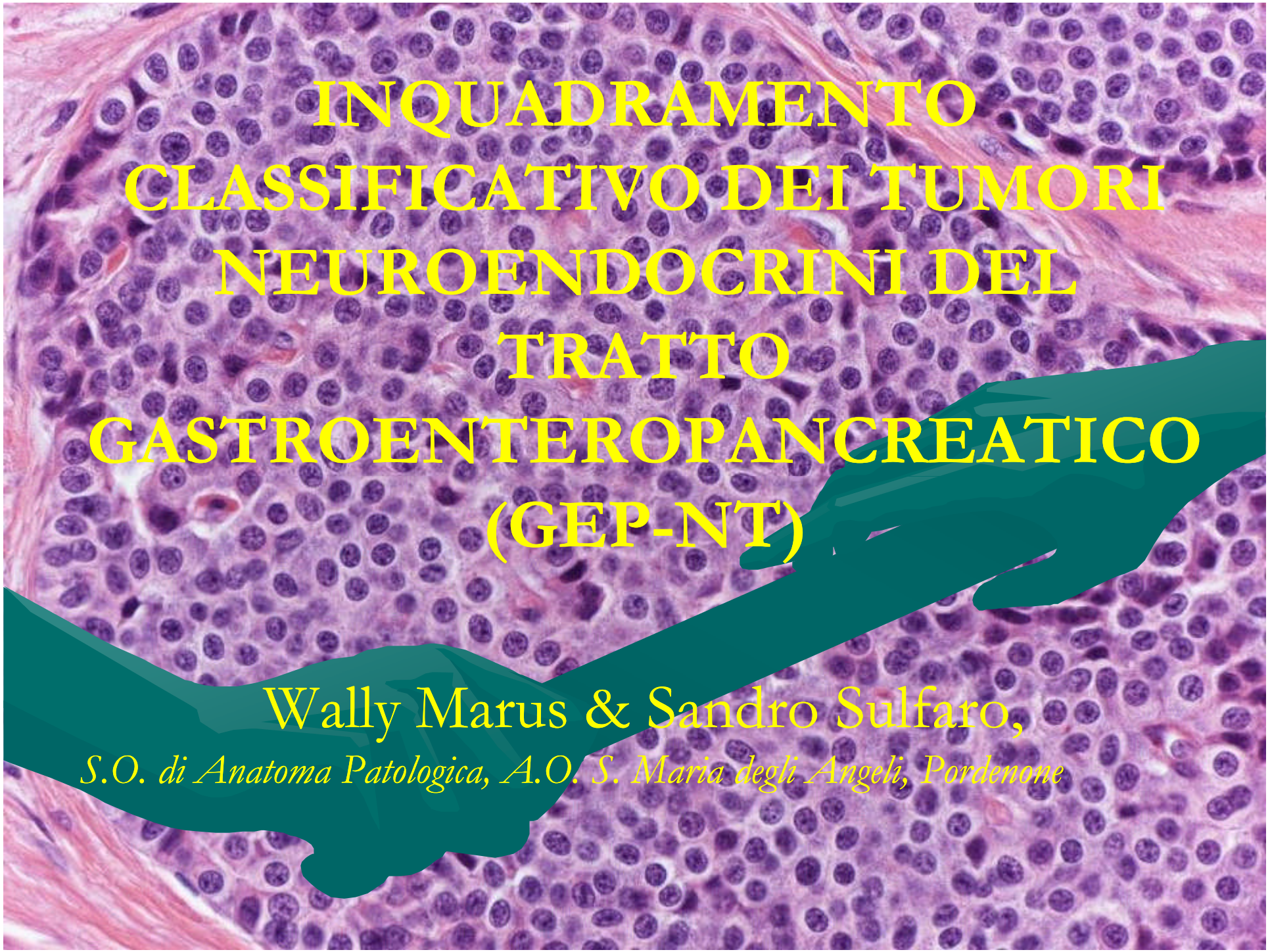


INQUADRAMENTO CLASSIFICATIVO DEI TUMORI NEUROENDOCRINI DEL TRATTO GASTROENTEROPANCREATICO (GEP-NT)

Wally Marus & Sandro Sulfaro,

S.O. di Anatoma Patologica, A.O. S. Maria degli Angeli, Pordenone

GEP-NET: origine e differenziazione fenotipica

- Cellule endocrine del c.d. "sistema endocrino diffuso" (DES)

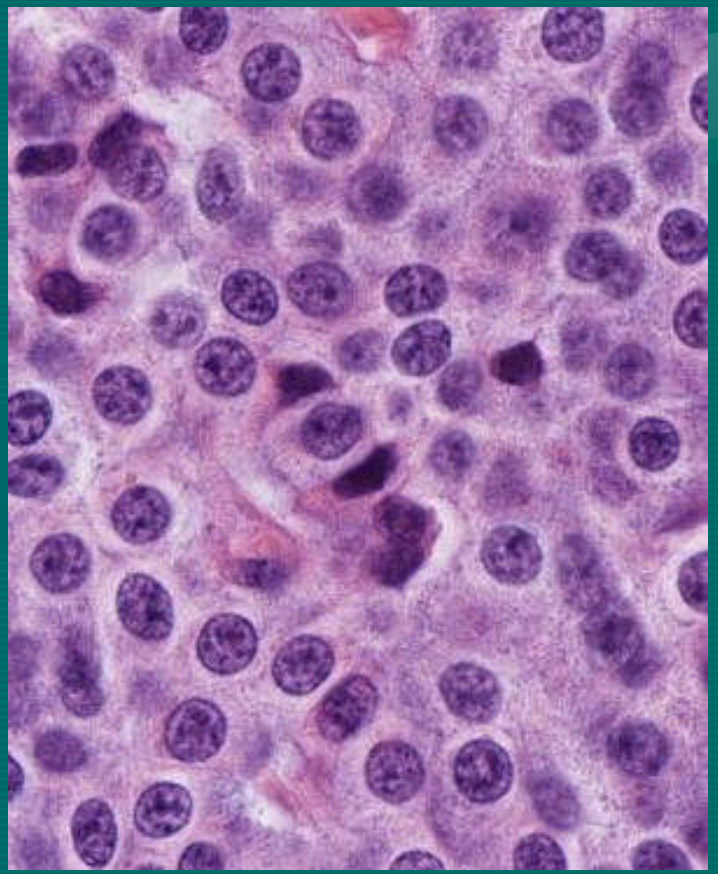
Caratteristiche morfologiche:

– Nuclei uniformi

– Citoplasma abbondante, granulare o "chiaro"

– In aggregati solidi o trabecolari o

– Disperse tra altri tipi cellulari



GEP-NET: origine e differenziazione fenotipica

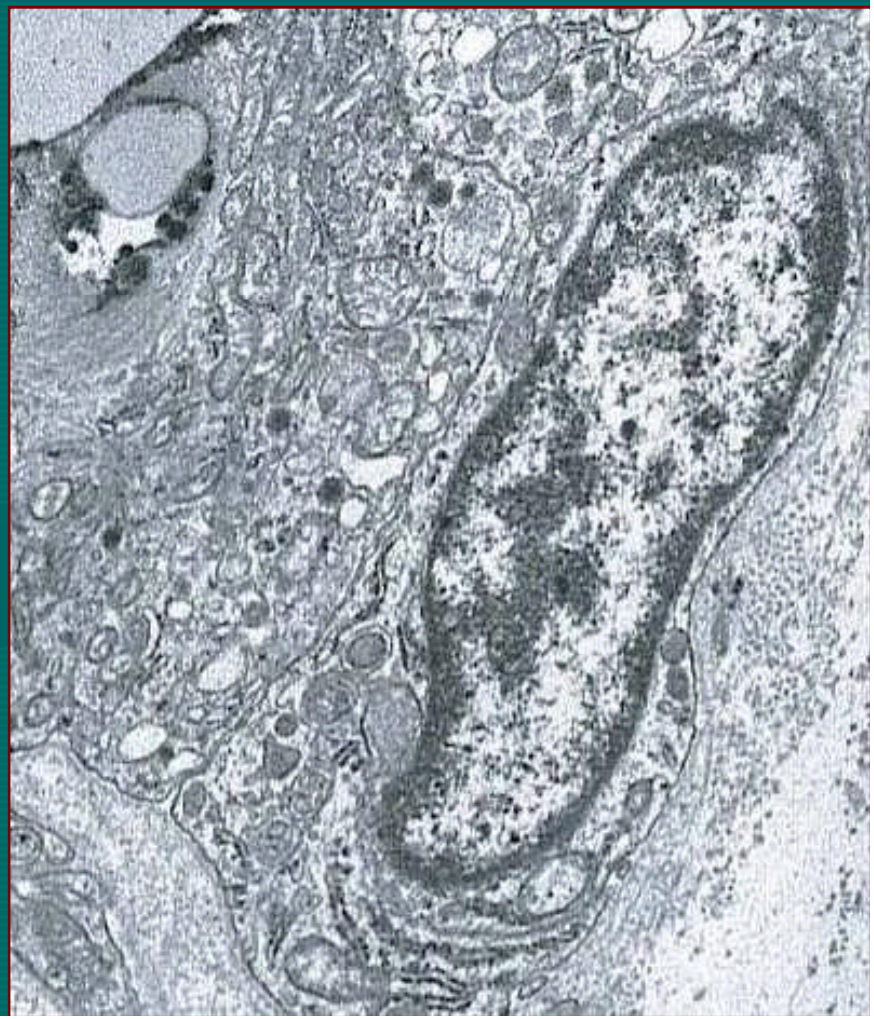
Caratteristiche fenotipiche:

- Almeno 15 tipi cellulari/ormoni sintetizzati accomunati dall'espressione di markers comuni anche ad elementi nervosi (cellule "neuro"endocrine)

GEP-NET: origine e differenziazione fenotipica

Caratteristiche fenotipiche "neurali":

- presenza di granuli secretori delimitati da membrane (large, "dense core", Ø >80 nm)
- presenza di vescicole "chiare" (small, Ø 40-80 nm) analoghe alle vescicole sinaptiche



GEP-NET: origine e differenziazione fenotipica

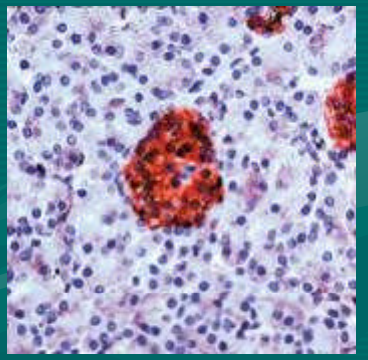
Markers funzionali e diagnostici:

- Citoplasmatici
- Associati alle vescicole sinaptiche
- Associati ai granuli secretori
- Associati alla membrana cellulare
- Associati a fattori di trascrizione e ormoni

GEP-NET: markers funzionali e diagnostici

Citoplasmatici:

- Enolasi neurono-specifica (NSE)
- Protein gene product 9.5 (PGP 9.5)

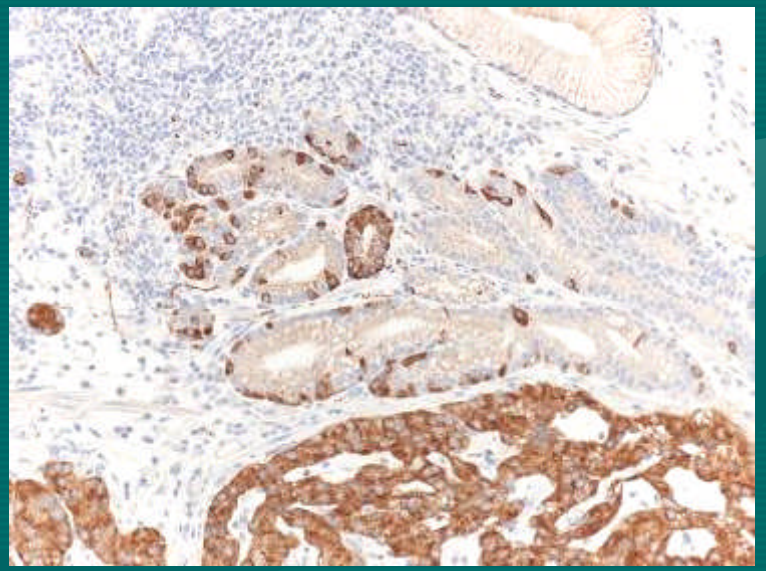


NSE +: non correlata alla presenza di granuli secretori. Marker aspecifico presente anche in tessuti e neoplasie non endocrine.

