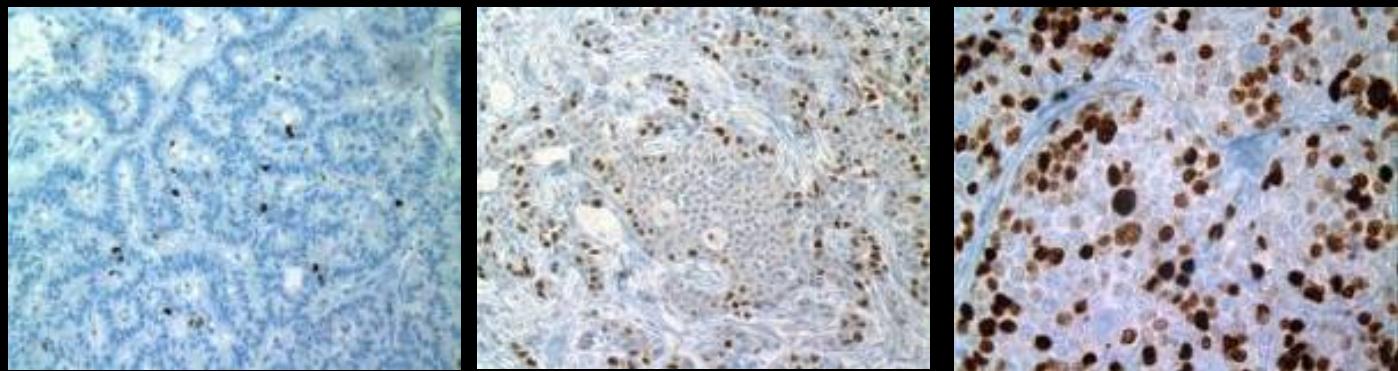
- Strong predictor of prognosis
- Basis for grading systems
- Correlates with mitotic index
- Sharp separation of well differentiated from poorly differentiated neuroendocrine neoplasms.

Ekeblad S. et all. (2008) Clinical Cancer Research 14 (23) 7798-7803

Jamali M, Chetty R. (2008) Endocr Pathol 19(4): 282-288

Grading dei GEP-NEN secondo ENETS/WHO/AJCC

Grade	G1	G2	G3
Ki67 index	≤ 2	3–20	>20
MI	<2	2-20	>20

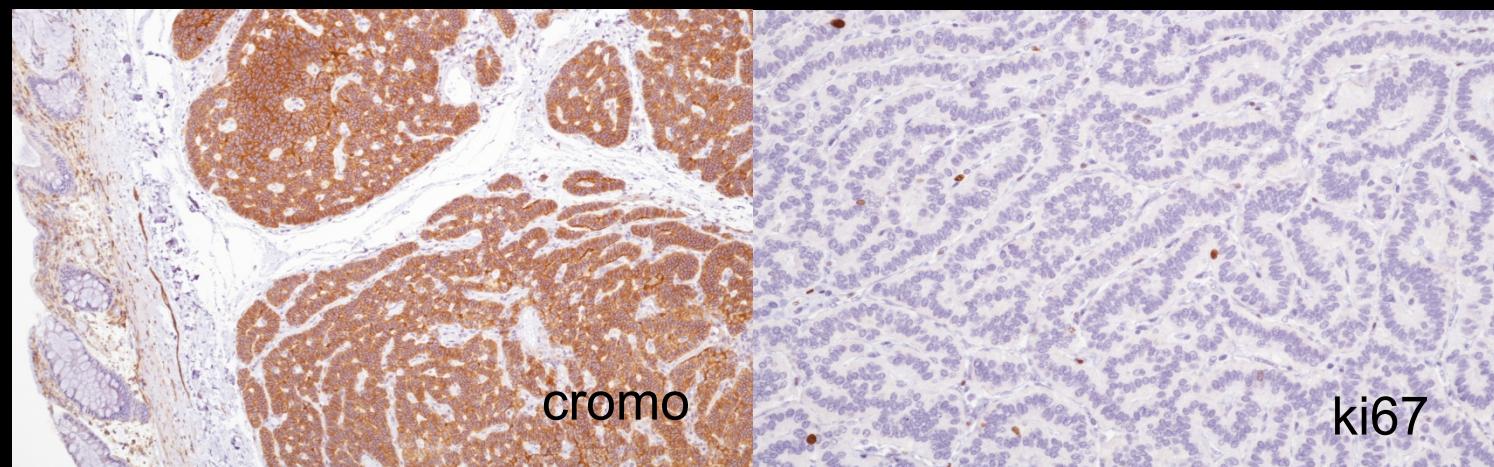
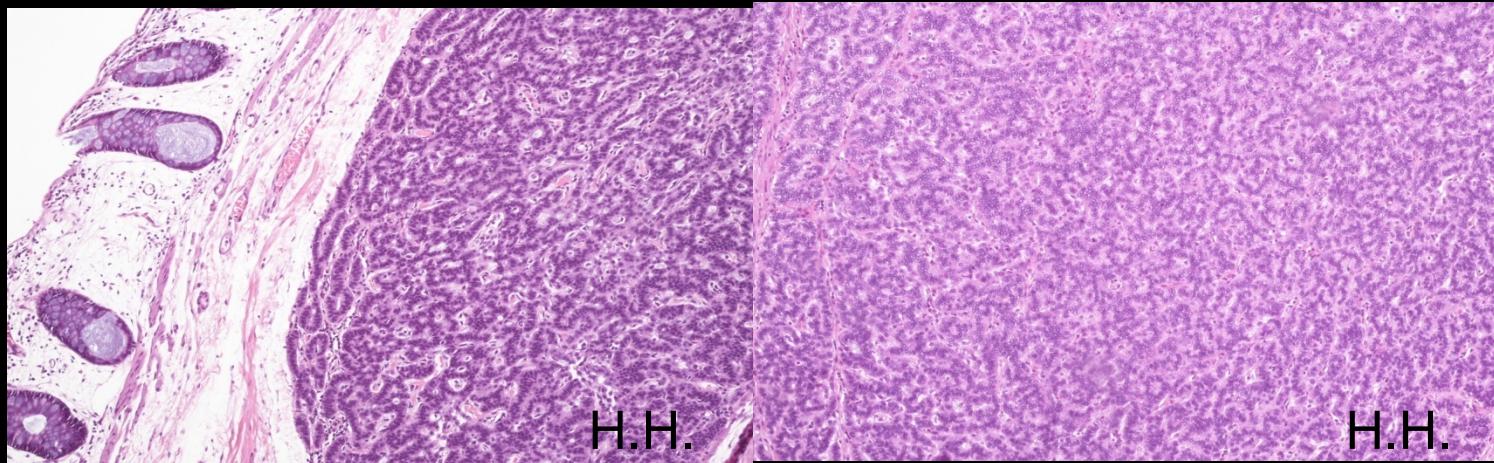


