

1869 - descrizione delle *insule pancreatiche* (Langherans)

1888 - descrizione di piccoli tumori ileali e appendicolari scarsamente aggressivi: *piccoli carcinomi* (Lubarsch)

1897 - individuazione delle *cellule cromaffini* nelle cripte della mucosa intestinale (Kultskitsky)

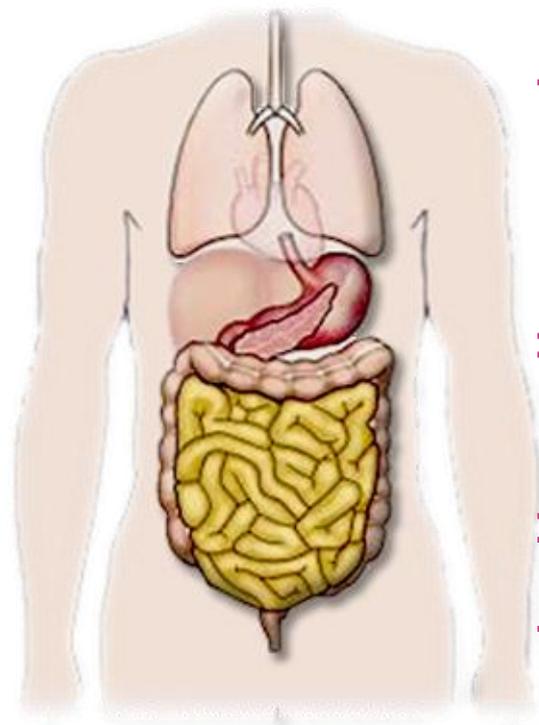
1907 - introduzione del termine *carcinoide* (Oberndorfer)

1930-40 - distribuzione diffusa di cellule endocrine a citoplasma chiaro (*helle zellen*) disperse singolarmente o in piccoli aggregati nelle mucose del tratto gastroenterico e delle vie respiratorie, nel pancreas e in vari altri organi (timo, mammella, cute, prostata, rene, vescica, ovaia) (Feyrter e Folich)

1963 - classificazione dei carcinoidi in base alla sede di origine embriologica dal tubo intestinale primitivo: *foregut* (timo, polmone, stomaco, duodeno, digiuno e pancreas), *midgut* (ileo, appendice, cieco) e *hindgut* (colon, cieco) (William e Sandler)

1979 - sistema endocrino diffuso, *sistema APUD* (Amine Precursors Uptake and Decarboxylation), ipotesi di derivazione dalla cresta neurale (Pearse)

Classificazione embriogenetica delle neoplasie neuroendocrine in rapporto alla derivazione dal tubo gastroenterico: *foregut*, *midgut* e *hindgut*



Foregut

- Timo
- Esofago
- Polmone
- Stomaco
- Duodeno
- Pancreas

Midgut

- Appendice
- Ileo
- Cieco
- Colon ascendente

Hindgut

- Colon trasverso e discendente
- Retto

Attualmente la derivazione dalla *cresta neurale (ectodermica)* è accettata solo per la midollare surrenalica, i gangli, i paragangli, i melanociti e le cellule parafolicolari della tiroide (Adams e Bronner-Fraser, 2009): **cellule neuroendocrine neurali**.

Le altre cellule del sistema endocrino diffuso derivano dalle stesse cellule staminali dell' *endoderma del tubo intestinale primitivo* da cui derivano le cellule epiteliali delle mucose del tratto gastroenterico e le cellule del pancreas: **cellule neuroendocrine epiteliali**.

Tumori neuroendocrini o tumori endocrini?

Le cellule di queste neoplasie - così come la loro controparte normale - esprimono molti antigeni normalmente espressi dalle cellule di derivazione neurale: per questi motivi è preferibile definire *neuroendocrine* le cellule del sistema endocrino diffuso e *neoplasie neuroendocrine* i tumori che ne derivano.

Marcatore neuroendocrini generali

Associati ai granuli di secrezione:

cromogranina A, cromogranina B, secretogranina II (cromogranina C), pancreastatina, parastatina, vasostatina, cromostatina, β -granina, **NESP-55 (neuroendocrine secretory protein 55)**, SV2

In rapporto alle strutture vescicolari:

sinaptofisina, SV2 (synaptic vesicle protein 2), sinaptobrevina

Liberi nel citosol:

NSE (enolasi neurono-specifica), PGP 9,5 (protein gene product 9,5), 7B2, endopeptidasi, carbossipeptidasi, istidina-decarbossilasi

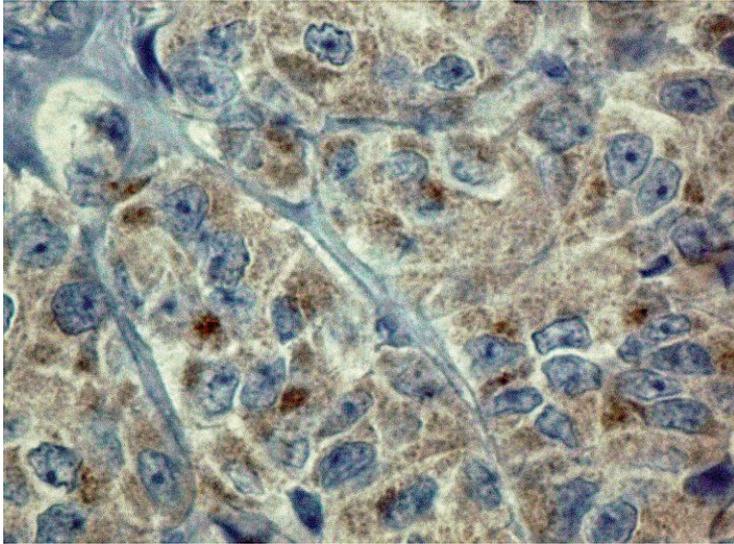
Sulla membrana cellulare:

CD56 (NCAM), **SSTR**, CD57, CD99

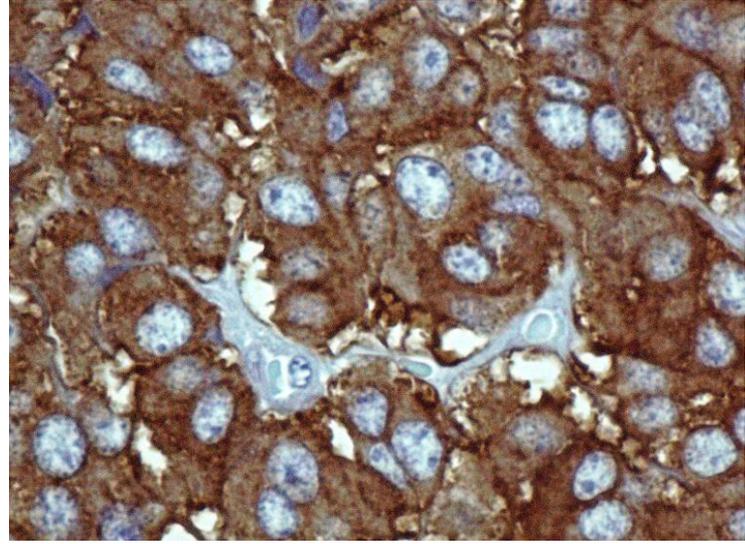
Filamenti intermedi (citoscheletro):

Citocheratine 8, 18, 19 (più espresse nelle cellule neuroendocrine di tipo epiteliale), neurofilamenti (più espressi nelle cellule neuroendocrine di tipo neurale)

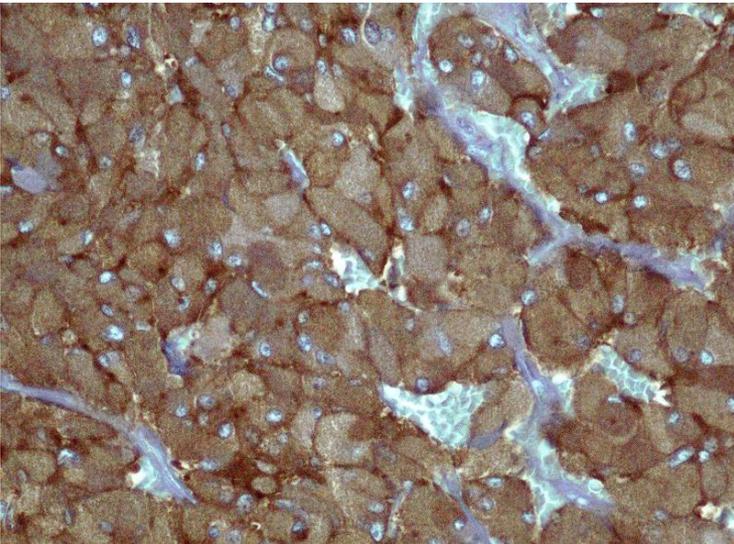
NESP-55: reattività nei tumori neuroendocrini pancreatici; negativo nei NET del tratto GI



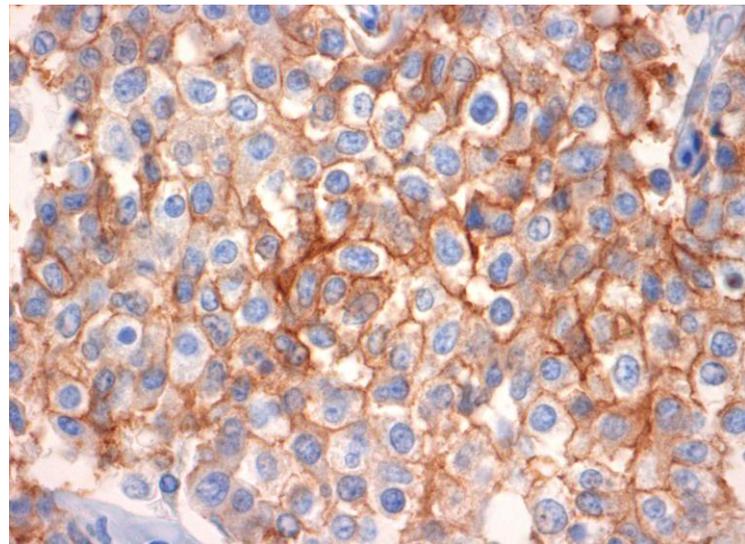
cromogranina A



sinaptofisina



NSE



CD56

Cellule neuroendocrine del tratto gastroenterico

tipo cellulare	localizzazione	argentaff	argirof	prodotto di secrezione
G	antro, duodeno	-	+	gastrina
ECL	fondo gastrico	-	+	istamina
D	stomaco, intestino tenue, colon	-	-	somatostatina
D1/P	fondo gastrico	-	+	grelina
EC	stomaco, tenue, colon, retto	+++	++++	serotonina, sostanza P
I	duodeno, digiuno	-	+/-	CCK
K	duodeno, digiuno	-	+	GIP
M	duodeno, digiuno	-	+	motilina
S	duodeno, digiuno	-	+	secretina
PP	duodeno	-	+	polipeptide pancreatico
L	intestino tenue, colon	-	++	enteroglucagone, peptide
YY				
N	intestino tenue, colon	-	+	neurotensina