GEP-NET: markers funzionali e diagnostici

Associati alle vescicole sinaptiche :

- Sinaptofisina
- Sinaptobrevina
- SV2

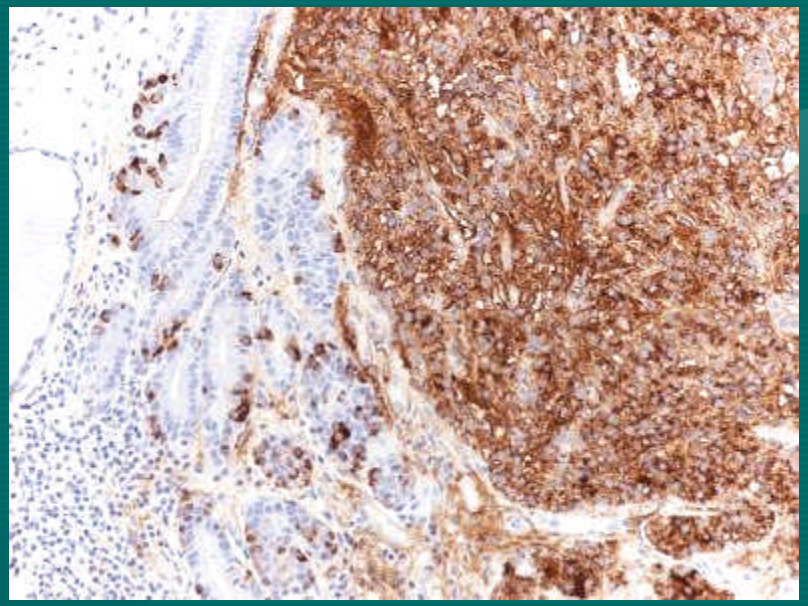


Sinaptofisina è una glicoproteina di membrana (p.m. 38.000) che accomuna le cellule del DES, normali e neoplastiche, ed è espressa indipendentemente da altri markers neuroendocrini

GEP-NET: markers funzionali e diagnostici

Associati ai granuli secretori:

- Cromogranina A, B, C
- Vesicular monoamine transporters 1&2 (VMAT1, VMAT2)

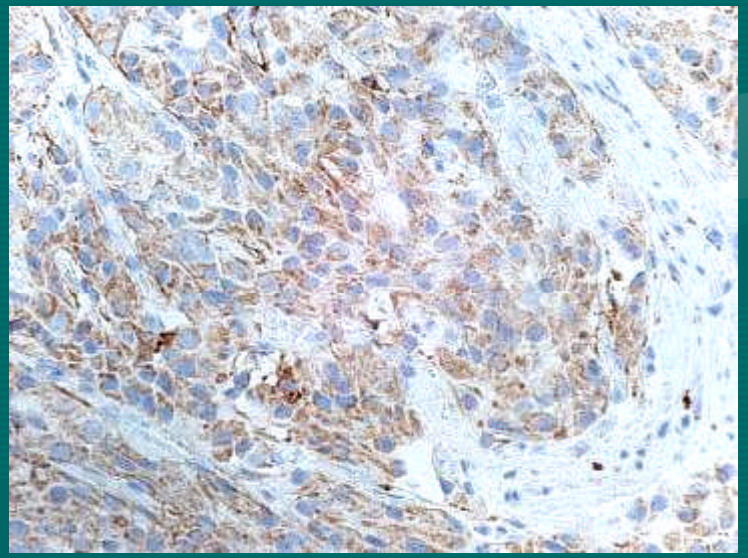


Cromogranina A +: dipende dal tipo cellulare e dal numero di granuli presenti.

GEP-NET: markers funzionali e diagnostici

Associati alla membrana cellulare:

- Neural cell adesion molecule (NCAM/CD56)
- Leu 7/CD57

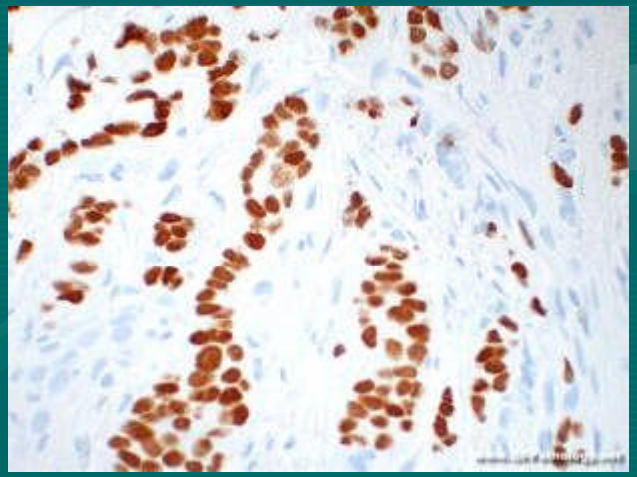


Presenti anche in tessuti e neoplasie di origine non neurale/neuroendocrina

GEP-NET: markers funzionali e diagnostici

Associati a fattori di trascrizione e ormoni :

CDX2: fattore di trascrizione che regola lo sviluppo del piccolo e grosso intestino.



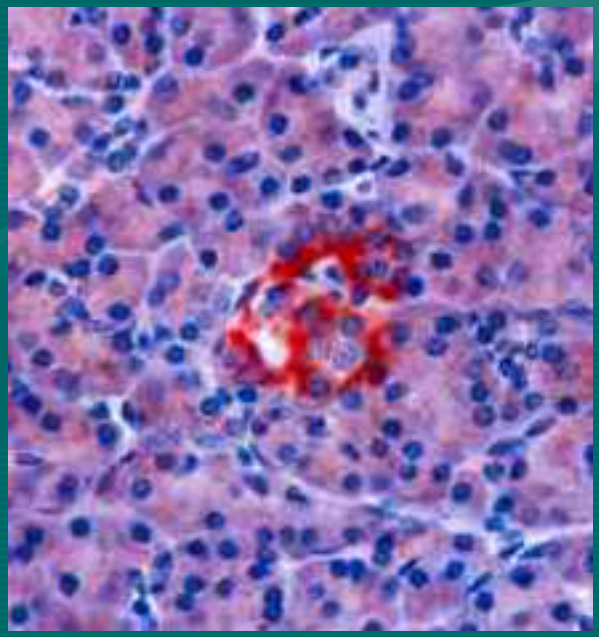
Positivo nei NET che originano da digiuno inferiore, ileo, appendice, cieco, pancreas, retto, polmone; negativo in quelli che originano da stomaco, tiroide e paragangli.

GEP-NET: markers funzionali e diagnostici

Associati a fattori di trascrizione e ormoni :

- Recettori per somatostatina (SSTR).

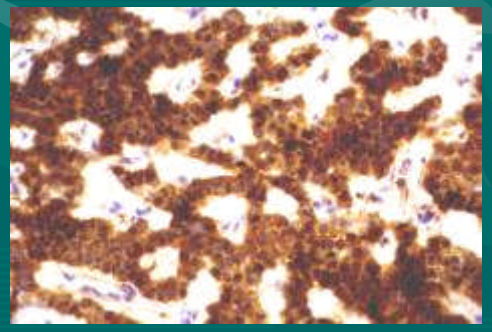
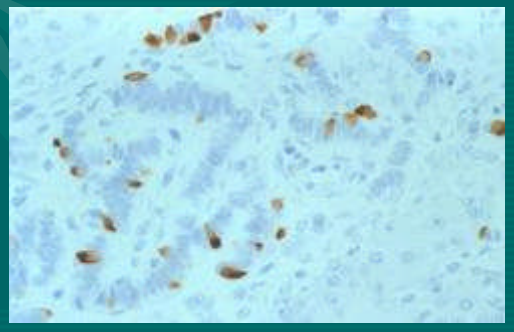
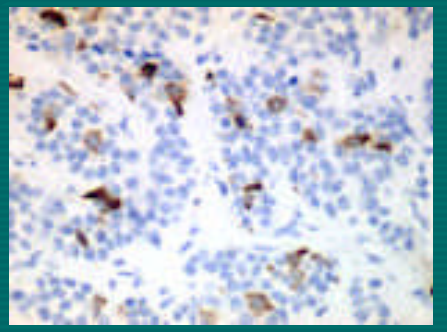
Cinque tipi identificati (SSTR1-5); IHC per SSTR2 correla con il segnale ottenuto con octreoscan. SSTR2 e 5 espressi nella maggior parte dei NET che secernono serotonina e nei gastrinomi.



GEP-NET: markers funzionali e diagnostici

Associati a fattori di trascrizione e ormoni :

- Prodotti cellulari (peptidi e amine biogene) con funzioni di ormoni o neurotrasmettitori permettono di identificare (con metodica di IHC o ISH) i diversi tipi di cellule del DES e delle neoplasie derivate.

Caratterizzazione del “fenotipo” ormonale

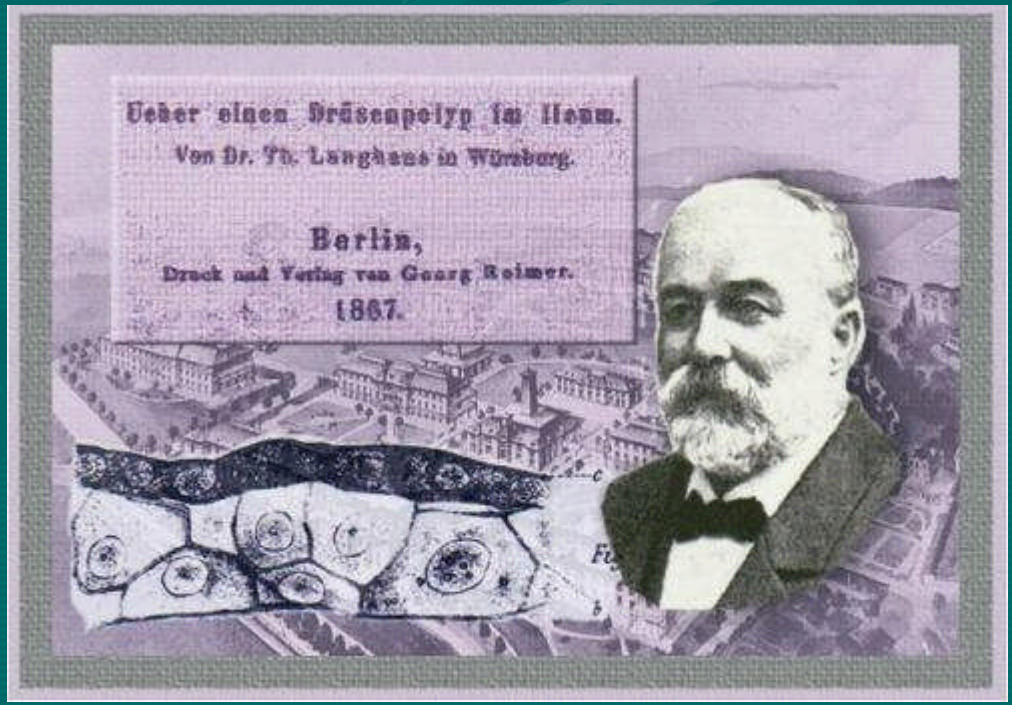
- La popolazione dei NET ben differenziati può essere eterogenea; riflette in genere la controparte normale presente nell’organo in cui originano, al contrario di quelli poco differenziati.
- Differenti ormoni possono essere prodotti da un unico NET.
- Non tutte le cellule del DES hanno una controparte neoplastica (e.g.: secretina, colecistochinina, motilina, peptide inibitore gastrico e neurotensina).

Caratterizzazione del "fenotipo" ormonale

- Indica l'alto grado di differenziazione cellulare dei NET ma non ha alcun significato clinico a meno che non vi sia associata una sindrome clinica direttamente correlata a ipersecrezione ormonale.
- L'attuale distinzione tra NET "secernenti" e "non secernenti" è basata esclusivamente sulla presenza o meno di sintomi correlati a ipersecrezione ormonale, non sulla caratterizzazione IHC o ISH.