1. Rindi G, et al. *Virchows Archiv*. 2006;449:395-401. 2. Rindi G, et al. *Virchows Archiv*. 2007;451:757-762.

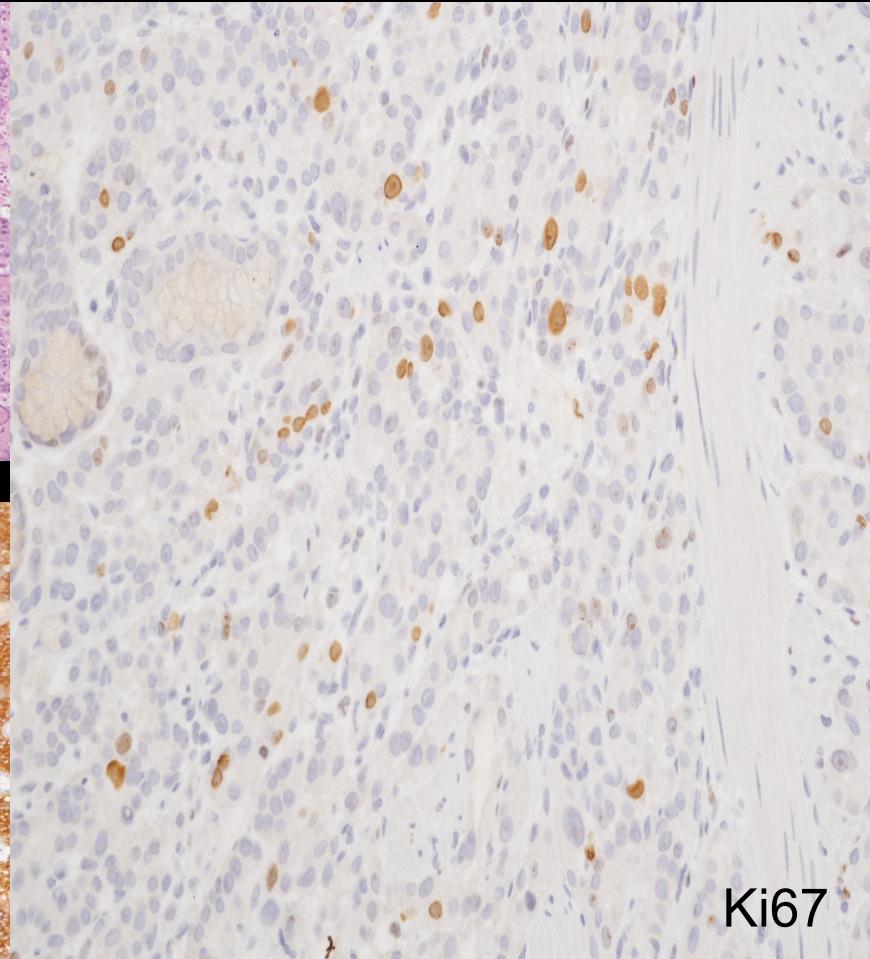
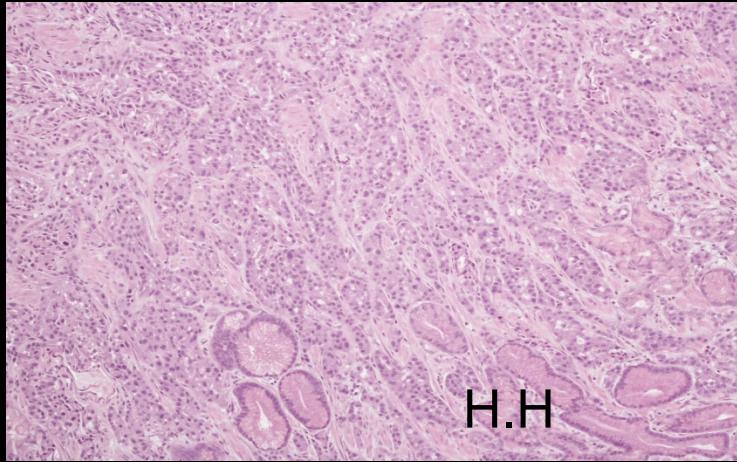
WHO 2010