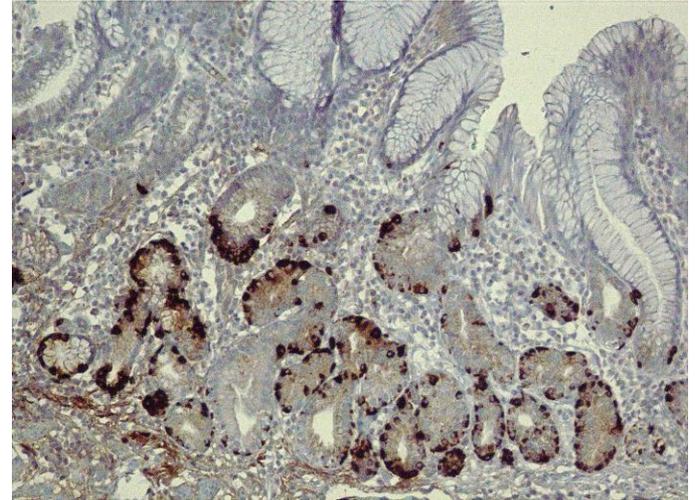
EC cellule Enterocromaffini

ECL cellule Entero Chromaffin Like

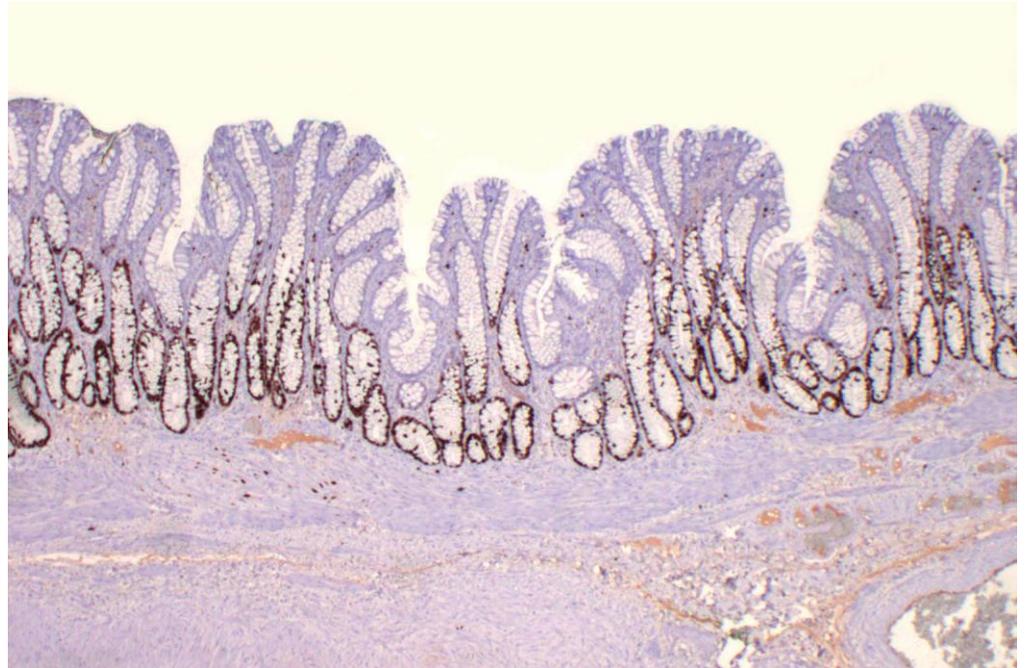
CCK colecistochinina

GIP Gastrin Inhibiting Peptide

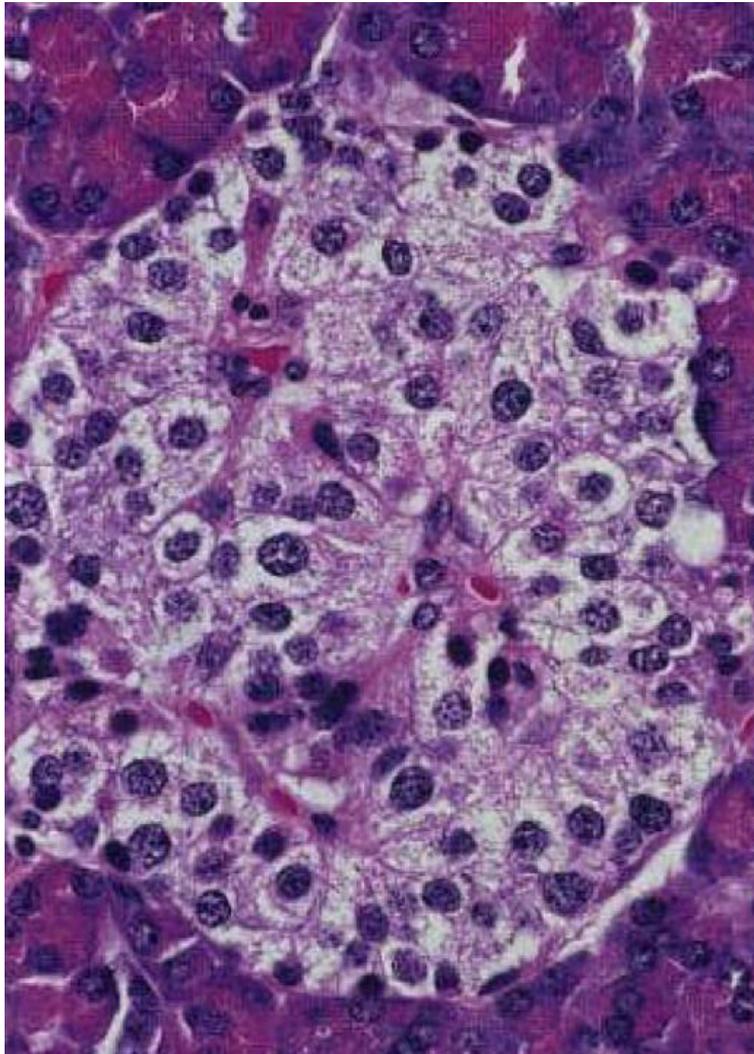
Cellule neuroendocrine del tratto gastroenterico
(cromogranina A)



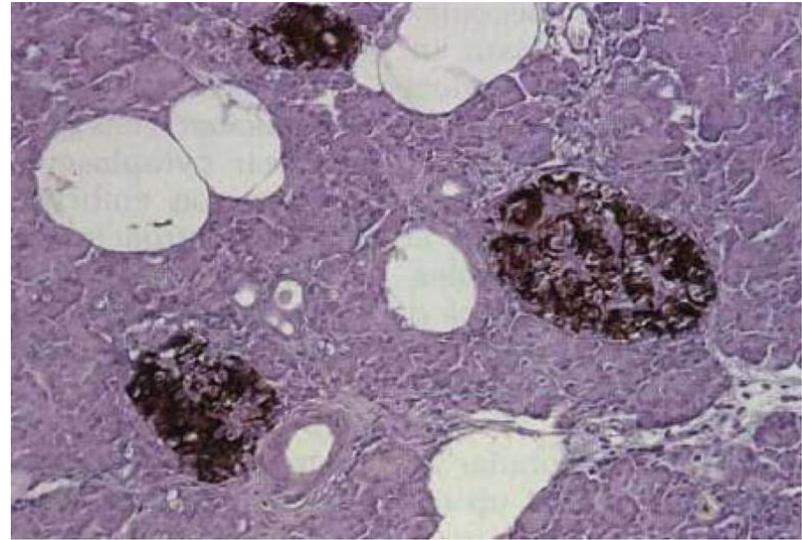
mucosa gastrica antrale



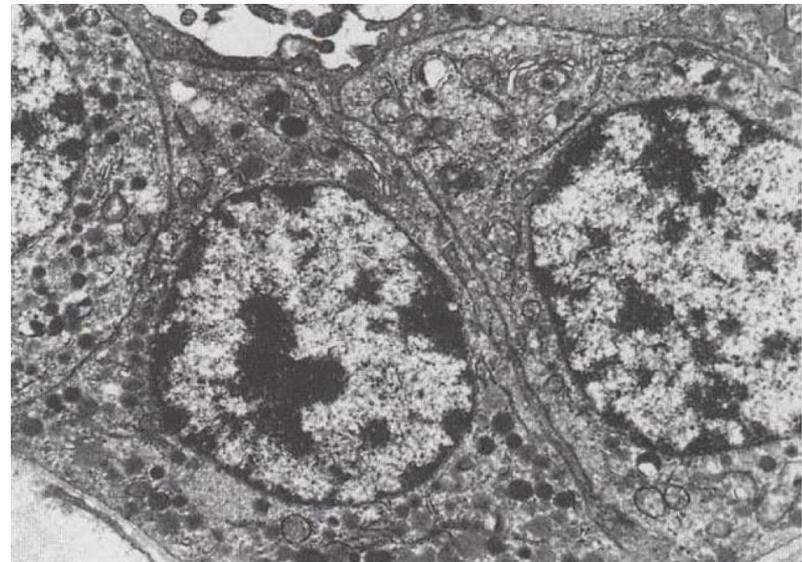
mucosa ileale



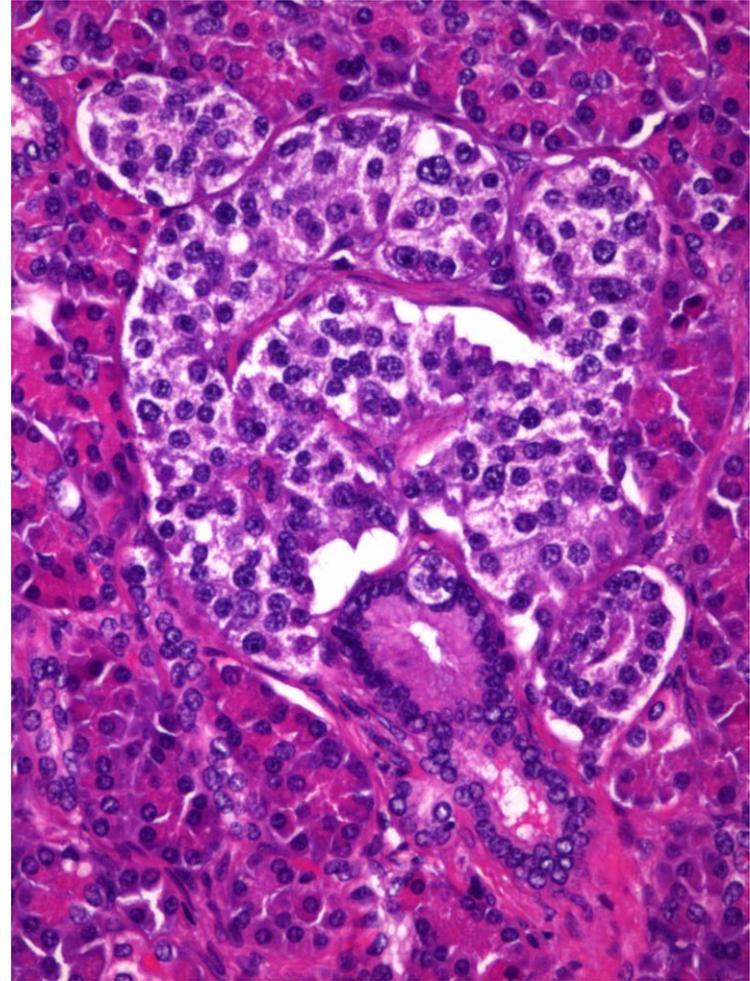
isola di Langerhans



prevalenza (70%) delle cellule B (MAB anti-insulina)



granuli secretori di insulina (ME)