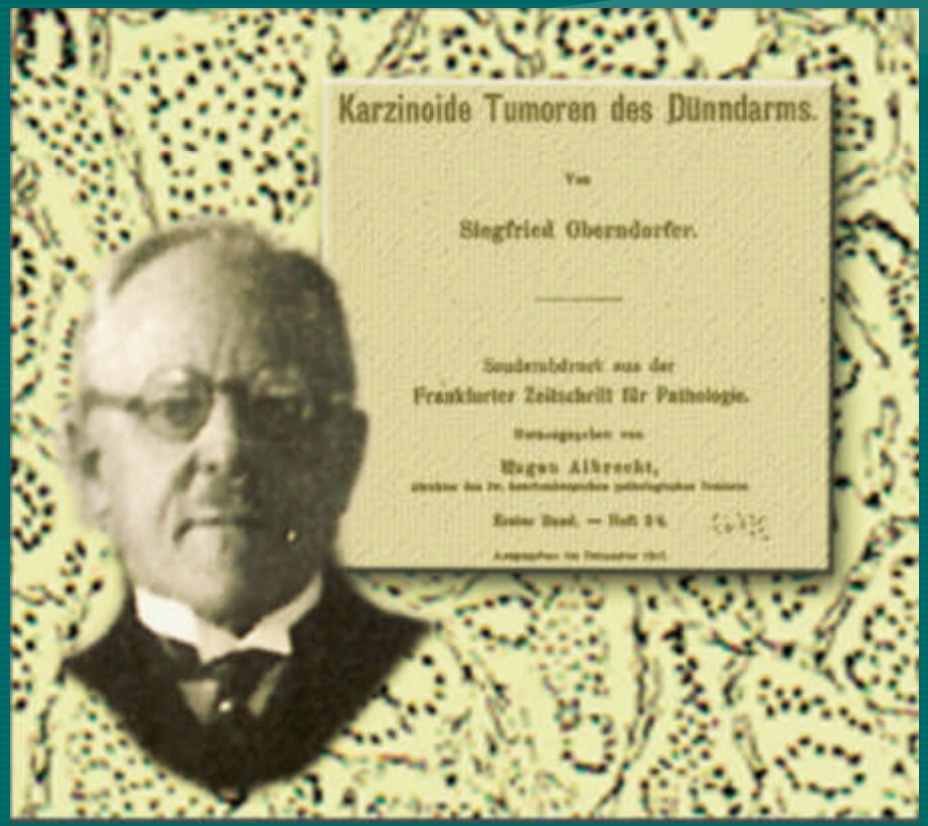
Classificazione dei GEP-NET

- 1867: Theodor Langhans pubblica la prima descrizione macroscopica e microscopica di una neoplasia neuroendocrina, un carcinoide del piccolo intestino repertato all'autopsia in una donna di 50 anni.



Classificazione dei GEP-NET

- 1907: Oberndorfer identifica come "carcinoidi" neoplasie epiteliali intestinali con pattern cito-architetturale relativamente monomorfo e comportamento biologico meno aggressivo degli usuali carcinomi intestinali.



Classificazione dei GEP-NET

1963: Williams E.D. & Sandler M.:

The classification of carcinoid tumours. *Lancet* ***1:*** *238–239.*

- "Foregut" (esofago, stomaco, pancreas, duodeno, digiuno superiore).
- "Midgut" (digiuno inferiore, ileo, appendice, cieco)
- "Hindgut" (Colon, retto)

Classificazione dei GEP-NET

- E' la prima classificazione che sottolinea le differenze clinicopatologiche correlate ai diversi NET
- Non consente, soprattutto nel primo gruppo, di differenziare tra neoplasie con morfologia, aspetti funzionali e comportamento biologico estremamente diversi tra loro.

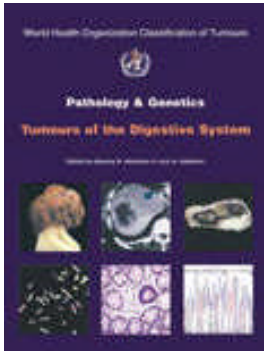
Classificazione dei GEP-NET

- **1980: prima classificazione WHO**
  - Mantiene la denominazione di "carcinoide" per la maggior parte dei NET, suddividendoli in carcinoidi a cellule EC, a cellule G (gastrina) e non specificati.
  - Oltre che essere prognosticamente scarsamente rilevante, genera confusione per il diverso uso del termine "carcinoide" che ne fanno i clinici (NET secernenti serotonina associati a sindrome da carcinoide).

Classificazione dei GEP-NET

- **2000: seconda classificazione WHO**

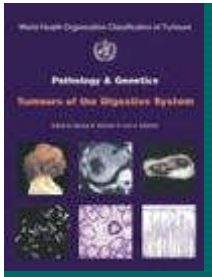
World Health Organization Classification of Tumours



WHO OMS

International Agency for Research on Cancer (IARC)

Pathology and Genetics of Tumours of the Digestive System

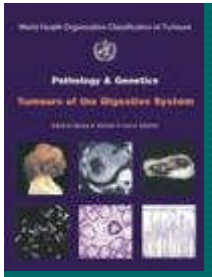


Classificazione dei GEP-NET

1. Distingue neoplasie (neuro)endocrine che originano da strutture ghiandolari e nervose o da elementi del DES

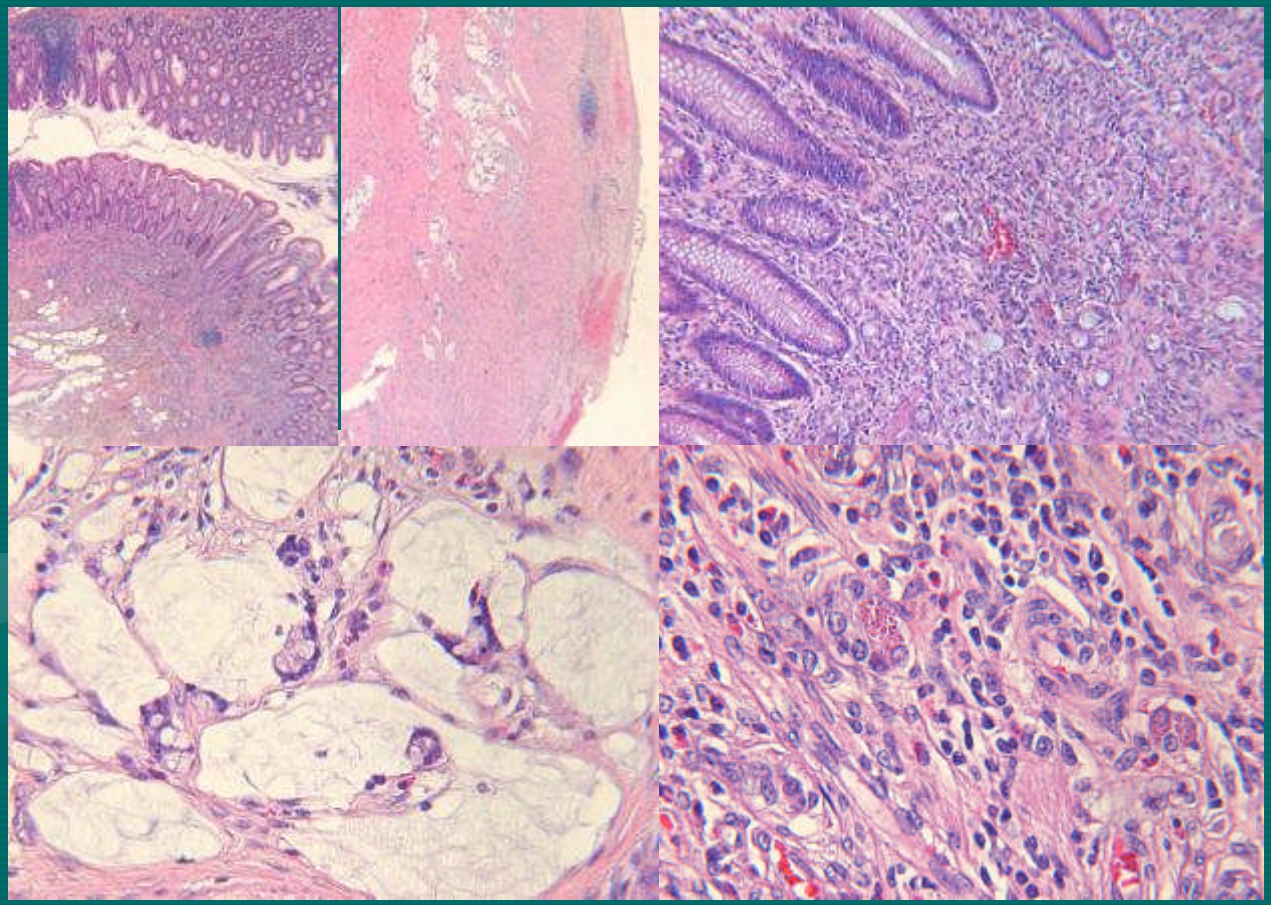
Table 1. Neuroendocrine cell system and tumour classification.

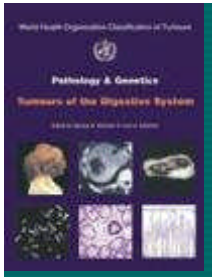
Gland forming	
Pituitary	Adenoma
Parathyroid	Adenoma/carcinoma
Paraganglia	Paraganglioma
Adrenal medulla	Phaeochromocytoma
Disseminated	
Gastrointestinal tract	Neuroendocrine tumour/carcinoma
Endocrine pancreas	Neuroendocrine tumour/carcinoma
Biliary tract	Neuroendocrine tumour/carcinoma
Respiratory tract	Carcinoid, neuroendocrine carcinoma
Thymus	Carcinoid
Thyroid C cells	Medullary thyroid carcinoma
Urogenital tract	Carcinoid
Skin	Merkel cell carcinoma



Classificazione dei GEP-NET

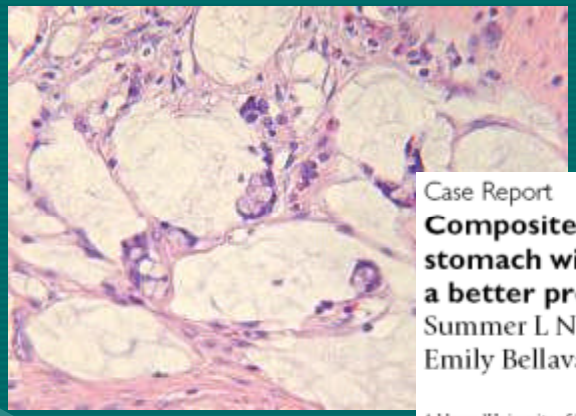
2. Distingue le neoplasie (neuro)endocrine pure da quelle miste, endocrine ed esocrine.