1. NET G1 = **Neuroendocrine Tumor, Grade 1**
2. NET G2 = **Neuroendocrine Tumor, Grade 2**
3. NEC = **Neuroendocrine Carcinoma
(Grade 3) (large/small cell)**
4. MANEC = **Mixed Adeno**Neuroendocrine**
Carcinoma**
5. Hyperplastic/preneoplastic lesions

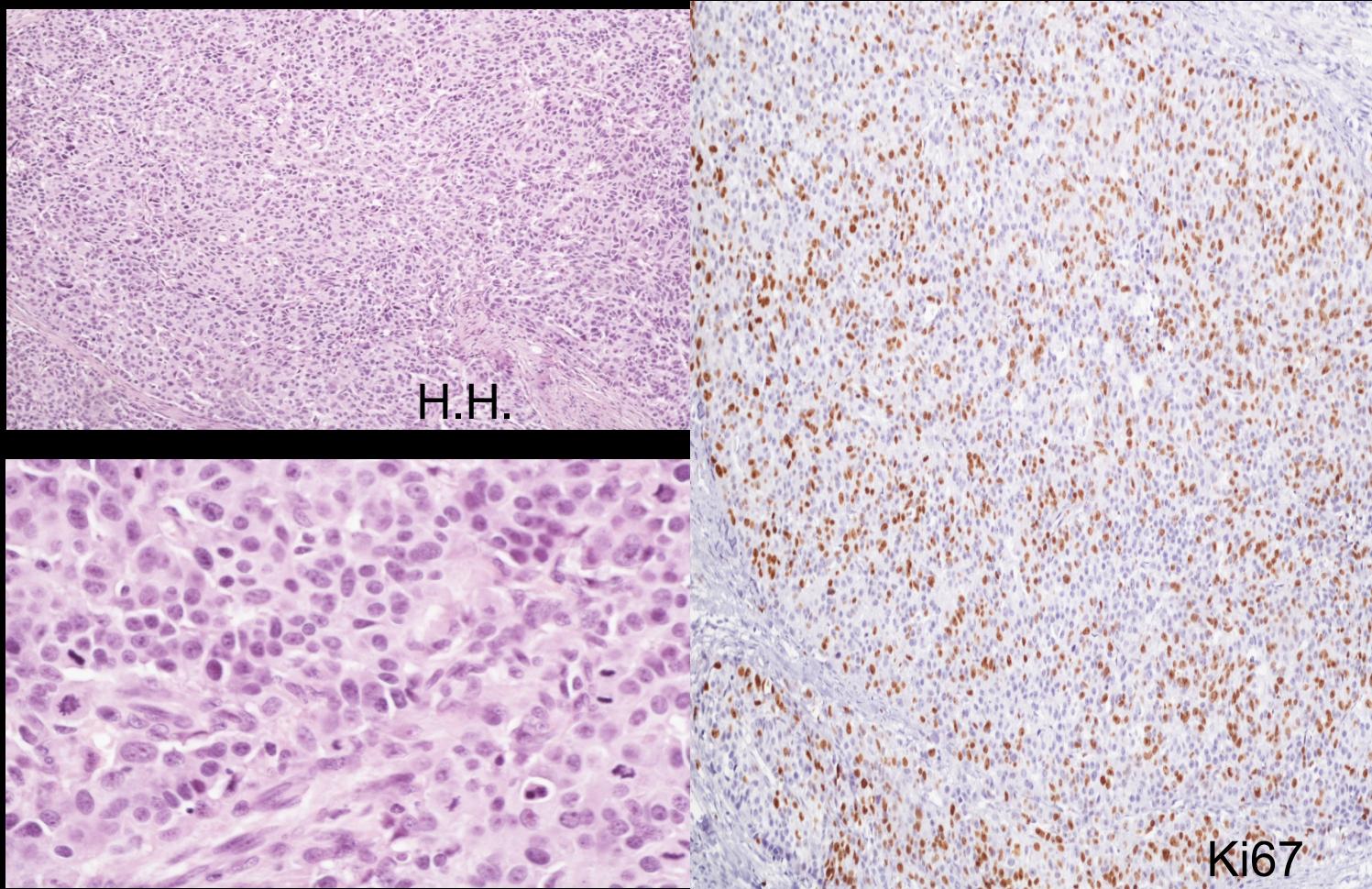
NET G1 (colonic)