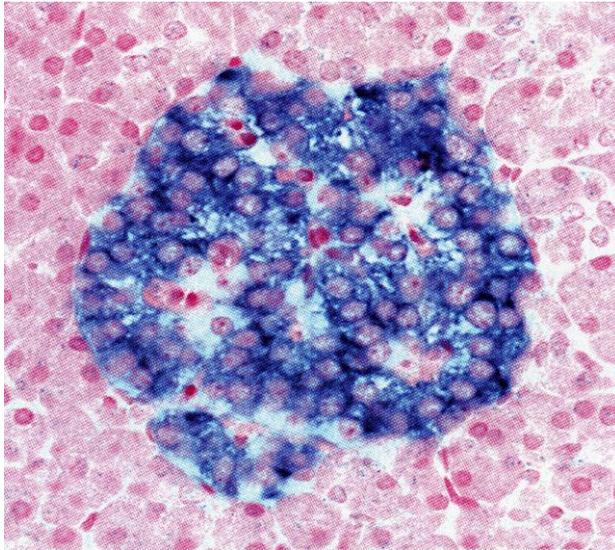
Le isole di Langerhans (e così anche i **tumori neuroendocrini pancreatici**) derivano da precursori presenti nell'epitelio dei dotti e cellule neuroendocrine extrainsulari sono presenti normalmente nel pancreas (MAB anti-PP); la definizione **tumori a cellule insulari** è meno corretta,

Caratteristiche delle cellule insulari

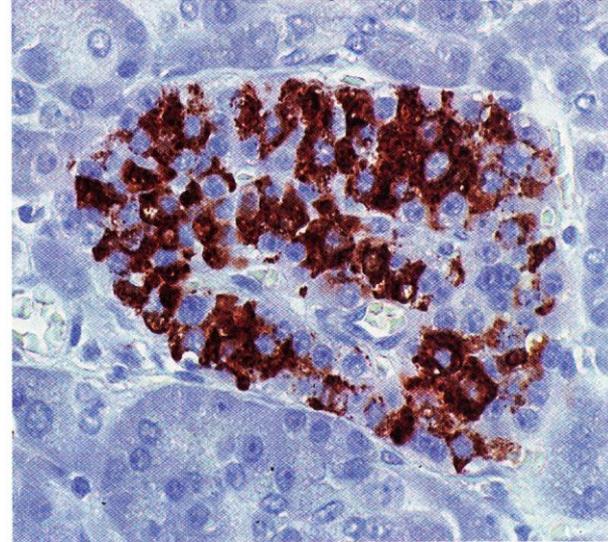
Tipo cellulare	Ormone	Morfologia dei granuli (M.E.)	%sul totale delle cellule endocrine
A	Glucagone	180-300 nm core elettrondenso, rotondo mantello periferico chiaro	15-20
B	Insulina	225-375 nm core cristallino o compatto granulare mantello periferico chiaro	60-70
D	Somatostatina	170-220 nm core uniforme membrana limitante netta	5-10
PP	Polipeptide pancreatico	138-208 nm forma, densita', struttura variabili	15-20

Distribuzione delle cellule B, A e D nelle isole di Langerhans

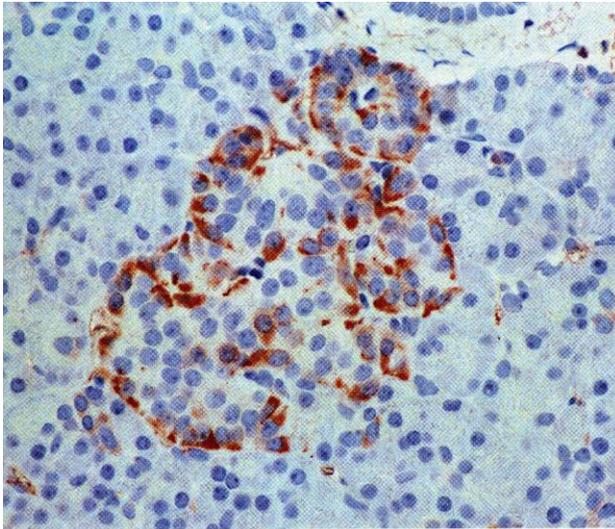
mRNA proinsulina
(ibridazione in situ)



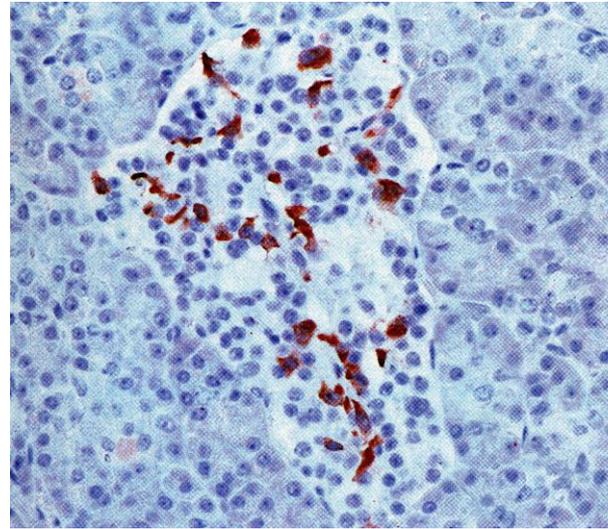
insulina (60-70%)



glucagone (15-20%)

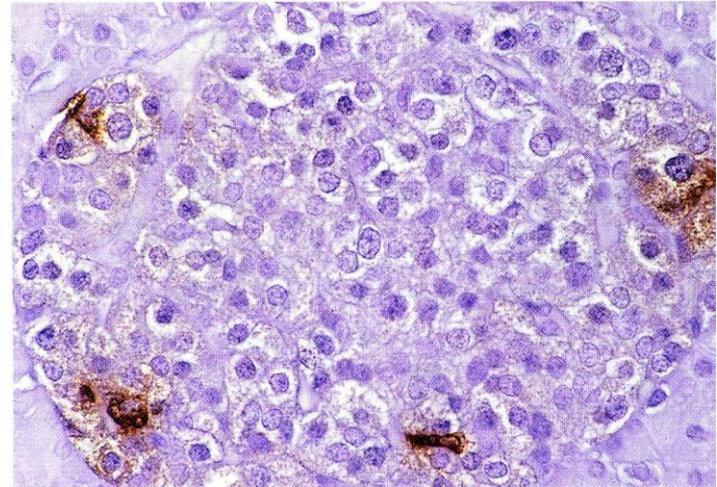
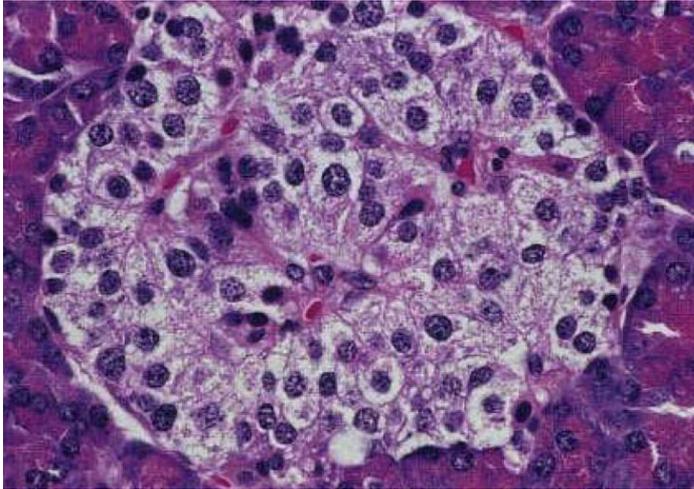


somatostatina (5-10%)

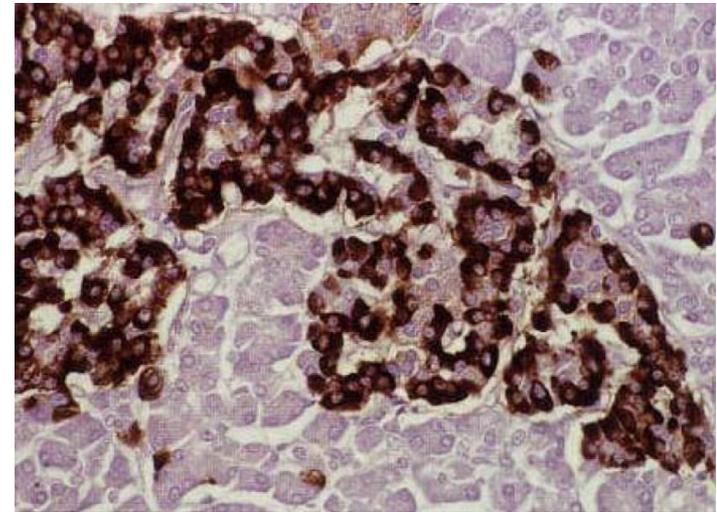
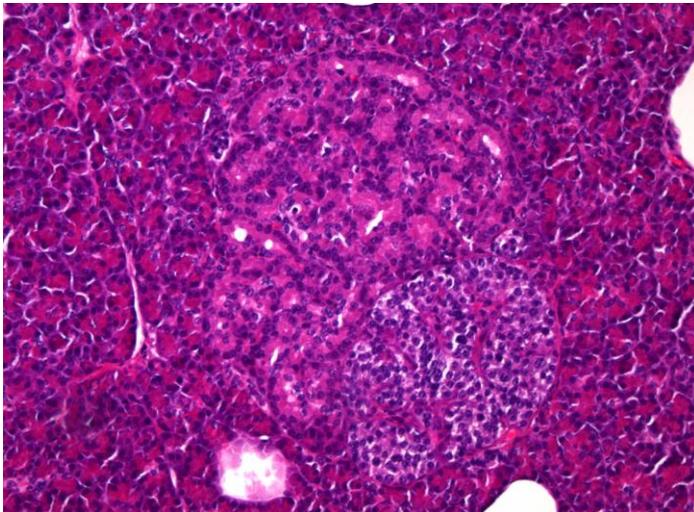