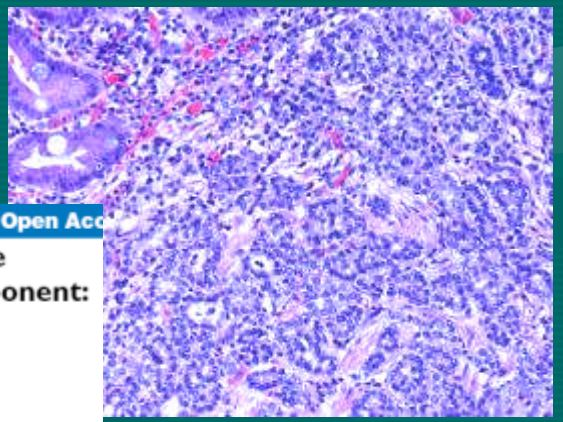




Classificazione dei GEP-NET

Nelle neoplasie miste la prognosi è correlata alla componente meno differenziata, in genere quella epiteliale non endocrina





Case Report

Composite signet-ring cell/neuroendocrine carcinoma of the stomach with a metastatic neuroendocrine carcinoma component: a better prognosis entity

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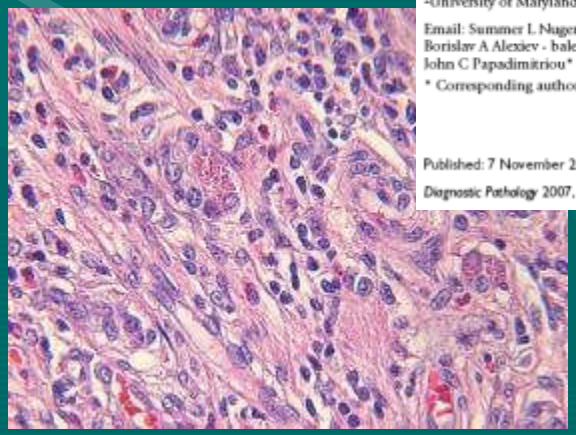
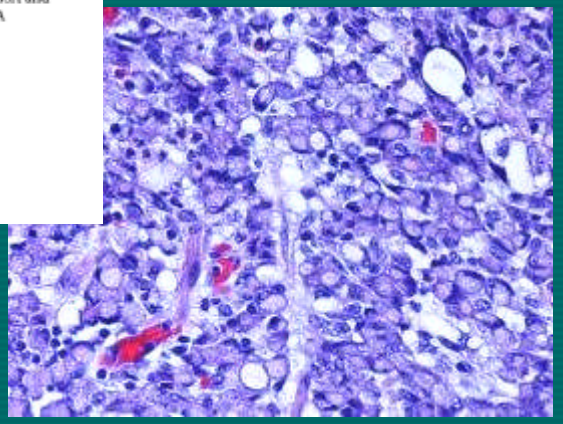
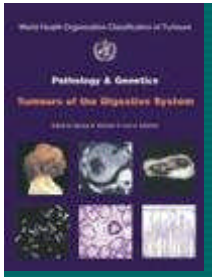


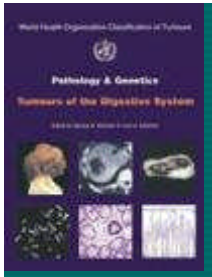




Classificazione dei GEP-NET

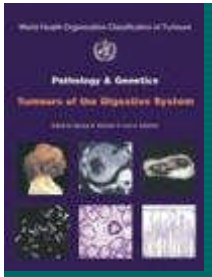
3. Individua tre categorie diagnostiche, indipendenti dalla sede.

1. well-differentiated endocrine tumours, with benign (1.1) or uncertain behaviour (1.2) at the time of diagnosis;
2. well-differentiated endocrine carcinomas with low-grade malignant behaviour;
3. poorly differentiated endocrine carcinomas, with high-grade malignant behaviour.



Classificazione dei GEP-NET

4. Le prime due categorie (tumori NE ben differenziati e carcinomi NE ben differenziati) sono quindi distinte in base:
   - Alla sede di origine
   - Agli aspetti morfologici
   - Agli aspetti funzionali



Classificazione dei GEP-NET

WHO - criteri di malignità:

- Assoluti: presenza di infiltrazione di organi adiacenti e/o di metastasi.
- Fattori prognostici:
  - Macro: Ø di T;
  - Micro: invasione vascolare
    I.M. e/o Ki67/Mib1 >2%

Prognosis

Good → **Poor**

WHO-Classification	Well-Differentiated Neuroendocrine Tumor	Well-Differentiated Neuroendocrine Carcinoma	Poorly-Differentiated Neuroendocrine Carcinoma
Biological Behaviour	benign / low malignant	low malignant	highly malignant
Metastases	-	+ / -	+
Ki-67 (%)	<2	>2	>30
Histological Differentiation	Well	Well	Poor
Infiltration / Angioinvasion	-	+	+
Tumor Size	≤2cm[a] >2cm[b]	>2cm[a] >3cm[b]	Any size

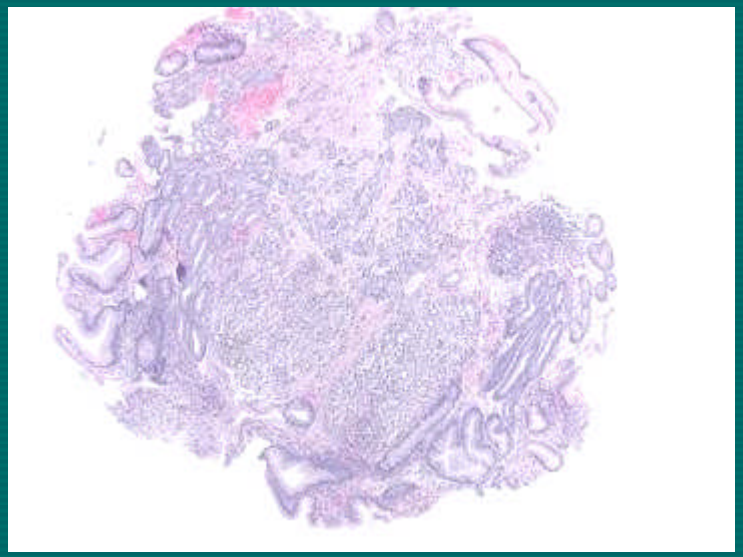
[a] NET of the GI Tract [b] Pancreatic NET

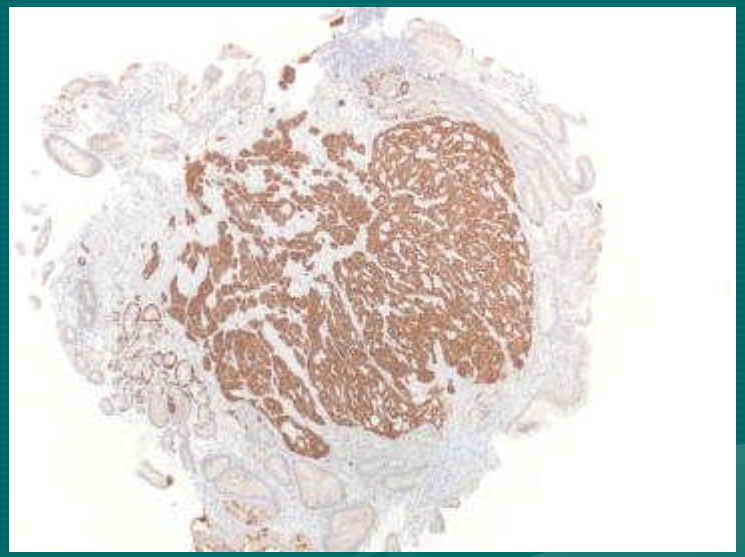
Classificazione WHO

- Fornisce importanti informazioni sul comportamento biologico utili all'approccio terapeutico
- La prognosi dipende dalla localizzazione del tumore, dalla dimensione alla diagnosi e dalla sua differenziazione istologica
- La prognosi del carcinoma poco differenziato e in progressione è scarsa, quella delle neoplasie ben differenziate è molto più favorevole e dipende principalmente dalla velocità di progressione
- Non permette una previsione del comportamento clinico dei NET ben differenziati

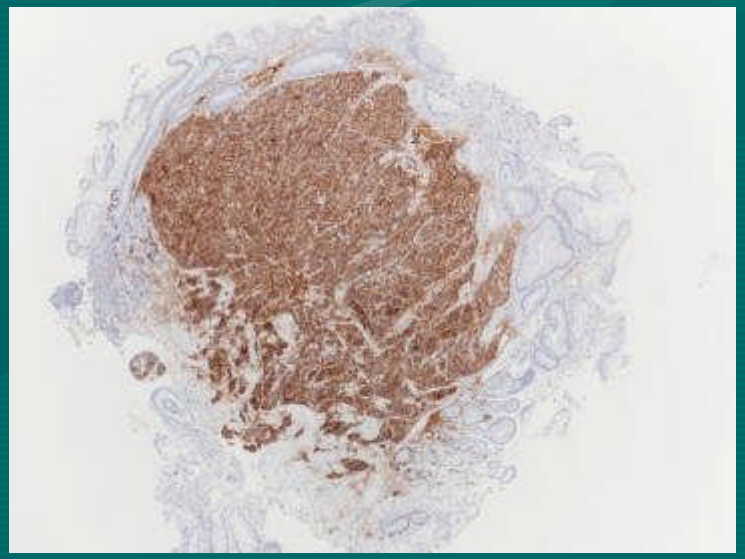
WHO – NET ESOFAGO

- Neoplasie estremamente rare
- 1/3 inferiore
- Prevalgono i Carcinomi NE poco differenziati o le forme miste
- IHC: positività solo per sinaptofisina





WHO – NET STOMACO



WHO – NET STOMACO

"TIPO 1" (70 – 80%):

- Associati a gastrite atrofica autoimmune
- Neoplasie spesso multifocali, 0,5 – 1 cm, ben differenziate, limitate a mucosa e sottomucosa del corpo gastrico
- Cellule EC-like (cromogranina+, VMAT2+)
- GCA→ acloridia → cellule G antrali: ↑ secrezione gastrina → ipergastrinemia → iperplasia ECLC → NET

WHO – NET STOMACO

"TIPO 2":

- Associati a MEN I con sindrome di Z.E.
- Neoplasie spesso multifocali, < 1,5 cm, ben differenziate, limitate a mucosa e sottomucosa del corpo gastrico
- Cellule EC-like (cromogranina+, VMAT2+)
- Associati a presenza di gastrinoma duodenale o pancreatico, con meccanismo analogo al tipo 1 (infatti non insorgono in pz con sola sindrome di ZE)

WHO – NET STOMACO

"TIPO 3":

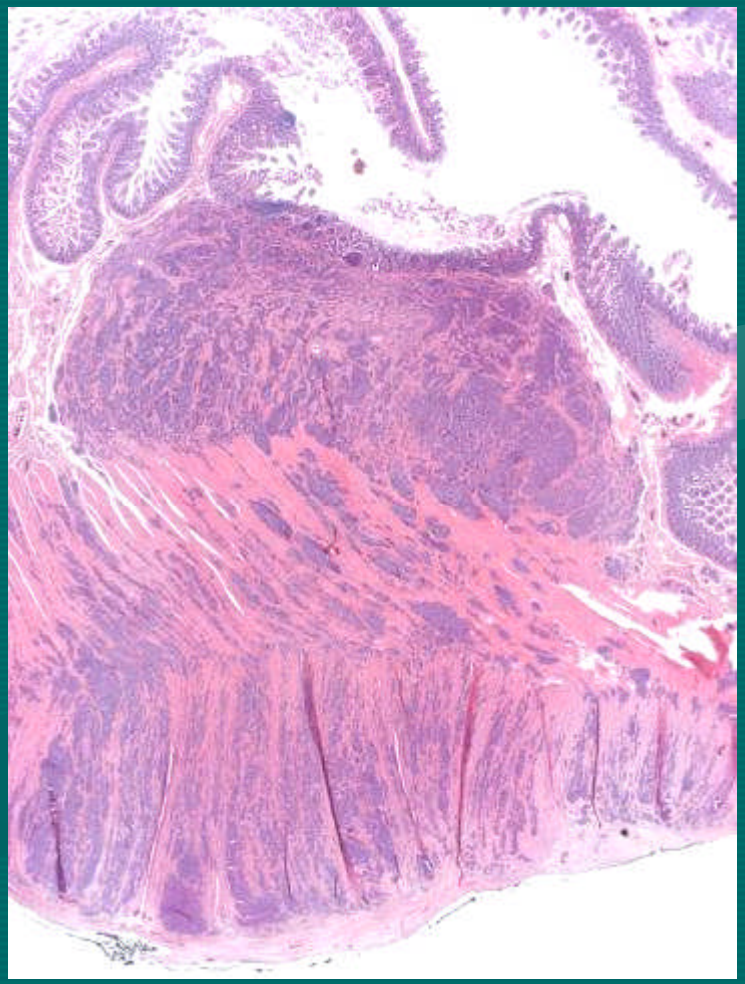
- Non associati a GCA autoimmune o MEN I
- Neoplasie spesso solitarie, > 2 cm, ben differenziate
- Cellule EC-like (cromogranina+, VMAT2+) o, più raramente, serotonina+ o gastrina+

WHO – NET STOMACO

"TIPO 4":