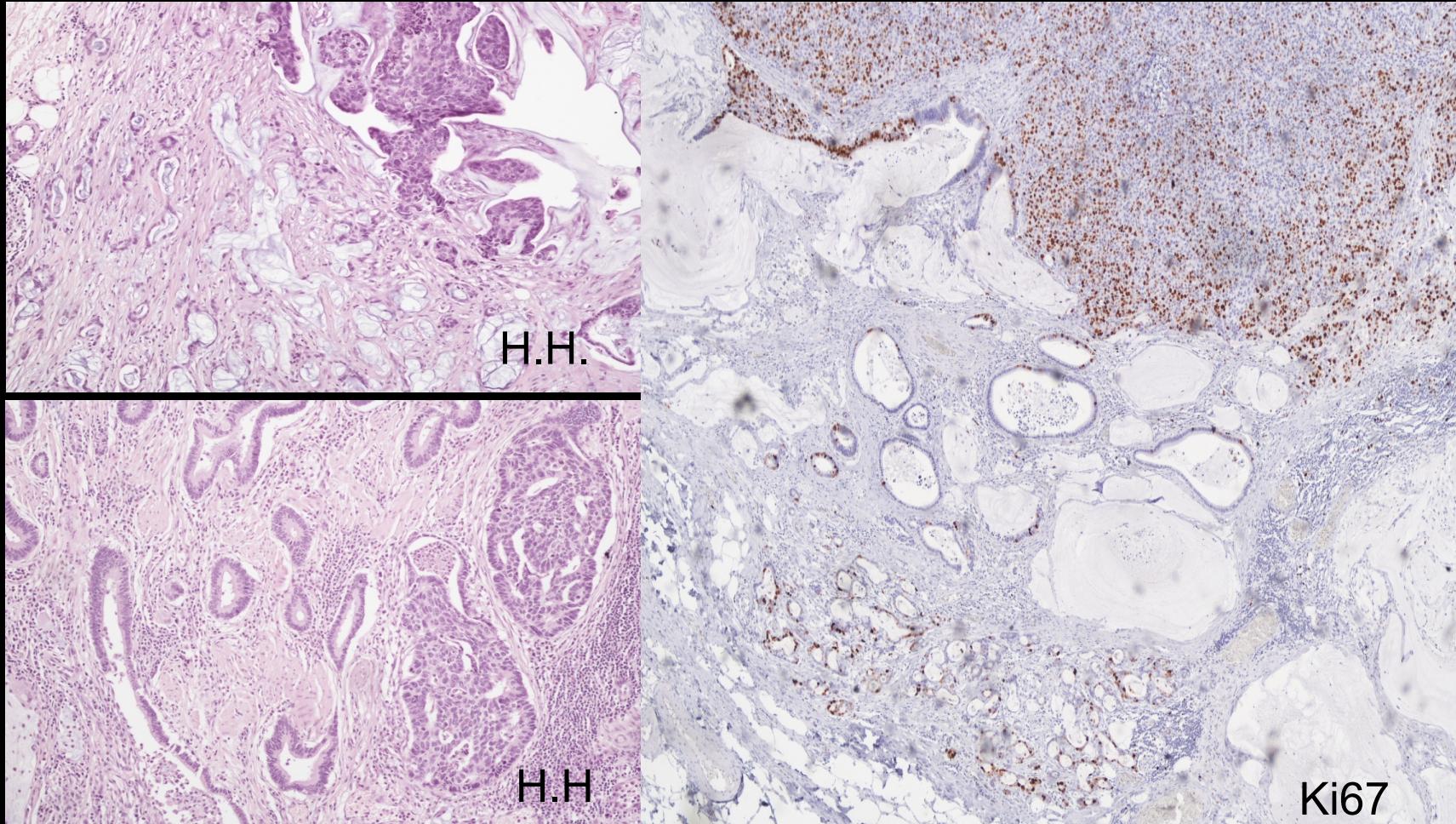
NET G2 (gastric)