Distribuzione delle cellule PP

Isola regolare
(ordinaria)



Isola irregolare



TUMORI NEUROENDOCRINI DEL PANCREAS

Incidenza attorno all' 1/100.000, lievemente più elevata (1,5/100.000) nelle casistiche autoptiche

Rappresentano circa 1-2% di tutte le neoplasie pancreatiche

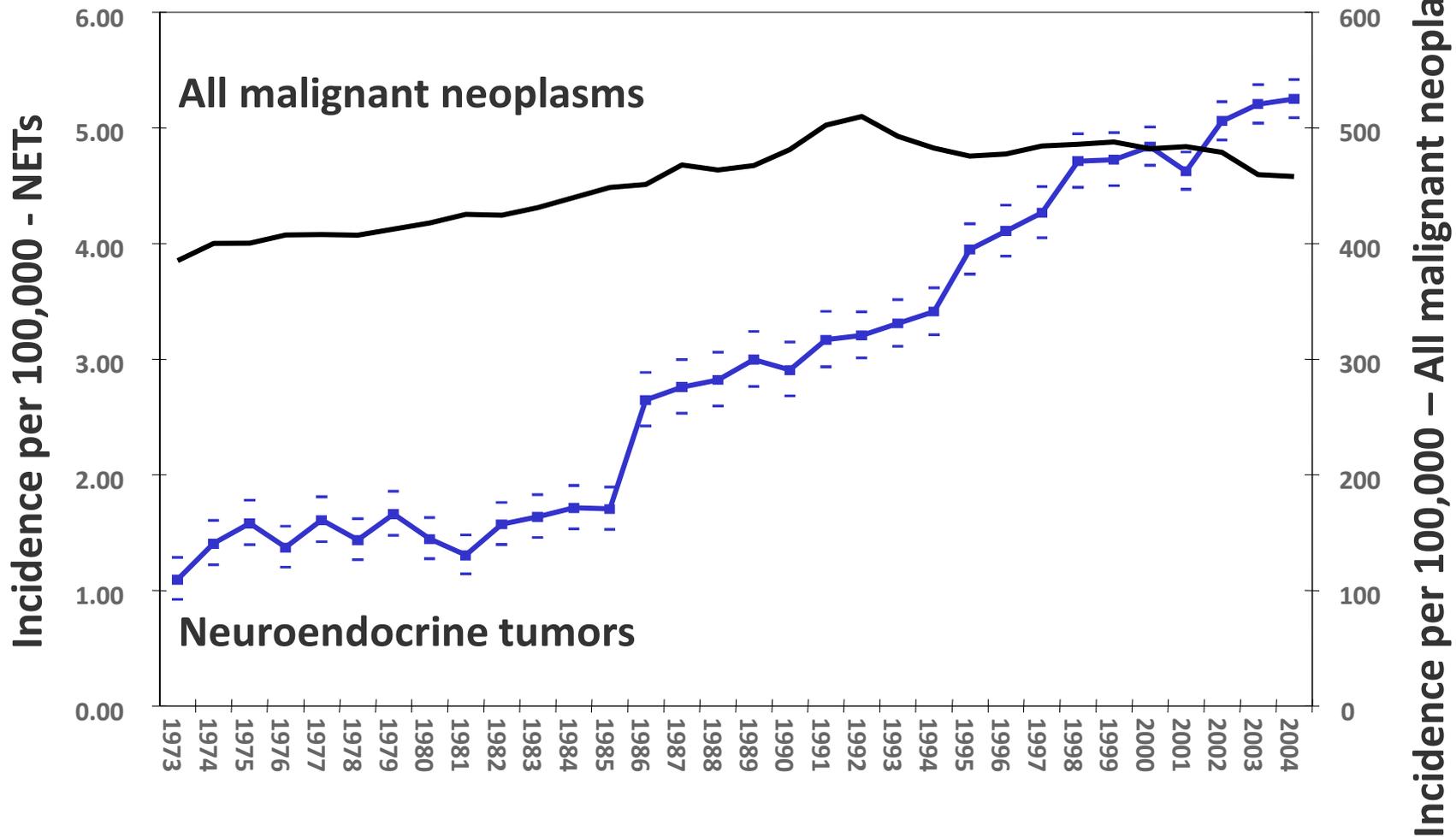
Non presentano differenze significative per genere

Insorgenza più frequente tra 30-60 anni, ma possibili in tutte le età

Associazione con sindromi familiari nel 2% circa dei casi (comparsa più precoce)

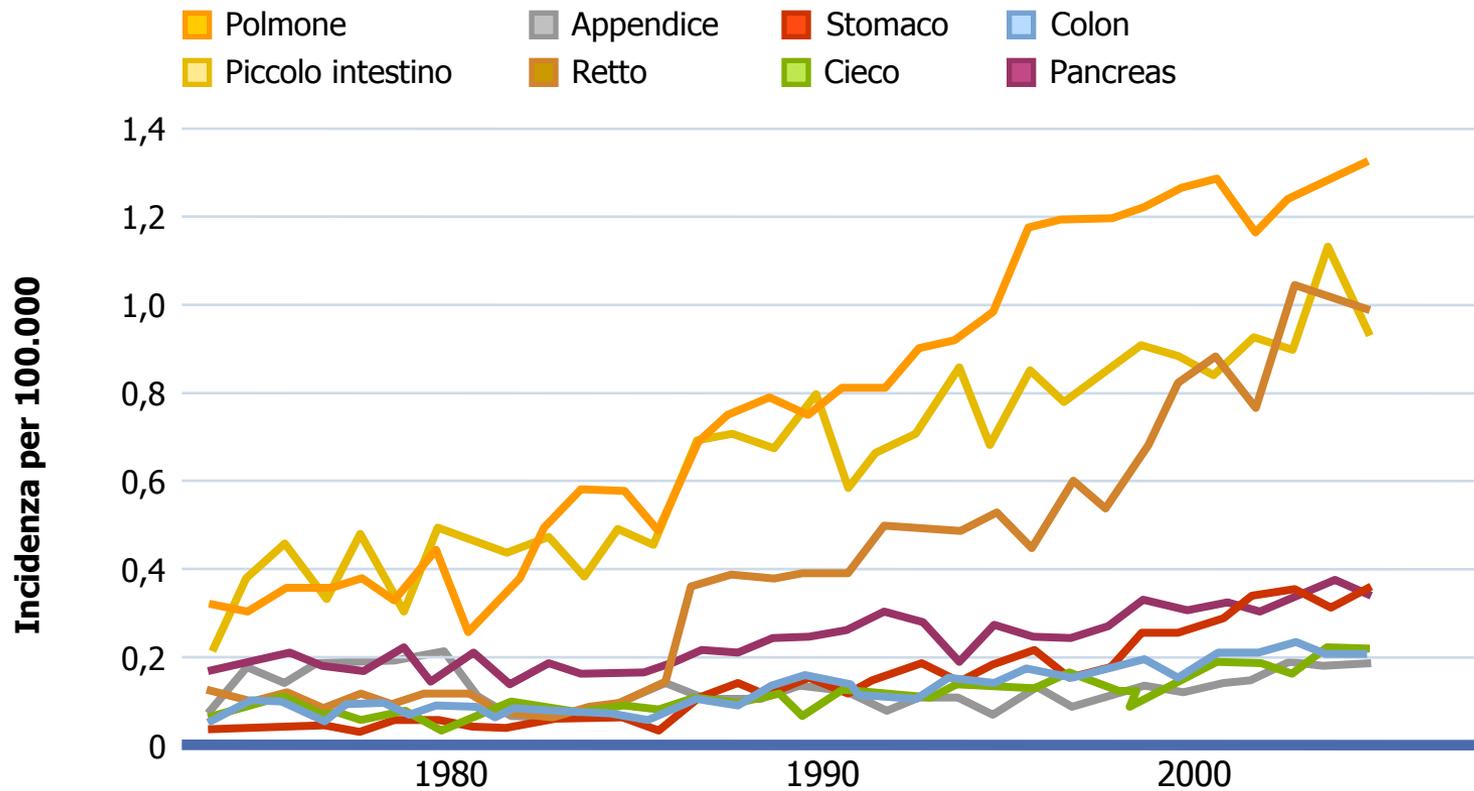
Nel 30-40% non funzionanti (non associati a particolari manifestazioni cliniche):
a diagnosi più tardiva per effetti di compressione, invasione locale, metastasi;
o riscontrati incidentalmente