- Carcinomi poco differenziati o indifferenziati
- sinaptofisina+, cromogranina -/+

WHO – NET DUODENO E DIGIUNO SUPERIORE



WHO – NET DUODENO E DIGIUNO SUPERIORE

1. Gastrinomi

- Sporadici (solitari) o associati a ZES (multipli)
- <1 cm, ma N+ (Ø> di T) anche se limitati a mucosa/sottomucosa
- MTS epatiche tardive (≠ gastrinomi pancreatici)

WHO – NET DUODENO E DIGIUNO SUPERIORE

2. Somatostatinomi

- Papilla di Vater
- Sporadici o associati a neurofibromatosi di tipo I (+ feocromocitomi bilaterali)
- N+ con invasione della muscolare propria
- Non associati a sindrome ormonale

WHO – NET DUODENO E DIGIUNO SUPERIORE

3. NET non funzionanti

- Cellule serotonina, gastrina o calcitonina +
- N+ con invasione della muscolare propria
- Prognosi migliore di 1 & 2

WHO – NET DUODENO E DIGIUNO SUPERIORE

4. Carcinoma NE poco differenziato

- Papilla di Vater
- Ormonalmente inattivo
- N+ e MTS epatiche alla diagnosi

WHO – NET DUODENO E DIGIUNO SUPERIORE

5. Paraganglioma gangliocitico

- Papilla di Vater
- Spesso > 2 cm e con localizzazione alla muscolare propria, ma comportamento benigno
- Cellule gagliari + cellule NE (S100+, Somatostatina+, PP+)

WHO – NET DIGIUNO INFERIORE, ILEO & DIVERTICOLO DI MECKEL

- Ileo terminale, valvola ileocecale
- 40% multipli
- N+ se > 2 cm e invasione della muscolare propria
- 20% con MTS epatiche (→ sindrome da carcinoide)
- Serotonina +, sostanza P+, callicreina +, catecolamine +, CEA + (2/3) e CDX2+

WHO – NET APPENDICE

- I più frequenti insieme a quelli ileali
- Neoplasie ben differenziate; forme miste
- Fondo appendicolare (misti: colletto)
- Quasi sempre con muscolare infiltrata, estensione al mesoappendice non rara
- N+ rari per T < 2 cm
- Serotonina +, sostanza P+

WHO – NET COLON

- Rari
- Carcinomi poco differenziati o indifferenziati
- sinaptofisina+

WHO – NET RETTO

- 10%
- In genere < 1 cm e limitati alla sottomucosa
- MTS se ≥ 2 cm e con muscolare infiltrata
- Glucagone +, glicentina +, PP+, cromogranina -

WHO – NET PRESACRALI

- Rari; in genere associati a cisti intestinali retroperitoneali disembriogenetiche
- Neoplasie ben differenziate, ma possono dare MTS

WHO – NET PANCREATICI

- Neoplasie in genere ben differenziate, ma, ad eccezione degli insulinomi, a comportamento maligno
- 50-60% funzionalmente attivi (insulina, gastrina, VIP, glucagone; raramente ACTH o GH

2006-….. Stadiazione dei GEP-NET

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. 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

2006-….. Stadiazione dei GEP-NET

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

CANCER July 15, 2008 / Volume 113 / Number 2

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

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Bertram Wiedenmann, MD[1]

BACKGROUND. Neuroendocrine tumors (NETs) of the gastroenteropancreatic (GEP) system comprise a rare but challenging group of malignant neoplasms and occur at virtually any site of the GEP system. In 2006, a new TNM classification system was proposed for the staging and grading of upper GEP NETs.

METHODS. The prognostic relevance of the TNM classification system was analyzed retrospectively in 202 patients from a referral center with histologically proven foregut NET. Patients were classified according to previous classification systems and the TNM classification. Survival data were acquired and statistical analyses were performed by using log-rank and Cox regression testing.

RESULTS. Primary tumors were gastric (n – 48), duodenal (n – 23), and pancre-

The Southwestern Surgical Congress

A proposed staging system for small bowel carcinoid tumors based on an analysis of 6,380 patients

Christine S. Landry, M.D.[a], Guy Brock, Ph.D.[b],
Charles R. Scoggins, M.D., M.B.A.[a], Kelly M. McMasters, M.D., Ph.D.[a],
Robert C.G. Martin, II, M.D.[a,*]

A proposed staging system for rectal carcinoid tumors based on an analysis of 4701 patients

Christine S. Landry, MD,[a] Guy Brock, PhD,[b] Charles R. Scoggins, MD,[a]
Kelly M. McMasters, MD, PhD,[a] *and* Robert C. G. Martin II, MD,[a] *Louisville, Ky*

Proposed Staging System for Colon Carcinoid Tumors Based on an Analysis of 2,459 Patients

Christine S Landry, MD, Guy Brock, PhD, Charles R Scoggins, MD, Kelly M McMasters, MD, PhD, FACS,
Robert CG Martin II, MD, FACS

Classificazione TNM

Table 3 Proposal for a TNM classification and disease staging for endocrine tumors of the pancreas

TNM			
T—primary tumor			
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)		
	For any T, add (m) for multiple tumors		
N—regional lymph nodes			
NX	Regional lymph node cannot be assessed		
N0	No regional lymph node metastasis		
N1	Regional lymph node metastasis		
M—distant metastases			
MX	Distant metastasis cannot be assessed		
M0	No distant metastases		
M1[a]	Distant metastasis		
Stage			
Disease stages			
Stage I	T1	N0	M0
Stage IIa	T2	N0	M0
IIb	T3	N0	M0
Stage IIIa	T4	N0	M0
IIIb	Any T	N1	M0
Stage IV	Any T	Any N	M1

[a]M1 specific sites defined according to Sobin and Wittekind [29]

TNM- classification

Tumor-staging

Classificazione pTNM

SEDE	pTis	pT1	pT2	pT3	pT4
Stomaco	CIS/displasia; <0,5 cm	LP/SM e ≤ 1cm	MP/SS o > 1 cm	Sierosa	Adiacenti strutture
Duodeno/ digiuno superiore	NA	LP/SM e ≤ 1cm (a)	MP/SS o > 1 cm	Pancreas o retroperitoneo	Peritoneo o adiacenti strutture
Pancreas	NA	Limitato al pancreas, ≤2 cm	Limitato al pancreas, 2 - 4 cm	Limitato al pancreas, >4 cm o invasione duodeno o dotto biliare	Adiacenti strutture o parete dei grossi vasi
Digiuno inferiore, ileo	NA	LP/SM e ≤ 1cm	MP o > 1 cm	SS	Peritoneo o adiacenti strutture
Appendice	NA	≤1 cm, SM/MP	≤2 cm, SM/MP e/o minimale (<3 mm) SS/meso	>2 cm, SM/MP e/o estesa (>3 mm) SS/meso	Peritoneo o adiacenti strutture
Colon, retto	NA	1a: LP/SM e ≤ 1cm 1b: LP/SM e >1 ≤ 2cm	MP o > 2 cm	SS/TFA pericolico/perirettale	Peritoneo viscerale e/o adiacenti strutture

a) Paraganglioma: limitato alla papilla di Vater

TNM-Grading

L'attività proliferativa del singolo tumore determina la storia naturale della malattia e può correlarsi con la responsività alla chemioterapia

Table 4 Grading proposal for foregut (neuro)endocrine tumors

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

[a] 10 HPF: high power field=2 mm^2, at least 40 fields (at 40× magnification) evaluated in areas of highest mitotic density
[b] MIB1 antibody; % of 2,000 tumor cells in areas of highest nuclear labeling

TNM-Grading

L'attività proliferativa, definita da conta mitotica e da Ki 67 /Mib1 migliora il grading dei NET ben differenziati

Table 4 Grading proposal for foregut (neuro)endocrine tumors

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

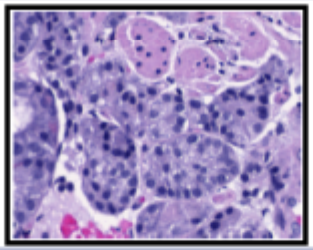
[a] 10 HPF: high power field=2 mm^2, at least 40 fields (at 40× magnification) evaluated in areas of highest mitotic density

[b] MIB1 antibody; % of 2,000 tumor cells in areas of highest nuclear labeling

Patient	[unknown]
DOB	[unknown]
Accession #	[unknown]
Specimen Site	[unknown]
Date Collected	[unknown]
Referring Physician	[unknown]

CASE SUMMARY REPORT

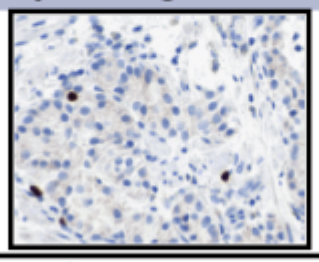
Case: B2009000677 **Study: [none]**

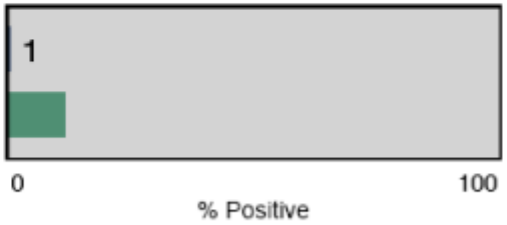
Summary of Findings		Test Name	Type	Path. Score
H&E		Ki-67	% Positive	1

Individual Assay Findings

Computer-Assisted Pathologist Score Negative Range

Ki-67





Computer-Assisted Pathologist Score: 1

Negative Range: 0 - 1

Barcode: 1458

Pathologist Comments:

[none given]

Contenuti minimi del referto
1) Prelievo bioptico

- Conferma della natura neuroendocrina della neoplasia (sinaptofisina, cromogranina, CD56)
- Classificazione sec. WHO
- Indice mitotico/Indice di proliferazione (mib 1)
- Presenza di invasione vascolare

Contenuti minimi del referto AP
2) Specimen operatorio

- Dimensione della neoplasia
- Conferma della natura neuroendocrina della neoplasia (sinaptofisina, cromogranina, CD56)
- Classificazione sec. WHO
- Livello dell'infiltrazione neoplastica
- Indice mitotico/Indice di proliferazione (mib 1)
- Presenza di invasione vascolare
- Stato dei margini di resezione
- Numero e stato dei linfonodi esaminati


smettila qui

2006-….. Stadiazione dei GEP-NET

TNM	Proposal for a TNM classification and disease staging for gastric endocrine tumors
T—primary tumor	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	In situ tumor/dysplasia (<0.5 mm)
T1	Tumor invades lamina propria or submucosa and ≤1 cm
T2	Tumor invades muscularis propria or subserosa or >1 cm
T3	Tumor penetrates serosa
T4	Tumor invades adjacent structures
	For any T, add (m) for multiple tumors
N—regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M—distant metastasis	
MX	Distant metastasis cannot be assessed
M0	No distant metastases
M1[a]	Distant metastasis

[a]M1 specific sites defined according to Sobin and Wittekind [29]

2006-….. Stadiazione dei GEP-NET

Proposal for a TNM classification for endocrine tumors of the duodenum/ampulla/proximal jejunum

T—primary tumor	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor invades lamina propria or submucosa and size ≤1 cm[a]
T2	Tumor invades muscularis propria or size >1 cm
T3	Tumor invades pancreas or retroperitoneum
T4	Tumor invades peritoneum or other organs
	For any T, add (m) for multiple tumors
N—regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M—distant metastases	
MX	Distant metastasis cannot be assessed
M0	No distant metastases
M1[b]	Distant metastasis

[a]Tumor limited to ampulla of Vater for ampullary gangliocytic paraganglioma
[b]M1 specific sites defined according to Sobin and Wittekind [29]

2006-….. Stadiazione dei GEP-NET

Proposal for a TNM classification and disease staging for endocrine tumors of the pancreas

T—primary tumor	
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)
	For any T, add (m) for multiple tumors
N—regional lymph nodes	
NX	Regional lymph node cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M—distant metastases	
MX	Distant metastasis cannot be assessed
M0	No distant metastases
M1[a]	Distant metastasis

[a] M1 specific sites defined according to Sobin and Wittekind [29]

2006-….. Grading dei GEP-NET

Grading proposal for foregut (neuro)endocrine tumors

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

[a] 10 HPF: high power field=2 mm^2, at least 40 fields (at 40× magnification) evaluated in areas of highest mitotic density

[b] MIB1 antibody; % of 2,000 tumor cells in areas of highest nuclear labeling

2006-….. Staging dei GEP-NET

Table 1 Proposal for a TNM classification for endocrine tumors of lower jejunum and ileum

T-primary tumor	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor invades mucosa or submucosa and size ≤1 cm
T2	Tumor invades muscularis propria or size >1 cm
T3	Tumor invades subserosa
T4	Tumor invades peritoneum/other organs
For any T add (m) for multiple tumors	
N regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M	Distant metastasis
MX	Distant metastasis cannot be assessed
M0	No distant metastases
M1[a]	Distant metastasis

[a] M1 specific sites defined according to Sobin LH, Wittekind C [32].