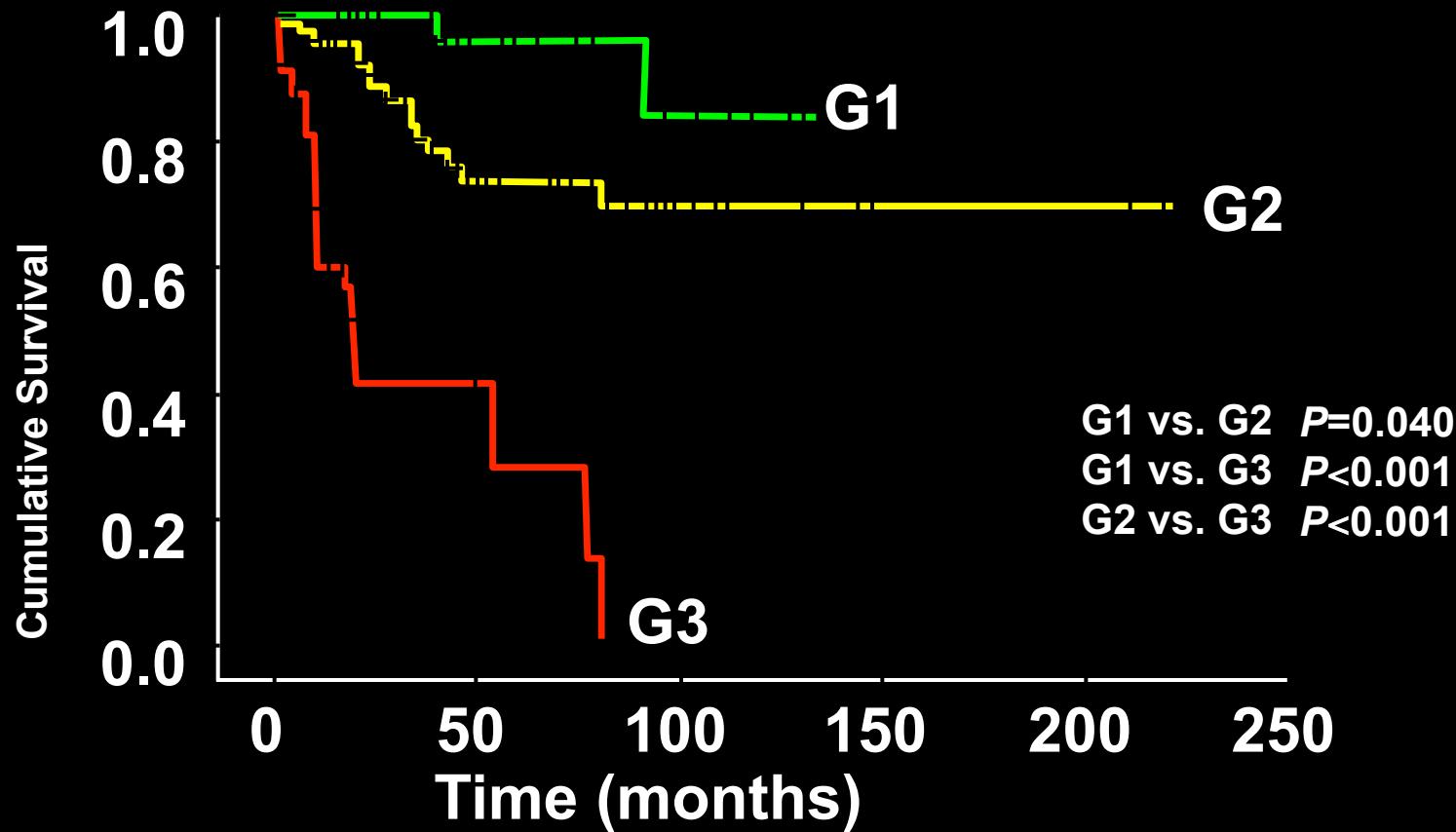
NEC G3 (gastric)