Incidenza dei tumori neuroendocrini



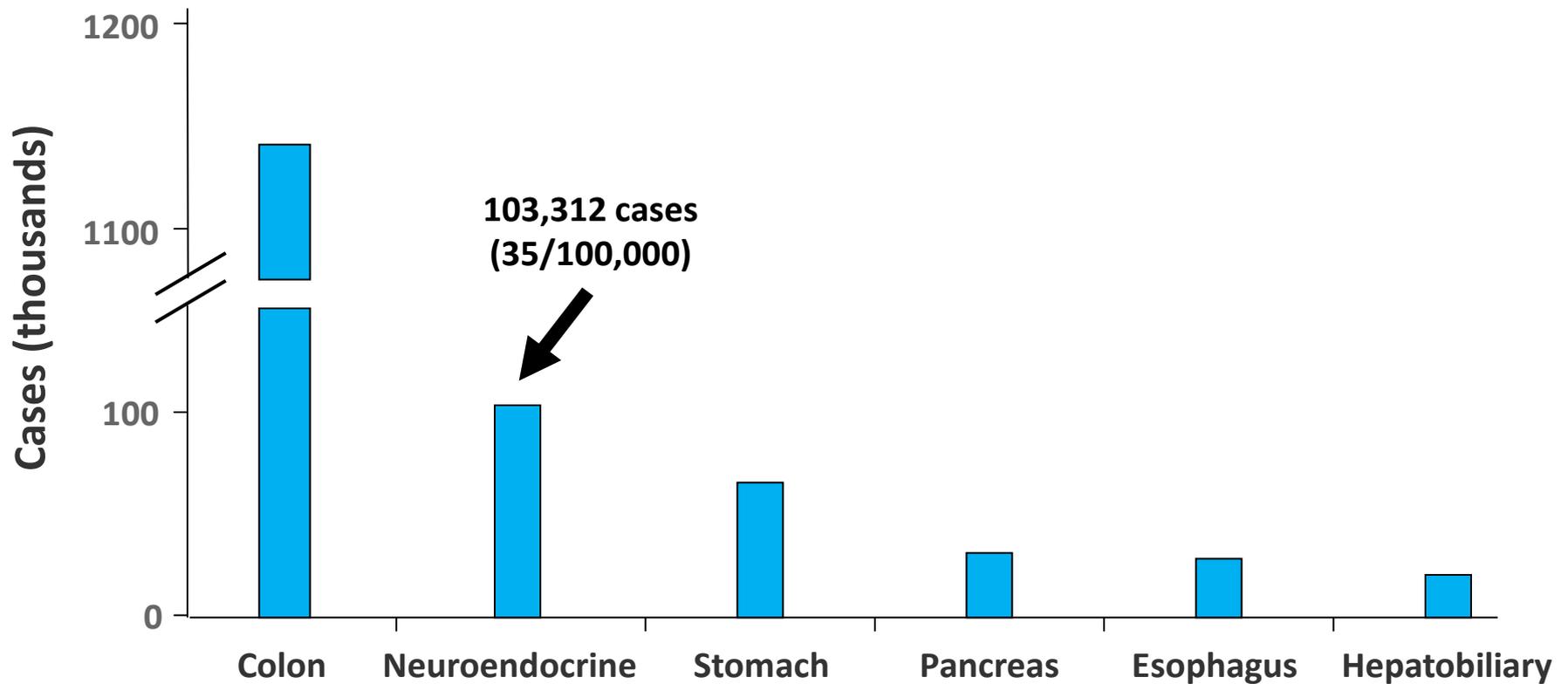
NEOPLASIE NEUROENDOCRINE

Incidenza 1988-2004 (registro USA SEER)



NETs Are Second Most Prevalent Gastrointestinal Tumor

NET Prevalence in the US, 2004



29-year limited duration prevalence analysis based on SEER.

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

SEER = Surveillance, Epidemiology, and End Results

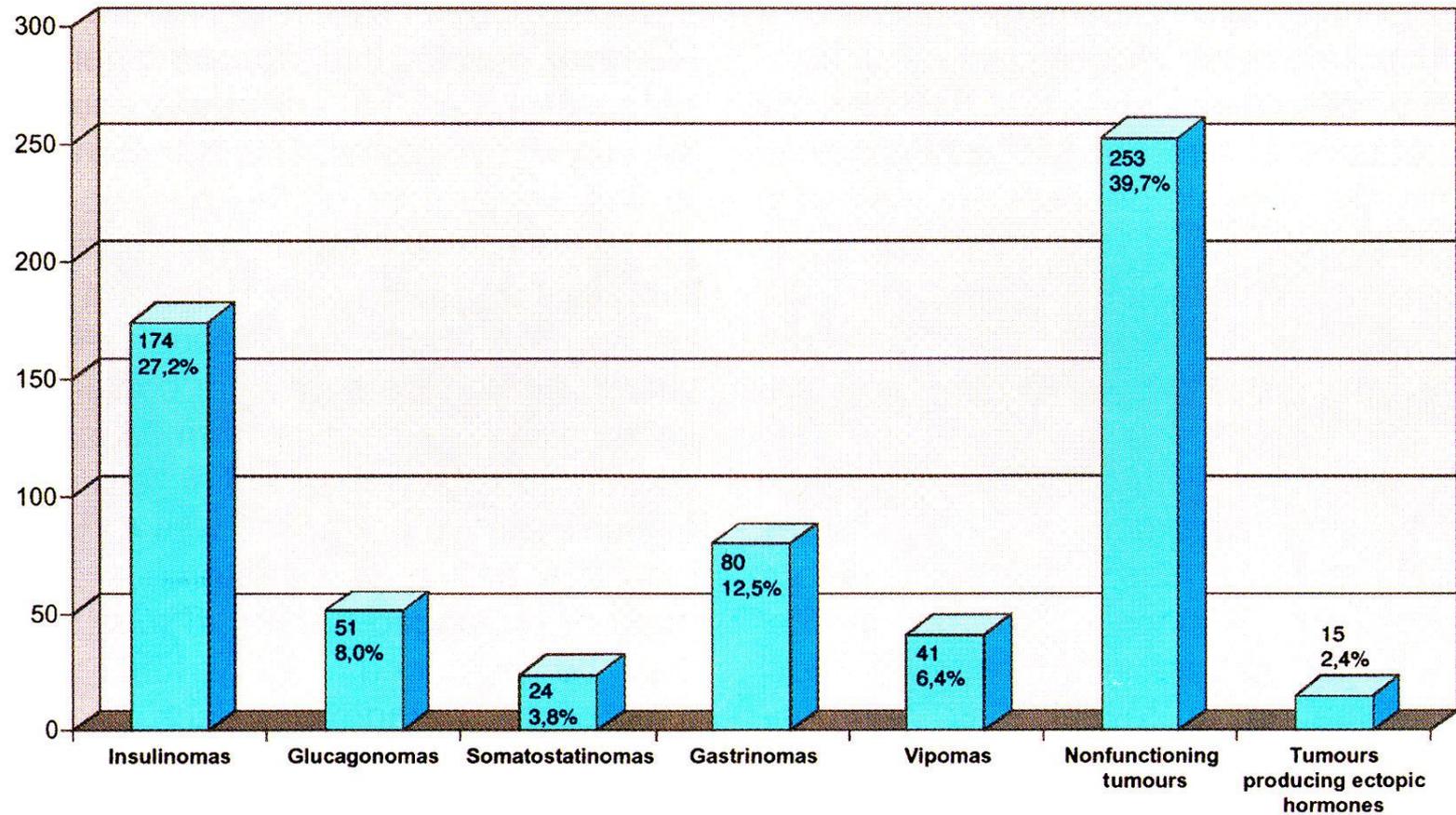


Fig. 4.01 Frequency of various types of pancreatic endocrine tumours, based on a series of 638 cases.

Neoplasie neuroendocrine: marcatori bioumoriali

- General NET markers
 - Chromogranin A
 - Affected by somatostatin analogues, proton pump inhibitors, kidney function, liver function
 - Neuron-specific enolase
- Midgut (small bowel, appendix, cecum)
 - 5 HIAA (5-hydroxyindoleacetic acid) (24-hr urine collection)
 - Serotonin (blood, more variable)

Neoplasie neuroendocrine: marcatori biumorali specifici

Insulinoma	<i>insulina pro-insulina peptide C</i>
Gastrinoma	<i>gastrina</i>
Glucagonoma	<i>glucagone</i>
Somatostatinoma	<i>somatostatina</i>
VIPoma	<i>Vasoactive Intestinal Peptide</i>
Carcinoide	<i>5-HT 5-HIAA (urina 24h)</i>

Tumori neuroendocrini gastroenteropancreatici

Tipo di neoplasia	citotipo	sede								sindrome clinica		
		pancreas	stomaco corpo	antro	duodeno	digiuno	ileo	appendice	colon		retto	
bene differenziata	B	+									PHH	
	A	+									glucagonoma	
	PP	+									-	
	D	+			+	+					somatostatinoma	
	EC	+	+	+	+	+	+	+	+	+	carcinoide	
	ECL		+									carcinoide atipico
	G	+		+	+	+						Zollinger-Ellison
poco differenziata	L				+	+	+	+	+	+	-	
	VIP	+									WDHA	
	s/l cell	+	+	+	+	+	+		+	+	-	