2006-….. Staging dei GEP-NET

Table 3 Proposal for a TNM classification for endocrine tumors of the appendix

T-primary tumor	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≤1 cm invading submucosa and muscularis propria
T2	Tumor ≤2 cm invading submucosa, muscularis propria and/or minimally (up to 3 mm) invading subserosa/ mesoappendix
T3	Tumor >2 cm and/or extensive (more than 3 mm) invasion of subserosa/mesoappendix
T4	Tumor invades peritoneum/other organs
N-regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M-distant metastasis	
MX	Distant metastasis cannot be assessed
M0	No distant metastases
M1[a]	Distant metastasis

2006-….. Staging dei GEP-NET

Table 5 Proposal for a TNM classification for endocrine tumors of colon and rectum

T-primary tumor	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor invades mucosa or submucosa
	T1 a size <1 cm
	T1 b size 1–2 cm
T2	Tumor invades muscularis propria or size >2 cm
T3	Tumor invades subserosa/pericolic/perirectal fat
T4	Tumor directly invades other organs/structures and/or perforates visceral peritoneum
For any T add (m) for multiple tumors	
N-regional lymph nodes	
NX	Regional lymph node status cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M-distant metastases (subspecification as in small bowel)	
MX	Distant metastasis cannot be assessed
M0	No distant metastases
M1[a]	Distant metastasis

2006-….. Grading dei GEP-NET

Table 7 Grading proposal for (neuro)endocrine tumors of ileum, appendix, colon and rectum

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

* 10 HPF (High Power Field)=2 mm^2, at least 40 fields (at 40× magnification) evaluated in areas of highest mitotic density; ** MIB1 antibody; % of 2000 tumor cells in areas of highest nuclear labeling.

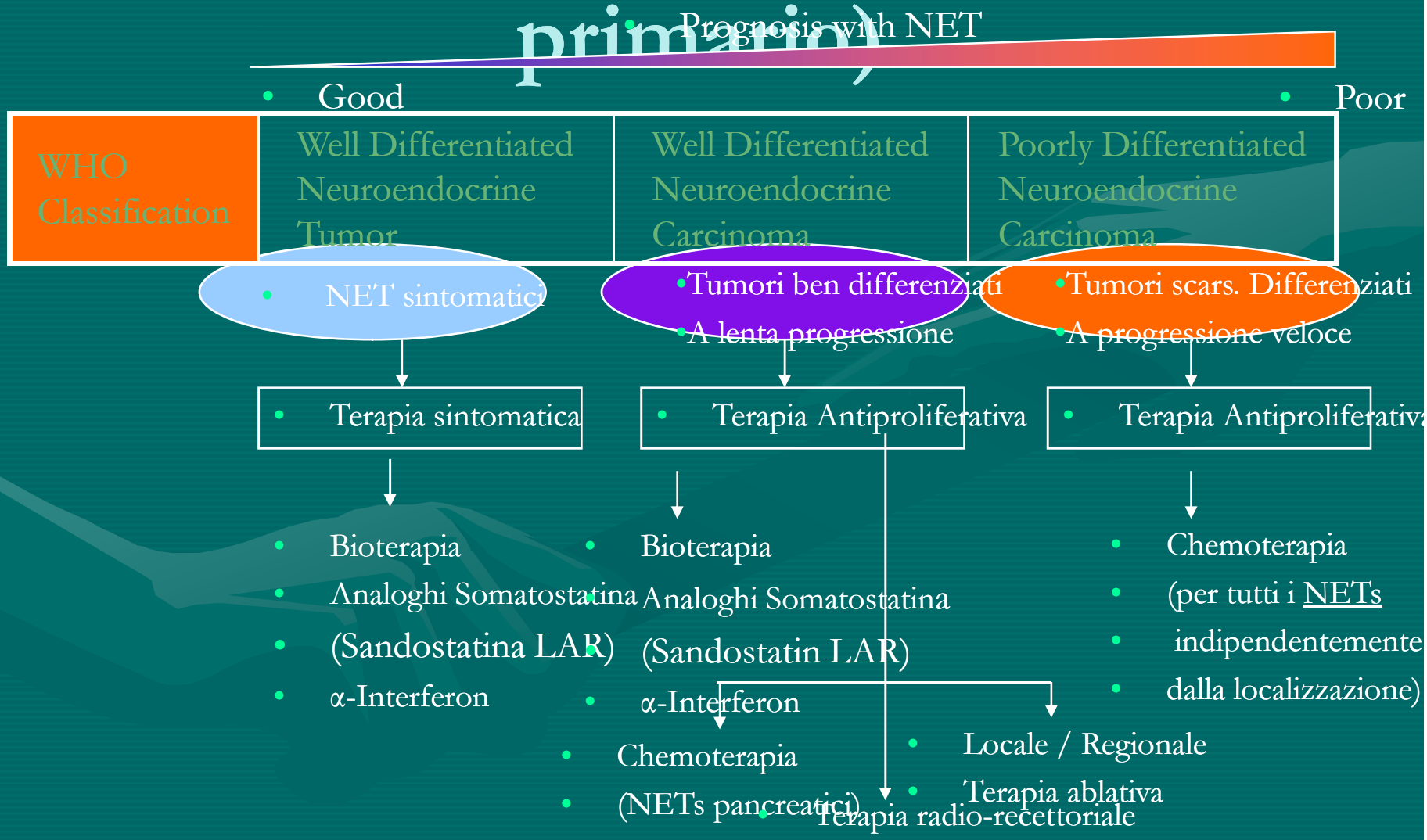
Classificazione TNM - NETs

- TNM →Tumor(Primary)- LympNodes- (distant) Metastasis

1. Classificazione TNM:
   - Descrive in modo dettagliato la dimensione tumorale e lo stato linfonodale senza però dare informazioni precise sul burden del tumore o sulla stratificazione del rischio
   - Permette di classificare i tumori in stadi specifici, applicare una diagnosi più differenziata e, di conseguenza, trattamenti più specifici che in passato
   - Presenta un grading più specifico che in passato (WHO)

- Here is a general overview of where carcinoid tumors begin:
- 39% occur in the small intestine
- 15% occur in the rectum
- 10% occur in the bronchial system of the lungs
- 7% occur in the appendix
- 5% to 7% occur in the colon
- 2% to 4% occur in the stomach
- 2% to 3% occur in the pancreas
- About 1% occur in the liver
- Rarely in ovaries, testicles, and other organs
- Carcinoid tumors make up only 1% of cancers of the gastrointestinal tract, but make up about 50% of all small intestine cancers.

dopo chirurgia non curativa (debulking, resezione del T. primario)



Punti fondamentali:

- Una esatta classificazione clinicopatologica determina la prognosi
- Le varie tipologie tumorali hanno un comportamento differente e richiedono un trattamento individualizzato
- L'attività proliferativa del singolo tumore determina la storia naturale della malattia e può correlarsi con la responsività alla chemioterapia
- Per la normale pratica clinica, i criteri dati dalla classificazione WHO possono essere usati come una checklist con la quale classificare ogni singolo tumore

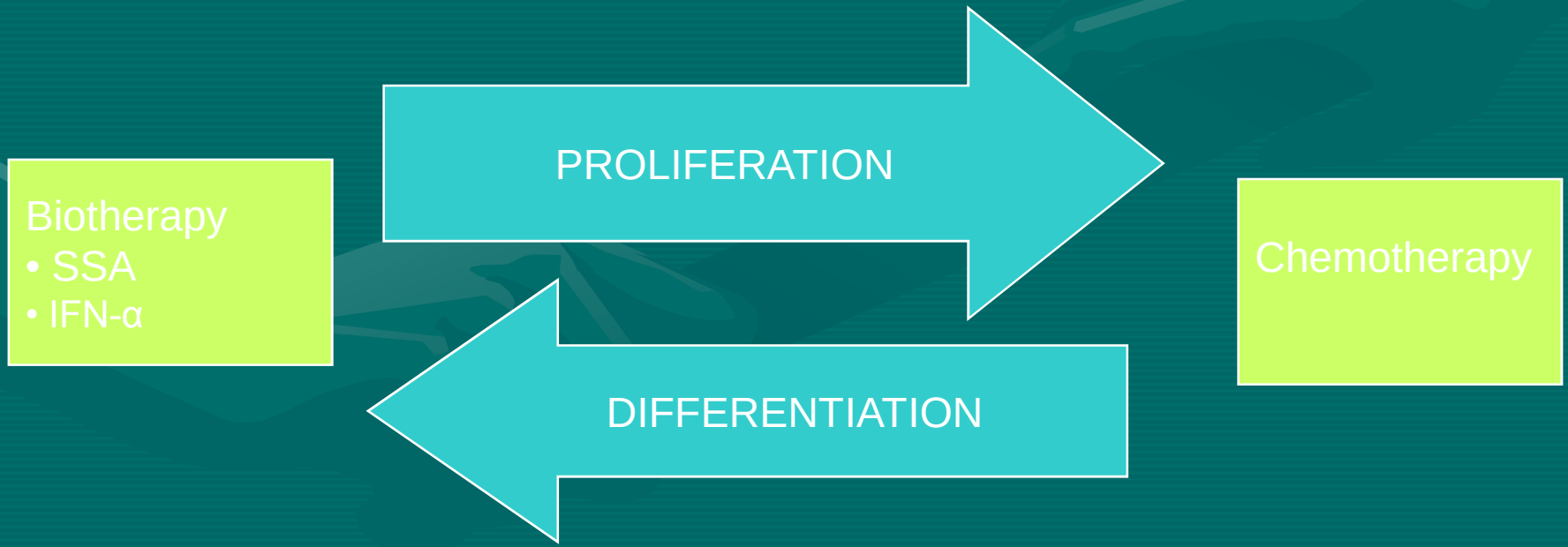
Kloeppel 2007, Best Practice&ResearchClinicalEndocrinol.&Metab.;*Tumor biology and histopathology of NETs*