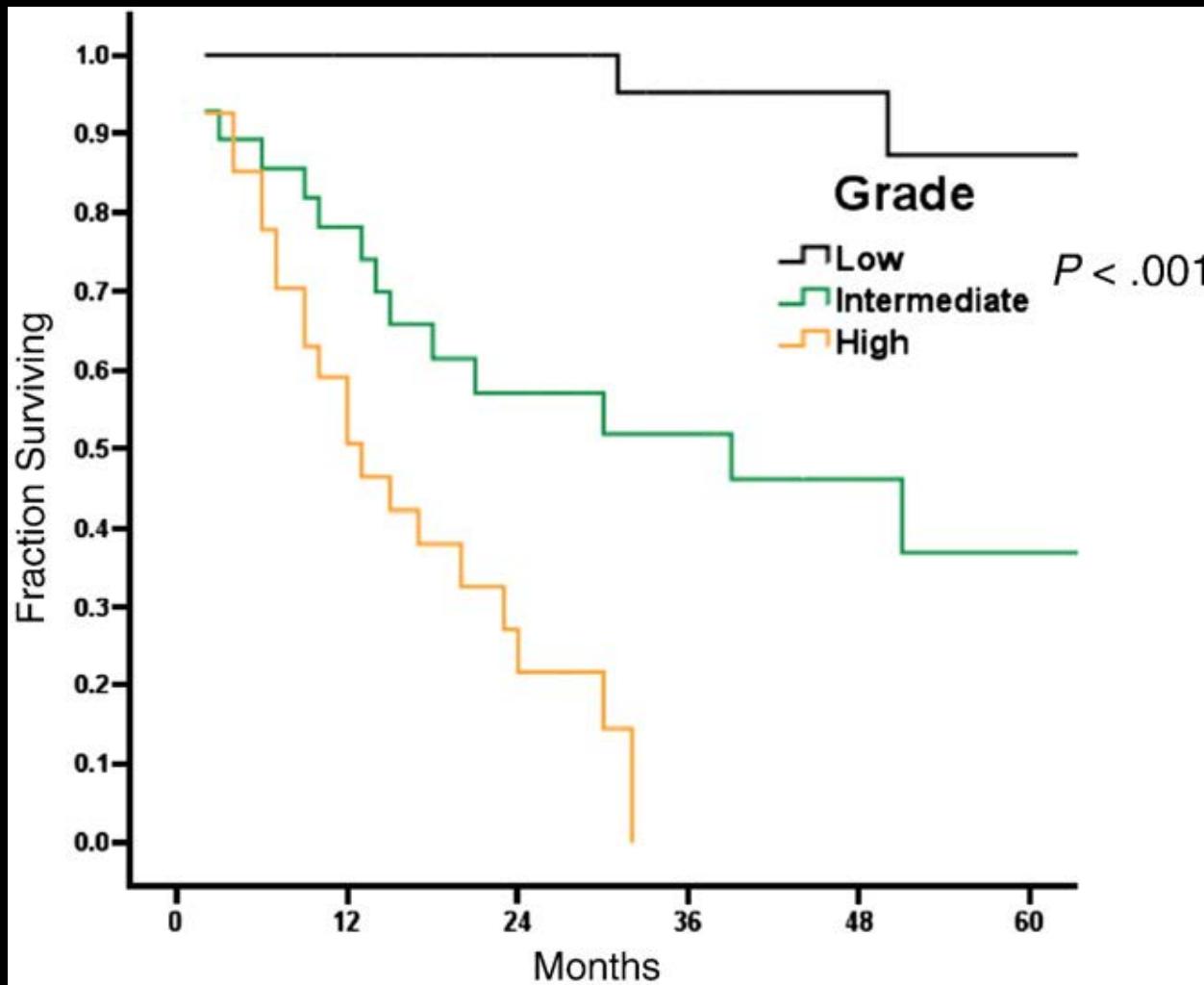
MANEC (gastric)



Significato prognostico del grading



Prognostic Significance of Grade in NETs



Neoplasie Neuroendocrine (NEN): Approccio diagnostico “a step”



- 1) Diagnosi di NEN**
- 2) NET vs NEC → struttura + grado**
- 3) Grado 1-2-3 → mitosi & Ki67**
- 4) Stadio TNM I-II-III-IV → dimensione ed invasività**

STADIAZIONE

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

G. Rindi · G. Klöppel · H. Alhman · M. Caplin ·
A. Couvelard · W. W. de Herder · B. Eriksson ·
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J. M. Lopes · A-M. McNicol · O. Nilsson · A. Perren ·
A. Scarpa · J-Y. Scoazec · B. Wiedenmann ·
and all other Frascati Consensus Conference
participants

1a stadiazione
separata

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

- TX Primary tumor cannot be assessed
- T0 No evidence of primary tumor
- T1 Tumor limited to the pancreas and size <2 cm
- T2 Tumor limited to the pancreas and size 2–4 cm
- T3 Tumor limited to the pancreas and size >4 cm or invading duodenum or bile duct
- T4 Tumor invading adjacent organs (stomach, spleen, colon, adrenal gland)
or the wall of large vessels (celiac axis or superior mesenteric artery)