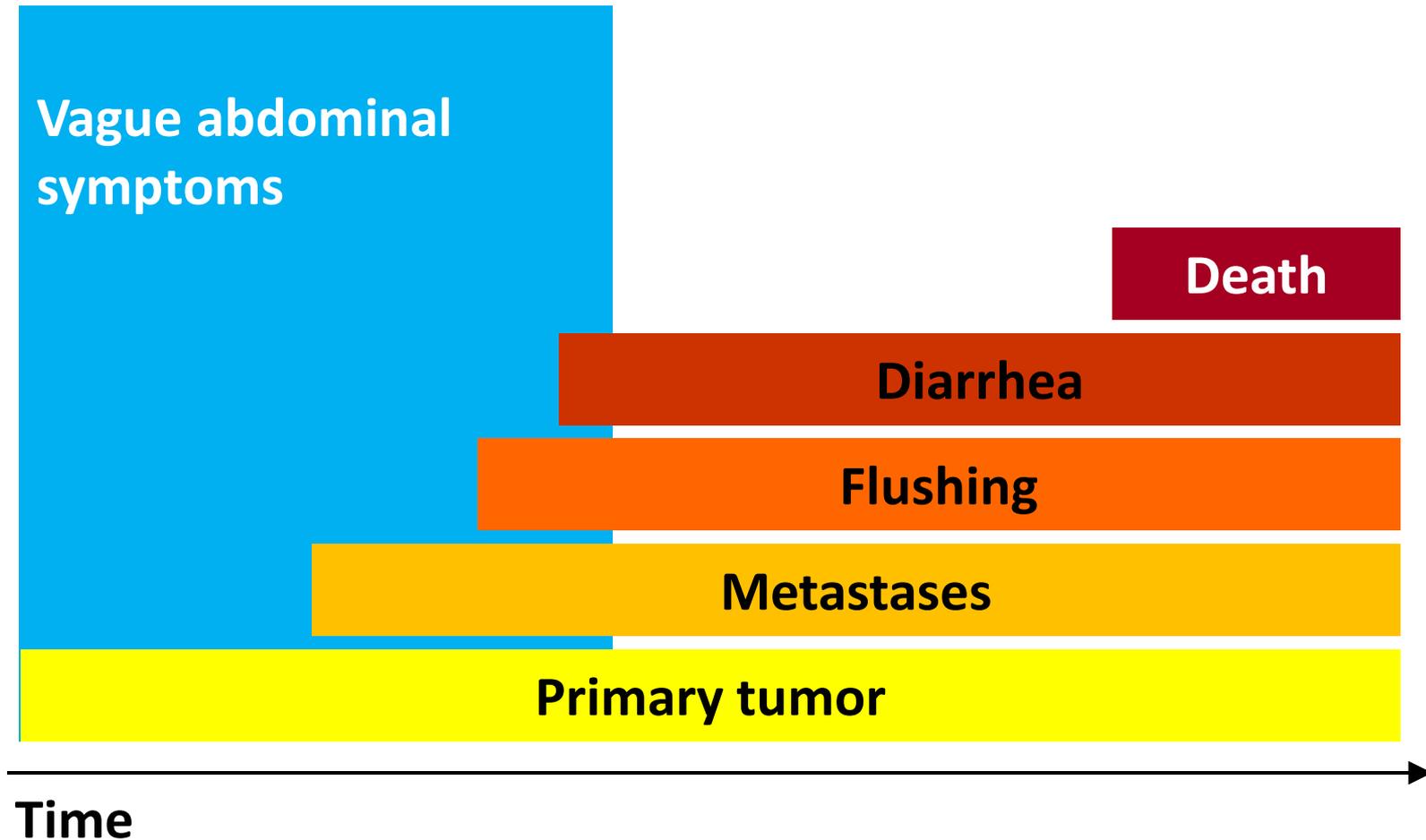
Table 1 | Gastrointestinal neoplasms

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

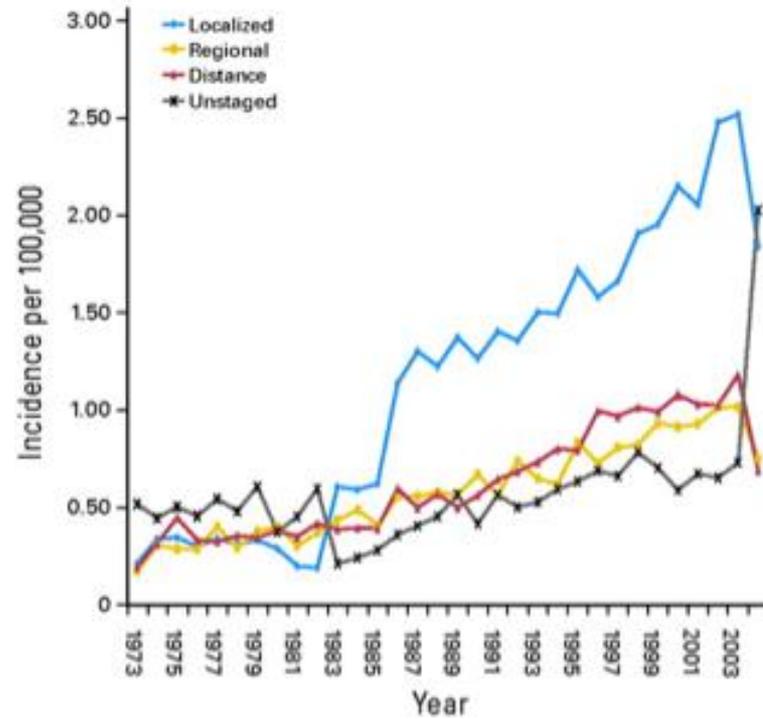
Neoplasm definitions and grading according to WHO 2010. ✓ signifies presence of tumor. On the basis of their main tumor cell type, NETs may determine high levels of circulating hormones, resulting in specific syndromes. Abbreviations: A, glucagon cell; B, insulin cell; D, somatostatin cell; EC, enterochromaffin cell; ECL, enterochromaffin-like cell; G, gastrin cell; L, enteroglucagon/peptide tyrosine-tyrosine cell; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumor; P/D1, ghrelin cell; PP, pancreatic polypeptide cell; S/L, small or large carcinoma cells. Permission obtained from John Libbey Eurotext © Rindi, G. *et al.* in *Recent Advances in the Pathophysiology and Management of Inflammatory Bowel Disease and Digestive Endocrine Tumors* (eds Mignon, M. & Colombel, J. F.) 177–191 (John Libbey Eurotext, Paris, 1999).

Rindi, G. & Wiedenmann, B. (2011) Neuroendocrine neoplasms of the gut and pancreas: new insights
Nat. Rev. Endocrinol. doi:10.1038/nrendo.2011.120

Manifestazioni cliniche in rapporto alla storia naturale della neoplasia



Incidenza dei NETs per stadio alla diagnosi



Alterazioni genetiche nei tumori neuroendocrini gastroenteropancreatici

Genetic changes frequently found in GEP-NETs

	Gene(s)	Involvement		
		Frequent	Rare	Absent
Genes characterizing endocrine tumor syndromes	<i>men1</i>	PET, D	G, I	
	<i>vhl</i>		PET	
	<i>nf-1</i>			
	<i>tsc-1/2</i>			
	<i>hrpt-2</i>			PET
	<i>SDHx</i>			PET, gasNET
Wnt signaling pathway	<i>b-catenin</i>	gasNET		PET
	<i>APC</i>		gasNET	
TGFbeta signaling pathway	<i>TGFbR2</i>			PET, gasNET
	<i>Smad4</i>		PET	
	<i>Smad3</i>			PET
Common tumor suppressor genes/oncogenes	<i>DCC</i>			PET, gasNET
	<i>p53</i>		PET, gasNET	
	<i>PTEN</i>		PET	
	<i>K-Ras</i>		PET, gasNET	
Mechanisms of tumorigenesis	CIMP pathway	gasNET	PET	
	Chromosomal instability	PET	gasNET	
	MSI		PET, gasNET	

GEP-NET Gastroenteropancreatic neuroendocrine tumor, *PET* pancreatic endocrine tumor, *D* duodenal endocrine tumor, *I* ileal endocrine tumor, *gasNET* gastrointestinal neuroendocrine tumor, *CIMP* CpG island methylator phenotype, *MSI* microsatellite instability

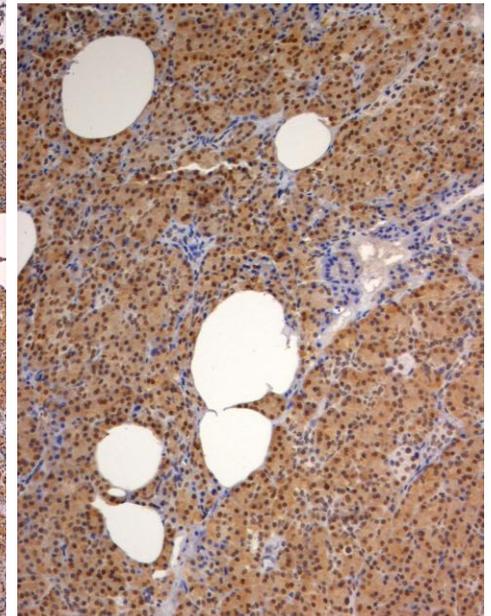
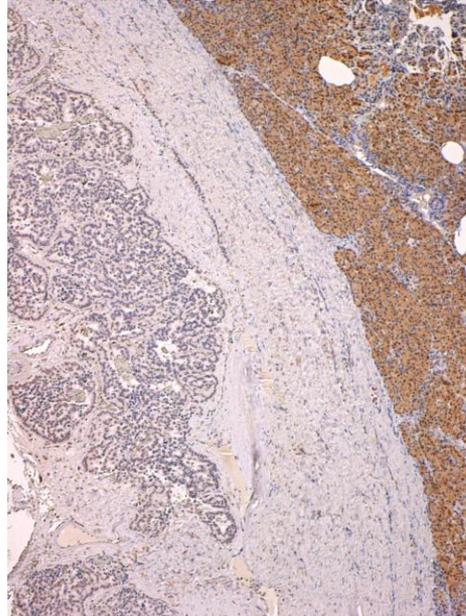
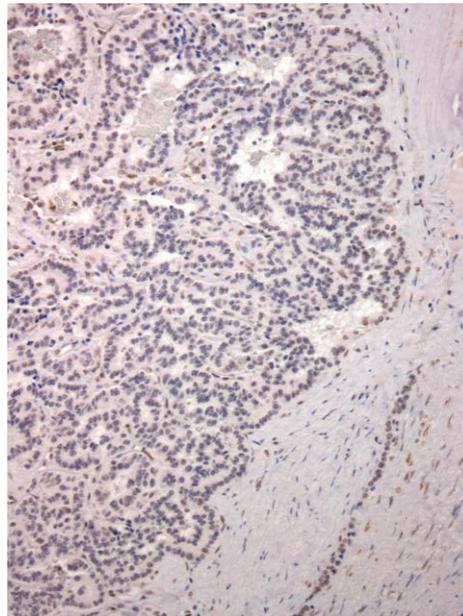
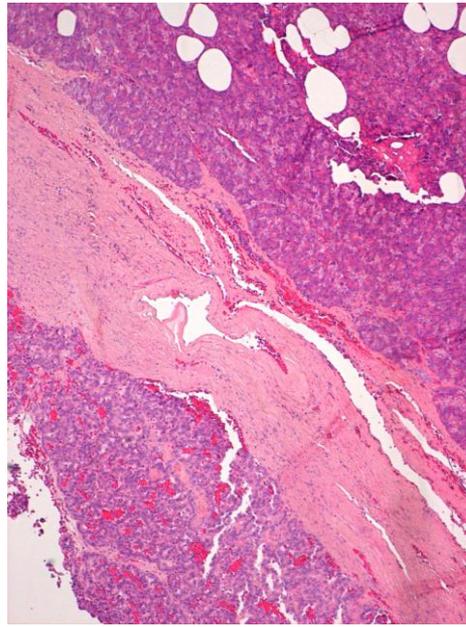
SINDROMI EREDITARIE PREDISPONENTI NEOPLASIE ENDOCRINE

SINDROME GENETICA	GENE IMPLICATO	SEDE DELLE NEOPLASIE
MEN1	<i>MEN-1 (menina)</i>	pancreas, timo, ipofisi
MEN2	<i>RET</i>	cellule C tiroide midollare surrenalica paratiroidi
VON HIPPEL LINDAU	<i>VHL</i>	pancreas midollare surrenalica
PARAGANGLIOMATOSI FAMILIARE	<i>SDH-B, SDH-C, SDH-D</i>	midollare surrenalica paragangli
SCLEROSI TUBEROSA	<i>TSC 1 – TSC 2</i>	duodeno, pancreas
NEUROFIBROMATOSI TIPO 1	<i>NF-1 (neurofibromina)</i>	duodeno, pancreas , midollare surrenalica