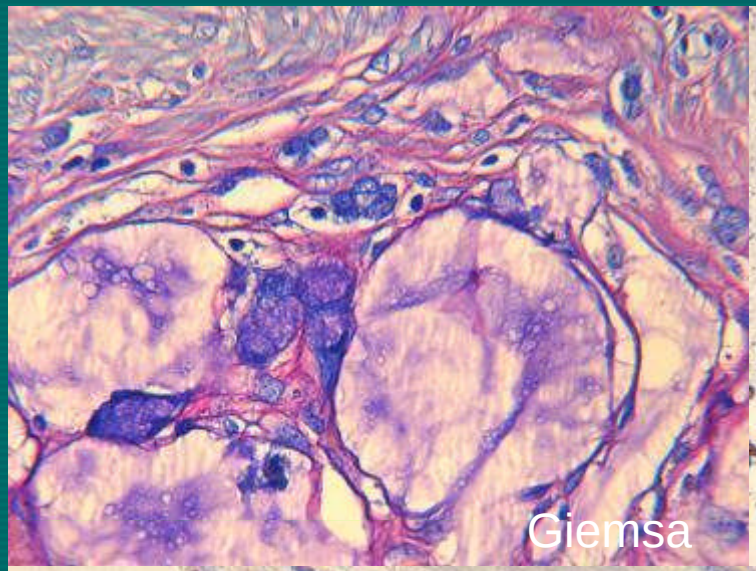
Proposed TNM classification and

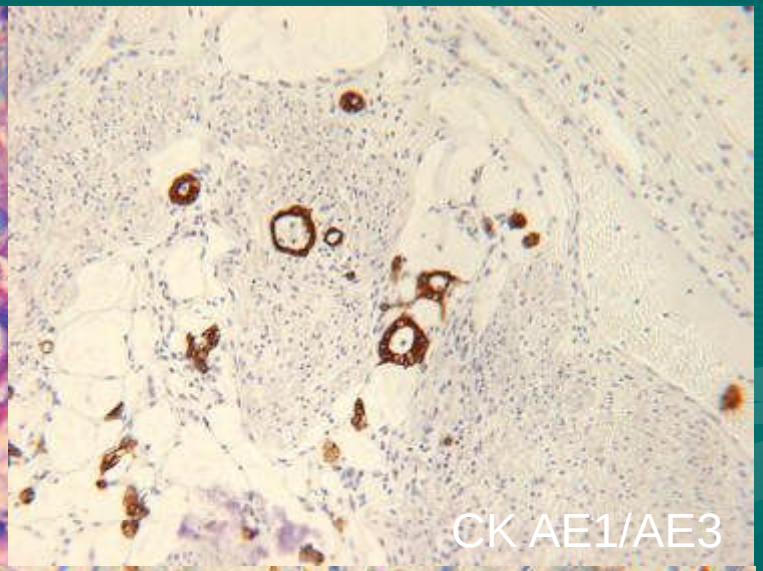
Table 4 Grading proposal for foregut (neuro)endocrine tumors

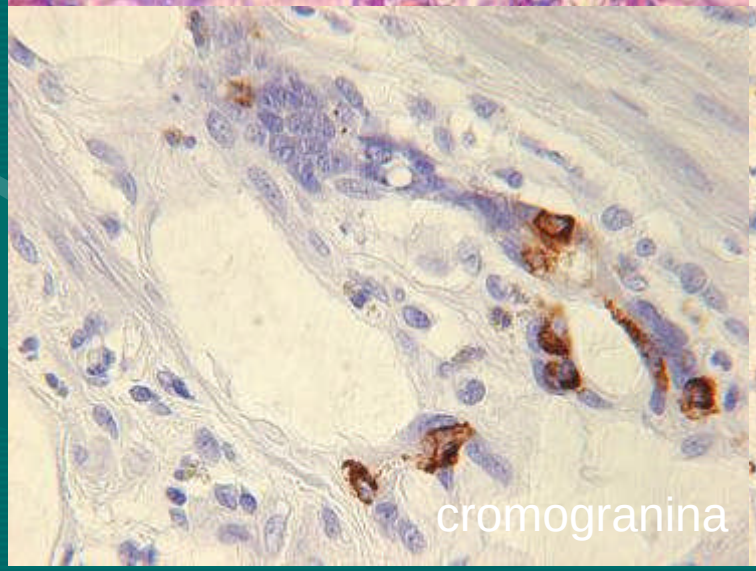
Grade	Mitotic count (10 HPF)[a]	Ki-67 index (%)[b]
G1	<2	≤2
G2	2–20	3–20
G3	>20	>20

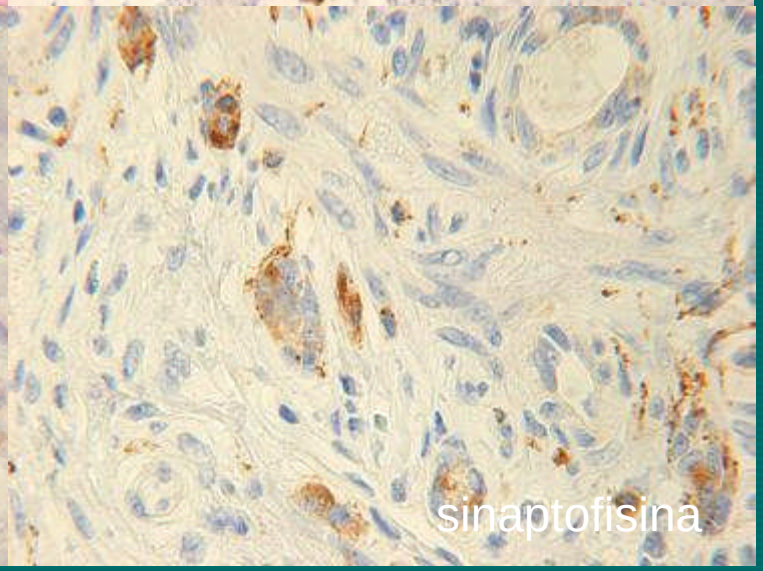
[a]10 HPF: high power field=2 mm^2, at least 40 fields (at 40× magnification) evaluated in areas of highest mitotic density
[b]MIB1 antibody; % of 2,000 tumor cells in areas of highest nuclear labeling