Classificazione TNM dei GEP-NEN

- ✓ SEDE-specifica

- ✓ Basata su:
 - diametro
 - profondità di invasione

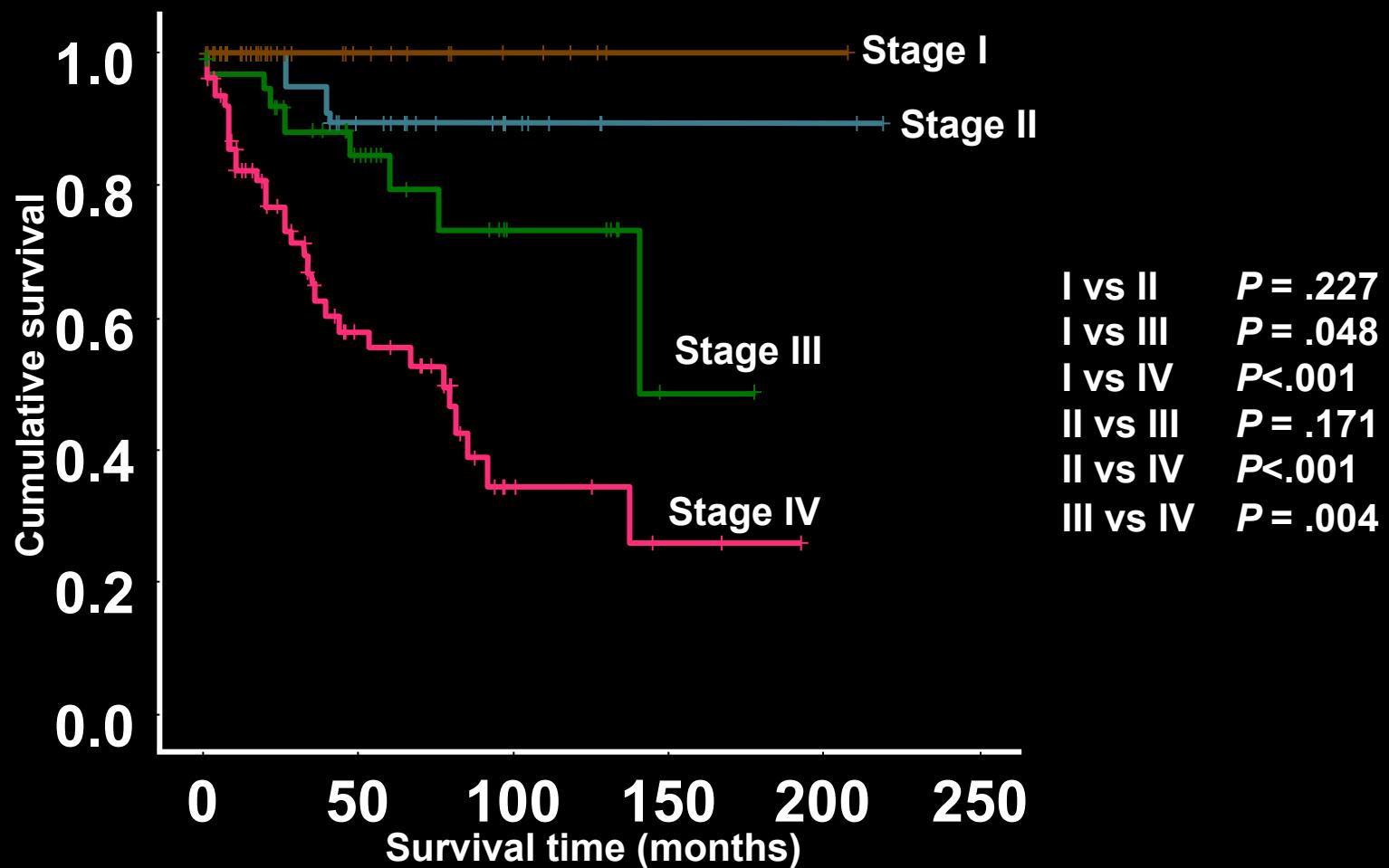
ENETS: 2006/2007 Rindi, Klöppel, Ahlman, Wiedenmann. TNM staging of foregut, midgut and hindgut (neuro) endocrine tumours: A consensus proposal including a grading system. *Virchows Archiv.* 2006;449:395-401, and 2007;451:757-762.

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

Confronto tra le classificazioni TNM ENETS 2006/2007 e UICC/AJCC 2009

- Simili per quanto riguarda:
 - Stomaco
 - Duodeno
 - Digiuno/ileo
 - Colon/retto

Significato prognostico del TNM



Confronto tra le classificazioni TNM ENETS 2006/2007 e UICC/AJCC 2009

✓ Simili per:

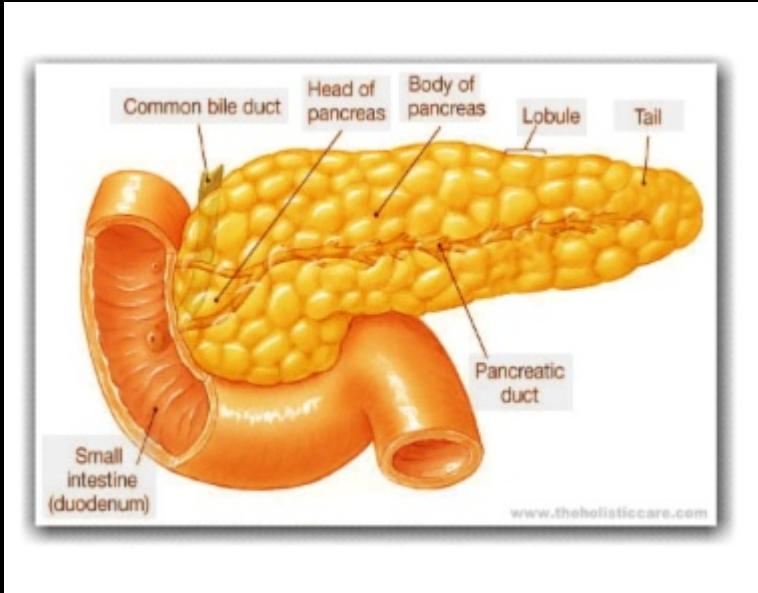
- Stomaco
- Duodeno
- Digiuno/ileo
- Colon/retto

✓ Differenti per:

- Pancreas
- Appendice

Categoria T per i NEN dell'Appendice secondo ENETS e UICC/AJCC

	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



PANCREAS



International Union Against Cancer

TNM Classification of Malignant Tumours

SEVENTH EDITION

EDITED BY

LESLIE SOBIN | MARY GOSPODAROWICZ | CHRISTIAN WITTE

The TNM applies to carcinomas of the exocrine pancreas and pancreatic neuroendocrine tumours including carcinoids



TNM STAGING: PANCREAS

Table 1 Comparison of the criteria for the T category in the ENETS and UICC TNM classifications of pancreatic neuroendocrine tumors

	ENETS TNM	AJCC/UICC TNM
T1	Confined to pancreas, ≤ 2 cm	Confined to pancreas, <2 cm ≤
T2	Confined to pancreas, 2–4 cm	Confined to pancreas, >2 cm
T3	Confined to pancreas, >4 cm, or invasion of duodenum or bile duct	Peripancreatic spread, but without major vascular invasion (Truncus coeliacus, A. mesent. sup.)
T4	Invasion of adjacent organs or major vessels	Major vascular invasion

Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs)

John K Ramage,¹ A Ahmed,² J Ardill,³ N Bax,⁴ D J Breen,⁵ M E Caplin,⁶ P Corrie,⁷ J Davar,⁸ A H Davies,⁹ V Lewington,¹⁰ T Meyer,¹¹ J Newell-Price,¹² G Poston,¹³ N Reed,¹⁴ A Rockall,¹⁵ W Steward,¹⁶ R V Thakker,¹⁷ C Toubanakis,¹⁸ J Valle,¹⁹ C Verbeke,²⁰ A B Grossman¹⁷

- Pathological characterisation and classification of NETs should be based on the WHO 2010 classification, the Union for International Cancer Control (UICC) TNM (7th edition), and the European Neuroendocrine Tumour Society (ENETS) site-specific T-staging system. Level of evidence 5, Grade of recommendation D.

Pathology Reporting of Neuroendocrine Tumors: Application of the Delphic Consensus Process to the Development of a Minimum Pathology Data Set

David S. Klimstra, MD, Irvin R. Modlin, MD, PhD,† N. Volkan Adsay, MD,‡
Runjan Chetty, MD,§ Vikram Deshpande, MD,|| Mithat Gönen, PhD,¶ Robert T. Jensen, MD,♯
Mark Kidd, PhD,† Matthew H. Kulke, MD, ** Ricardo V. Lloyd, MD, PhD, ††
Cesar Moran, MD,‡‡ Steven F. Moss, MD,§§ Kjell Oberg, MD,||| Dermot O'Toole, MD,¶¶¶
Guido Rindi, MD,## Marie E. Robert, MD,*** Saul Suster, MD,††† Laura H. Tang, MD, PhD,*
Chin-Yuan Tzen, MD, PhD,††† Mary Kay Washington, MD,§§§ Betram Wiedenmann, MD,|||||
and James Yao, MD¶¶¶¶¶*

Refertazione patologica dei NEN

Cosa definire?

- Sede e istotipo (classificazione WHO 2010)
- Grado tumorale (valore di Ki-67)
- Aspetti istologici rilevanti: multifocalità, necrosi, invasione vascolare o perineurale
- Stadio TNM
- Margini di resezione
- Produzione ormonale

A richiesta: marcatori prognostici o predittivi utili: recettori della somatostatina, molecole della via mTOR, enzimi del metabolismo dei chemioterapici.