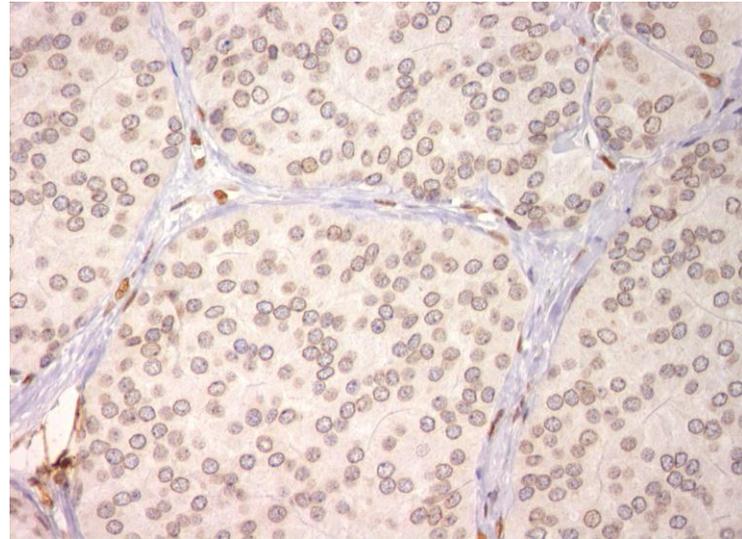
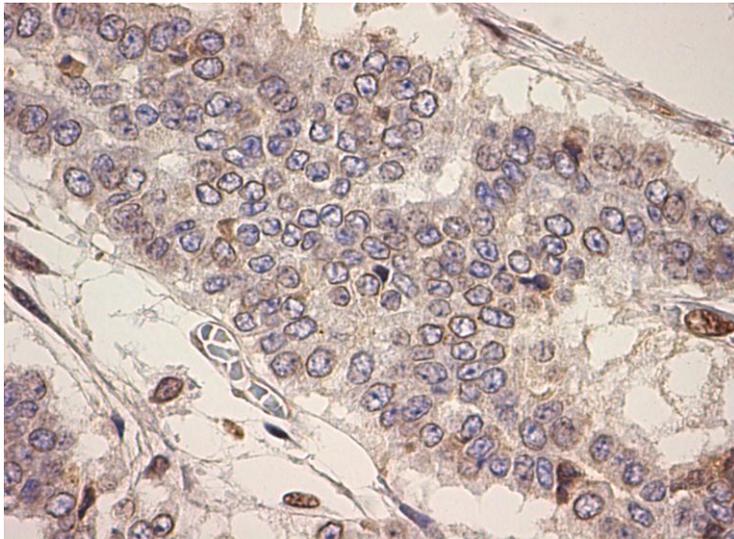
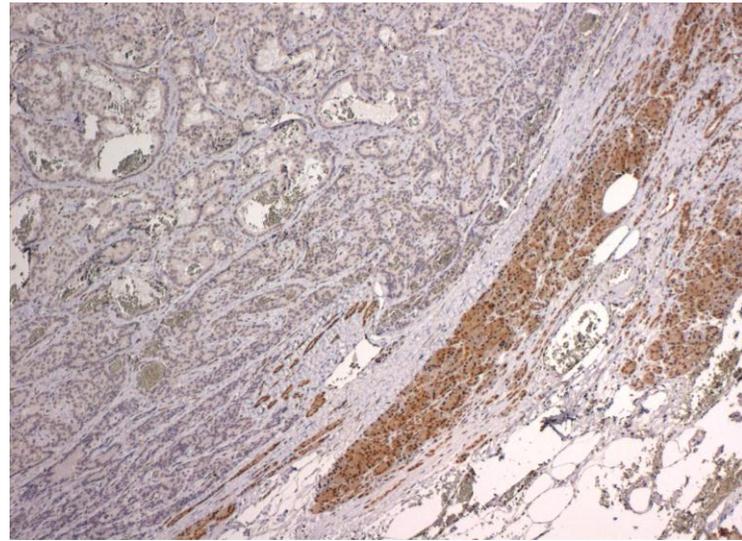
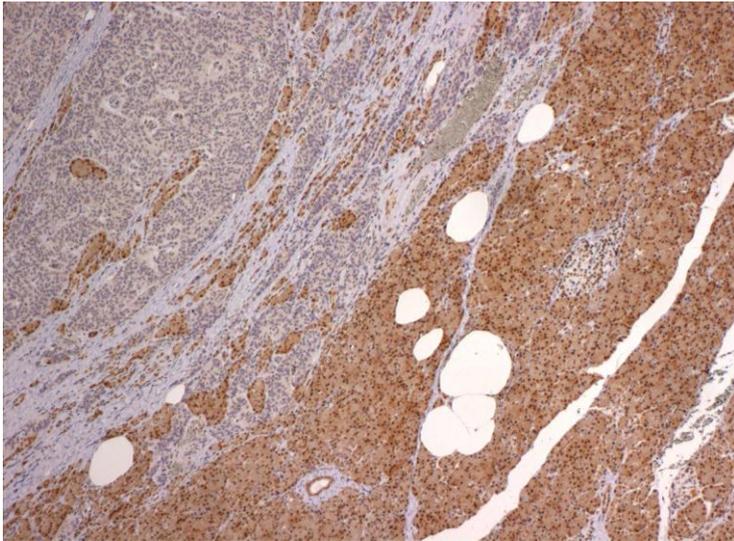
Inherited genetic neuroendocrine syndromes

Syndrome	Gene location	Protein	Incidence	Tumor type/Location
MEN1	11q13	Menin	80-100%	Multiple pancreas/duodenum (nonfunctional>gastrinoma>insulinoma)
VHL disease	3p25.5	VHL	12-17%	Pancreas (all nonfunctioning)
Von Recklinghausen's disease (NF-1)	17q11.2	Neurofibromin	6%	Pancreatic (somatostatinoma)
TSC	9q34 (TSC1) 16p13.3 (TSC2)	Namartin, tuberin	<5%	Pancreas

MEN 1
Tumore neuroendocrino
pancreatico G1



menina



menina

MEN 1: tumore neuroendocrino pancreatico

TUMORI NEUROENDOCRINI (OMS 2000)

a) Tumori neuroendocrini (bene differenziati)

benigni

indefiniti (a potenziale malignità)

b) Carcinomi neuroendocrini basso grado (bene differenziati)

c) Carcinomi neuroendocrini alto grado (scarsamente differenziati)

Tumori neuroendocrini bene differenziati gastroenteropancreatici (WHO 2000)

citologia tipica

struttura organoide

positività per cromogranina A

argirofilia

mitosi $< 2 / 10$ HPF

indice di attività proliferativa (Ki67/Mib-1) $< 2\%$

benigni

dimensioni < 1 cm	stomaco, duodeno, digiuno, ileo, pancreas (eccetto insulinomi)
< 2 cm	colon, retto, appendice,
non funzionanti	pancreas (eccetto insulinomi)

ad incerto
potenziale
maligno

dimensioni $>1 < 2$ cm	stomaco, tenue
> 2 cm	colon, retto (contenuti entro la sottomucosa) pancreas, appendice (contenuti entro i confini dell'organo)
angioinvasività +/-	stomaco, tenue
non funzionanti	(eccetto pancreas)

NEOPLASIE NEUROENDOCRINE

CRITERI ISTOPATOLOGICI DI MALIGNITA'

- Dimensioni del tumore ($> 2\text{cm}$)
- Superamento della tonaca sottomucosa (stomaco, intestino)
- Invasione del tessuto adiacente (appendice, pancreas)
- Angioinvasione e/o invasione degli spazi perineurali
- Atipie strutturali (crescita solida, non organoide)
- Presenza di necrosi
- Atipie citonucleari (ridotto rapporto nucleo:citoplasma, nucleoli evidenti, cromatina addensata)
- Assenza di immunoreattività per cromogranina A, perdita di argirofilia, assenza di espressione ormonale
- Aumentato indice mitotico ($> 2/10$ HPF)
- Elevato indice di attività proliferativa (valutata con mib-1 o Ki67: $>100/10$ HPF o $> 2\%$ delle cellule neoplastiche)
- Espressione di p53

Carcinomi neuroendocrini gastroenteropancreatici (WHO 2000)

Stomaco, duodeno, digiuno, colon-retto

- organoidi
- dimensioni > 2 cm
oltre la sottomucosa
- non funzionanti

Basso grado

- tutti i funzionanti,
indipendentemente dagli altri criteri

Pancreas

- non funzionanti > 3 cm, angioinvasivita' +/-

- funzionanti insulinomi > 3 cm
tutti gli altri > 2cm
o angioinvasivi

Carcinomi

Alto grado

- funzionanti +/-
- indifferenziati
- a piccole cellule

Neoplasie neuroendocrine WHO 2000

POLMONE

carcinoide

carcinoide
atipico

carcinoma a piccole cellule

carcinoma neuroendocrino
a grandi cellule

TIMO

carcinoma neuroendocrino
bene differenziato

carcinoma neuroendocrino
bene differenziato

carcinoma neuroendocrino
scarsamente differenziato

carcinoma neuroendocrino
scarsamente differenziato

TRATTO GASTROINTESTINALE

tumore neuroendocrino
bene differenziato

carcinoma neuroendocrino
bene differenziato

carcinoma neuroendocrino
scarsamente differenziato

carcinoma neuroendocrino
scarsamente differenziato

TUMORI DEL PANCREAS ENDOCRINO

Classificazione WHO 2004

Well-differentiated endocrine tumour

Functioning

- Insulin-producing (insulinoma)
- Glucagon-producing (glucagonoma)
- Somatostatin-producing (somatostatinoma)
- Gastrin-producing (gastrinoma)
- VIP-producing (VIPoma)
- Others

Non-functioning

- Microadenoma (<0.5 cm)
- Others

Well-differentiated endocrine carcinoma

Functioning

- Insulin-producing (insulinoma)
- Glucagon-producing (glucagonoma)
- Somatostatin-producing (somatostatinoma)
- Gastrin-producing (gastrinoma)
- VIP-producing (VIPoma)
- Serotonin producing with carcinoid syndrome
- ACTH producing with Cushing syndrome

Non-functioning

Poorly-differentiated endocrine carcinoma - small cell carcinoma

Mixed exocrine – endocrine carcinoma

TUMORI DEL PANCREAS ENDOCRINO Classificazione WHO (2004)

<i>Classification</i>	<i>WHO type</i>	<i>Local invasion</i>	<i>Features</i>
Well-differentiated endocrine tumor, benign behavior	1.1	Confined to pancreas	< 2 cm, no angioinvasion or perineural invasion, < 2 mitoses per 10 HPF; Ki67-labeling index < 2%
Well-differentiated endocrine tumor, uncertain behavior (one or more high-risk features)	1.2	Confined to pancreas	One or more of the following features: ≥ 2 cm, angioinvasion, perineural invasion, 2-10 mitoses per 10 HPF; Ki67-labeling index 2% or greater
Well-differentiated endocrine carcinoma	2	Gross local invasion and/or metastases	Generally shows one or more of the following features: ≥ 2 cm, angioinvasion, perineural invasion, 2-10 mitoses per 10 HPF; Ki67-labeling index 2% or greater
Poorly differentiated endocrine carcinoma, benign behavior (small cell carcinoma or large cell endocrine carcinoma)	3	Often widely invasive or metastatic	High-grade carcinoma with > 10 mitoses per 10 HPF

Neoplasie neuroendocrine

Proposta di sistema di gradazione

grado	mitosi (10HPF)*	Ki-67 index (%) [°]
G1	< 2	< 2
G2	2 - 20	3 - 20
G3	> 20	> 20

*almeno 40 HPF

[°] con anticorpo Mib-1 (% su 2.000 cellule)

Kloppel G *et al* (Virchows Arch 2007, 451,suppl 1: S9-S27)