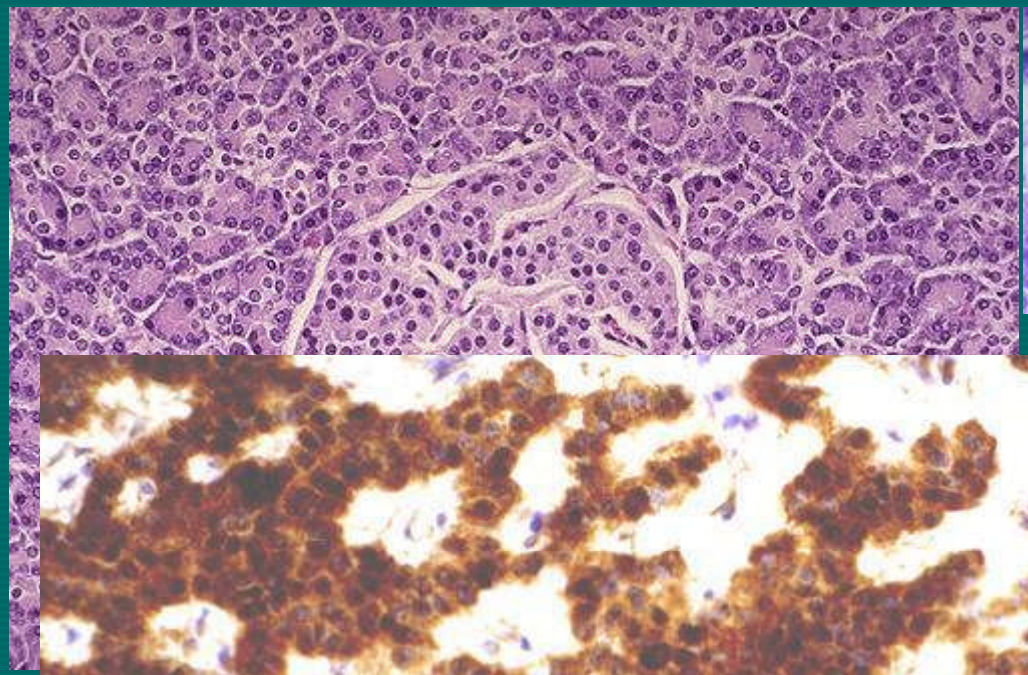


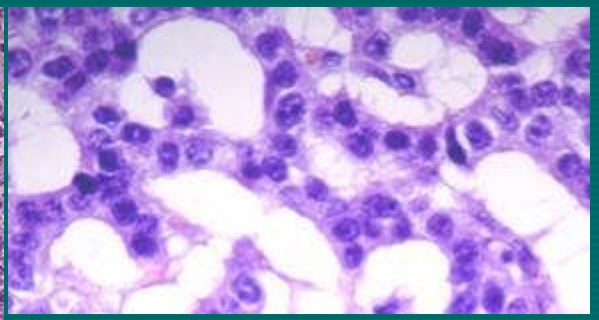

Giemsa

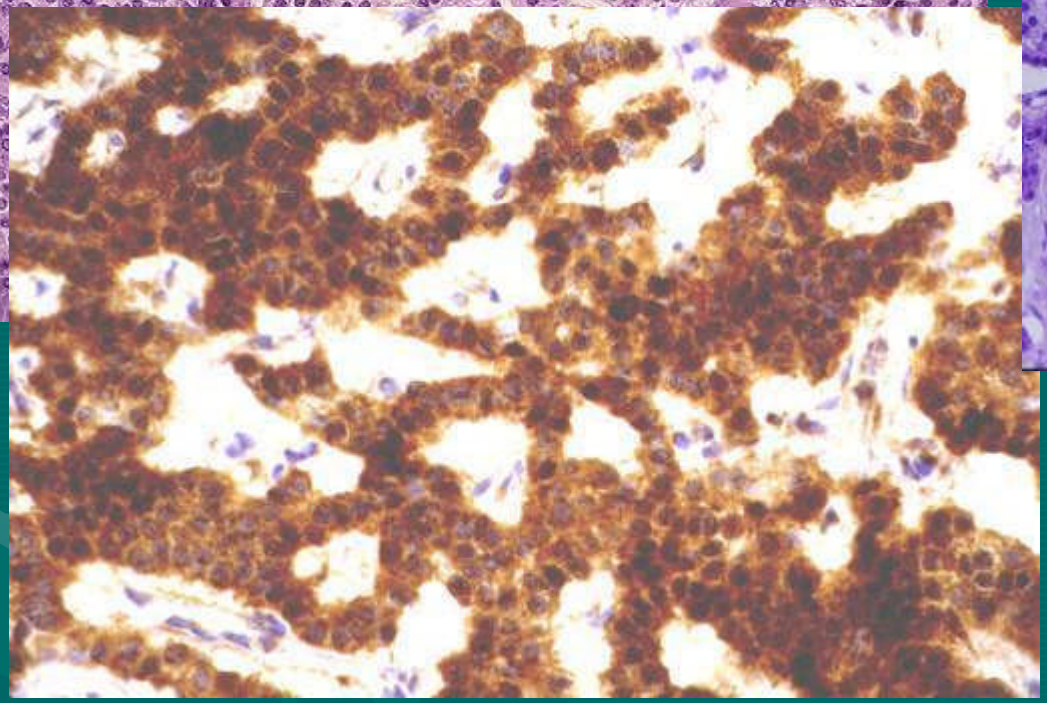

CK AE1/AE3

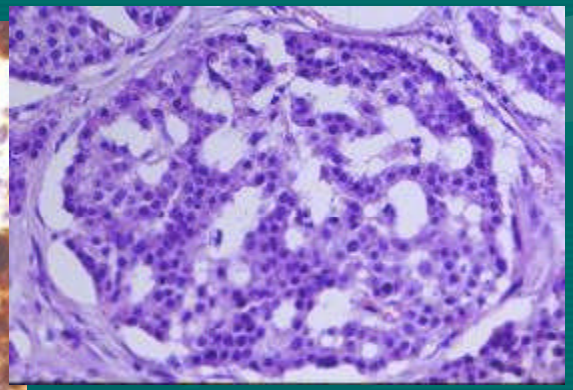

cromogranina


sinaptofisina

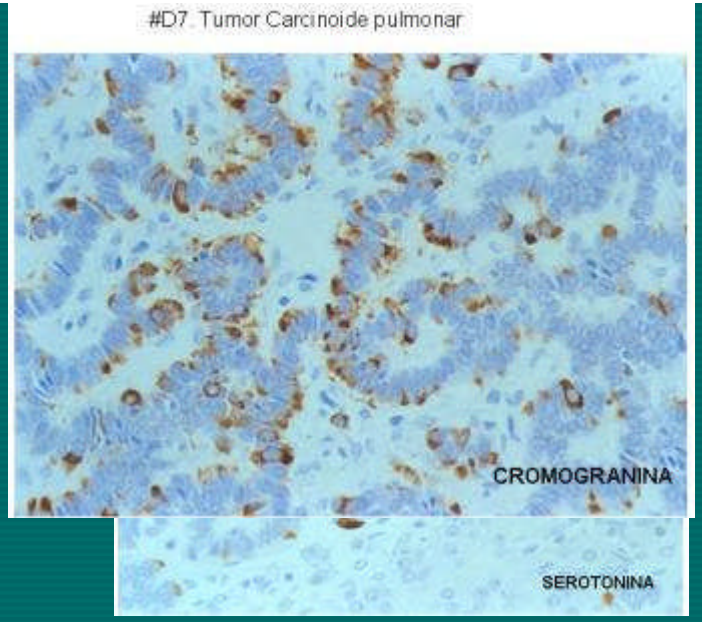


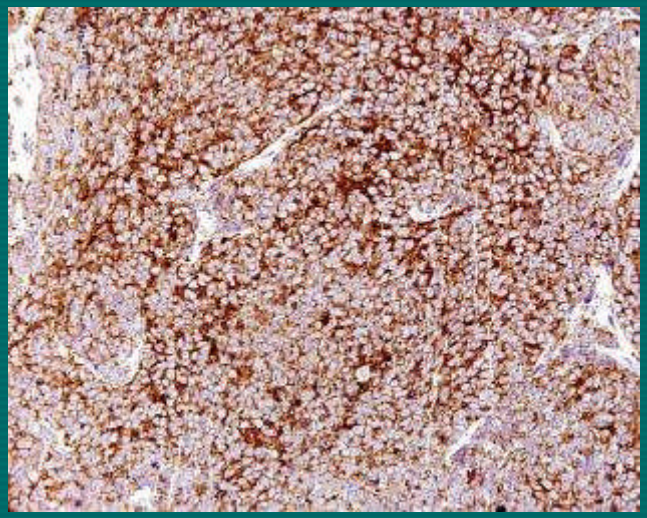




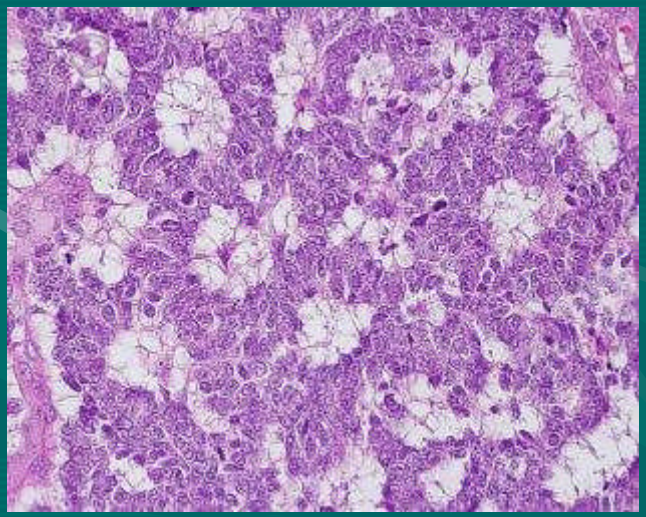


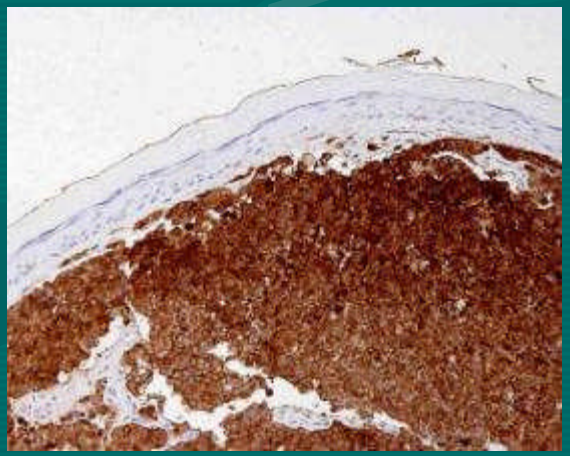
Glucagone+



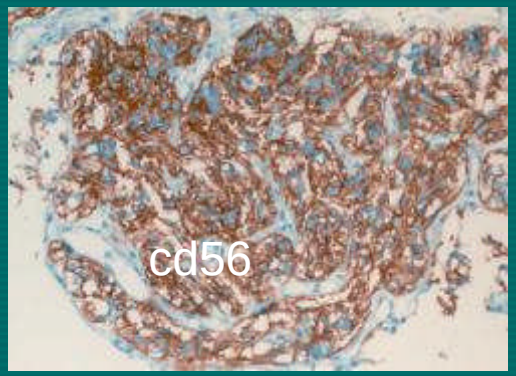


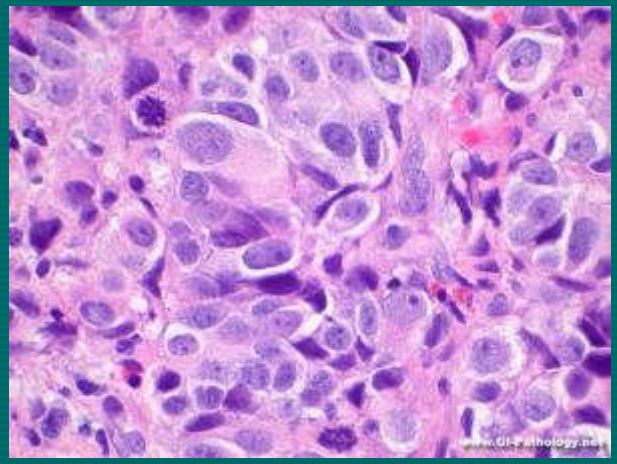
syna
pto



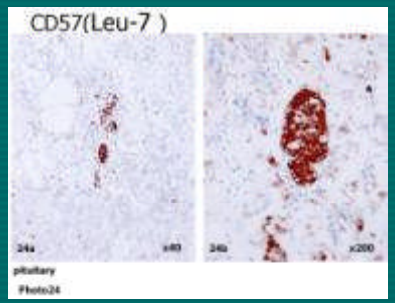


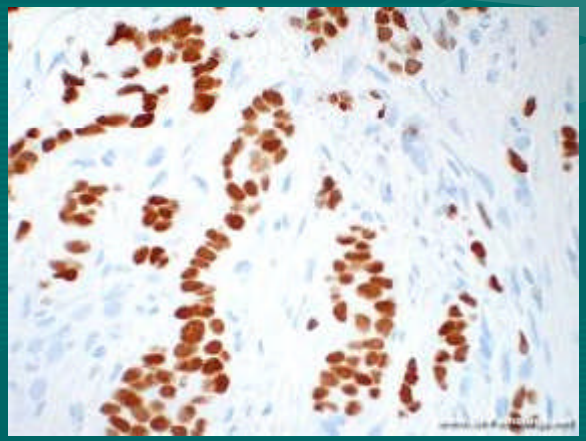
nse



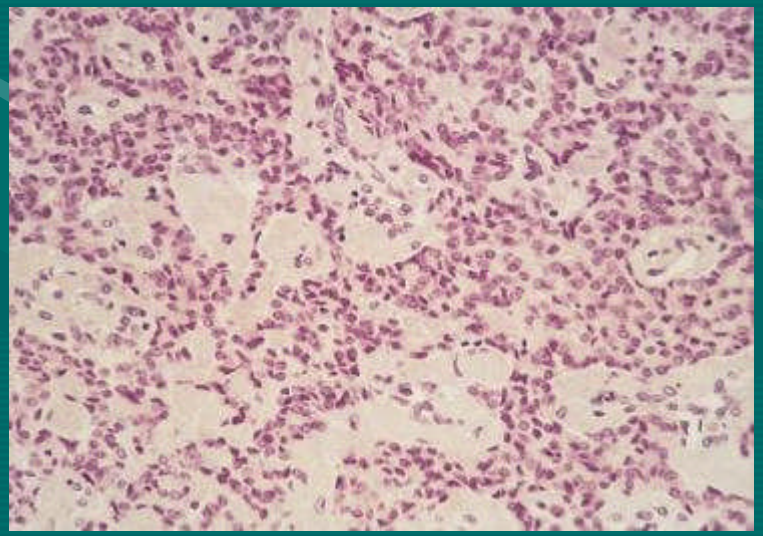


LC
stomaco





Cdx2
colon



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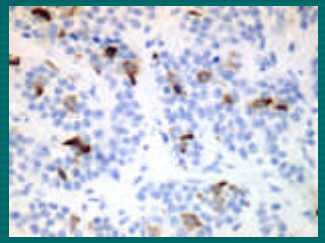

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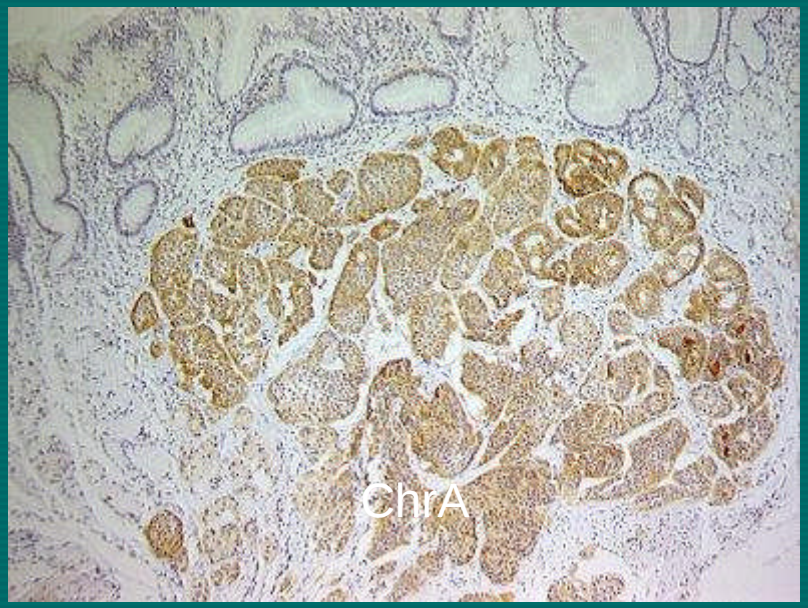
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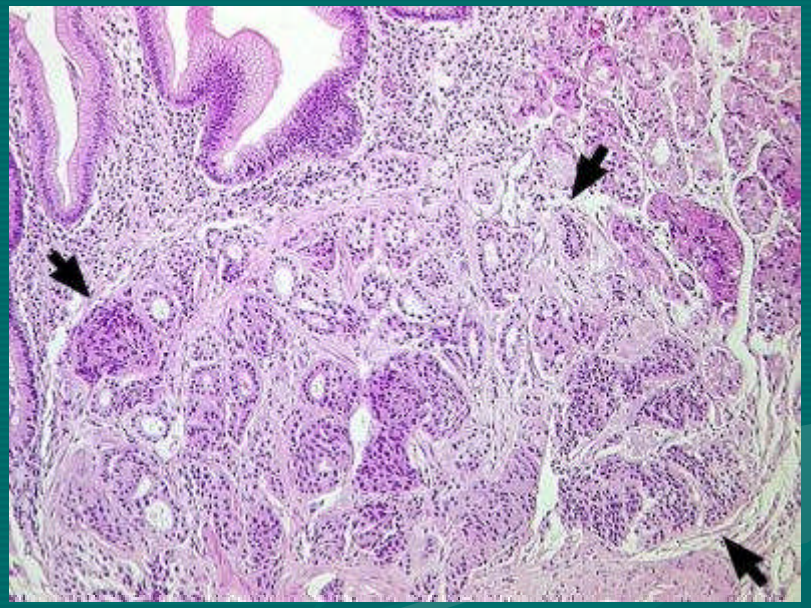

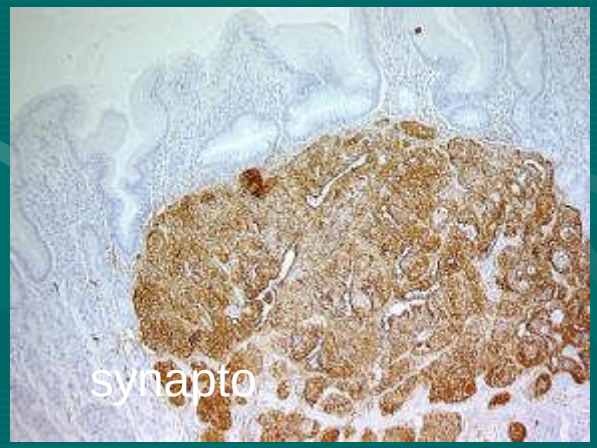
synapto


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