TUMORI DEL PANCREAS

Classificazione WHO 2010

Epithelial tumours

Benign

Acinar cell cystadenoma

Serous cystadenoma

Premalignant lesions

Pancreatic intraepithelial neoplasia, grade 3 (PanIN-3)

Intraductal papillary mucinous neoplasm with low- or intermediate-grade dysplasia

Intraductal papillary mucinous neoplasm with high-grade dysplasia

Intraductal tubulopapillary neoplasm

Mucinous cystic neoplasm with low- or intermediate-grade dysplasia

Mucinous cystic neoplasm with high-grade dysplasia

Malignant

Ductal adenocarcinoma

Adenosquamous carcinoma

Colloid carcinoma (mucinous noncystic carcinoma)

Hepatoid carcinoma

Medullary carcinoma

Signet ring cell carcinoma

Undifferentiated carcinoma

Undifferentiated carcinoma with osteoclast-like giant cells

Acinar cell carcinoma

Acinar cell cystadenocarcinoma

Intraductal papillary mucinous neoplasm with an associated invasive carcinoma

Mixed acinar-ductal carcinoma

Mixed acinar-neuroendocrine carcinoma

Mixed acinar-neuroendocrine-ductal carcinoma

Mixed ductal-neuroendocrine carcinoma

Mucinous cystic neoplasm with an associated invasive carcinoma

Pancreatoblastoma

Serous cystadenocarcinoma

Solid-pseudopapillary neoplasm

Neuroendocrine neoplasms

Pancreatic neuroendocrine microadenoma

Neuroendocrine tumour (NET)

Nonfunctional pancreatic NET, G1, G2

NET G1

NET G2

Neuroendocrine carcinoma (NEC)

Large cell NEC

Small cell NEC

EC cell, serotonin-producing NET (carcinoid)

Gastrinoma

Glucagonoma

Insulinoma

Somatostatinoma

VIPoma

Mature teratoma

Mesenchymal tumours

Lymphomas

Secondary tumours

CLASSIFICATION OF ENDOCRINE NEOPLASMS OF THE PANCREAS

Endocrine microadenoma

Well-differentiated pancreatic endocrine neoplasm

Functional pancreatic endocrine neoplasms

Insulinoma

Glucagonoma

Somatostatinoma

Gastrinoma

VIPoma^a

PP-cell pancreatic endocrine neoplasm

Other ectopic and mixed hormone-producing
neoplasms

Nonfunctional pancreatic endocrine neoplasms

Poorly differentiated endocrine carcinoma

Small cell carcinoma

Large cell poorly differentiated endocrine carcinoma

Mixed endocrine carcinomas

Mixed ductal-endocrine carcinoma

Mixed acinar-endocrine carcinoma

Mixed acinar-endocrine-ductal carcinoma

^aVIP = vasoactive intestinal polypeptide; PP = pancreatic polypeptide.

(AFIP, 2007)

TUMORI NEUROENDOCRINI DEL PANCREAS (Classificazione WHO 2010)

Microadenoma neuroendocrino

Tumore neuroendocrino (NET) G1, G2

NET G1

NET G2

NET non funzionante G1,G2

Carcinoma neuroendocrino (NEC) G3

NEC a grandi cellule

NEC a piccole cellule

NET a cellule EC produttore serotonina (carcinoide)

Gastrinoma

Glucagonoma

Insulinoma

Somatostatinoma

VIPoma

Carcinoma misto adenoneuroendocrino (MANEC)

combinati o composti, con almeno il 30% delle
cellule neoplastiche di natura neuroendocrina

NEOPLASIE NEUROENDOCRINE DEL PANCREAS

WHO 1980

carcinoide

WHO 2000

tumore endocrino bene differenziato (WDET)
benigno
incerto potenziale maligno

carcinoma endocrino bene differenziato (WDEC)

carcinoma neuroendocrino poco differenziato/
carcinoma a piccole cellule (PDEC)

carcinoma misto esocrino-endocrino (MEEC)

pseudotumori

lesioni similtumorali

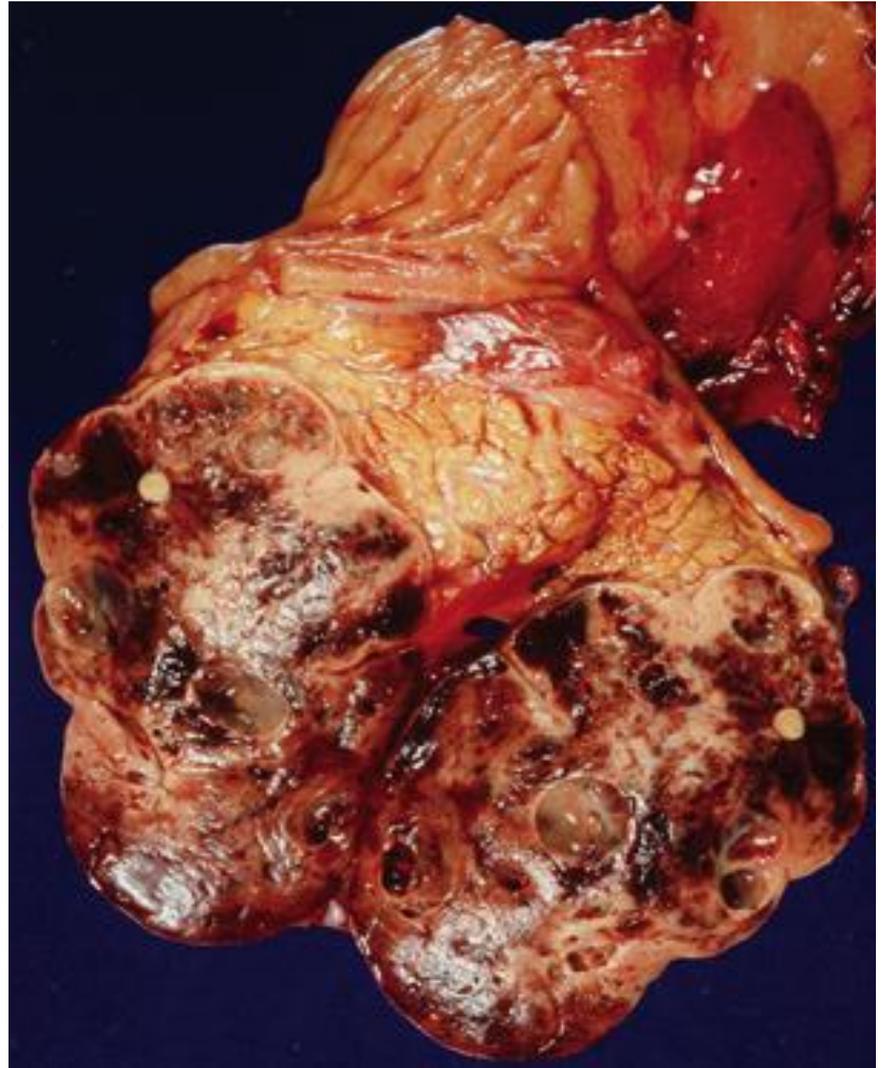
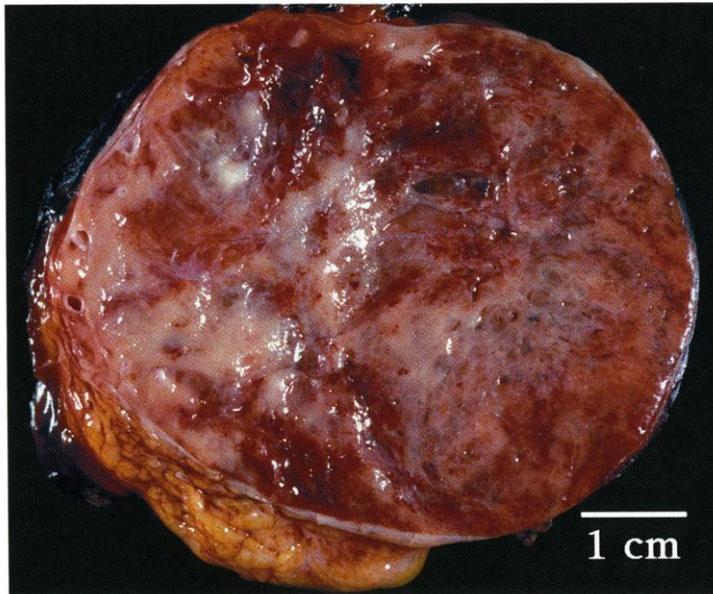
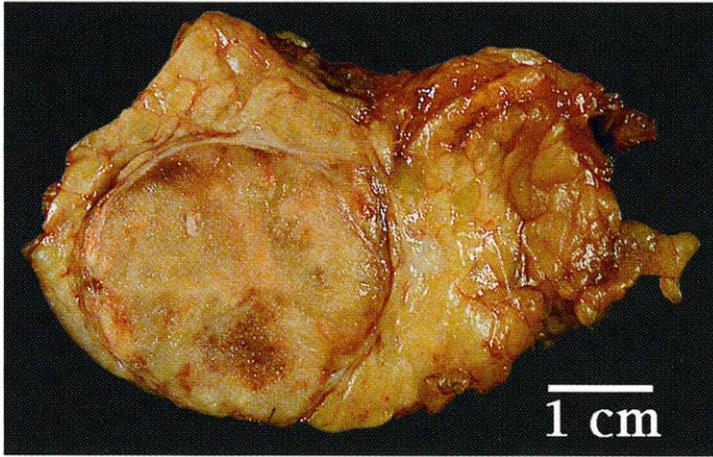
WHO 2010

tumore neuroendocrino (NET) G1-G2

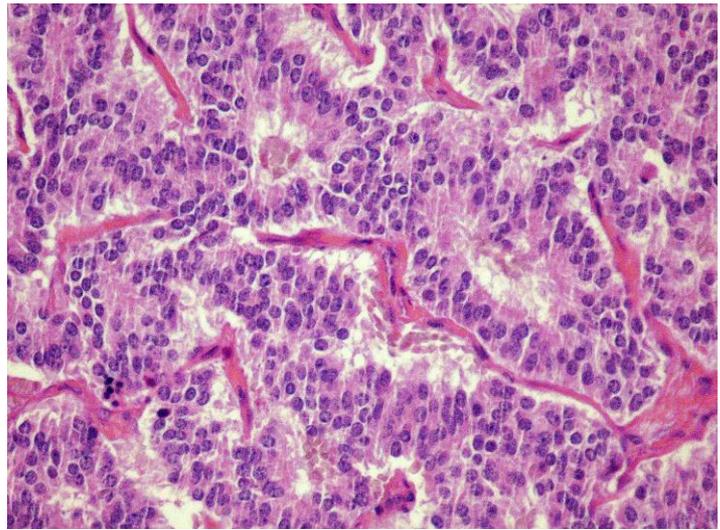
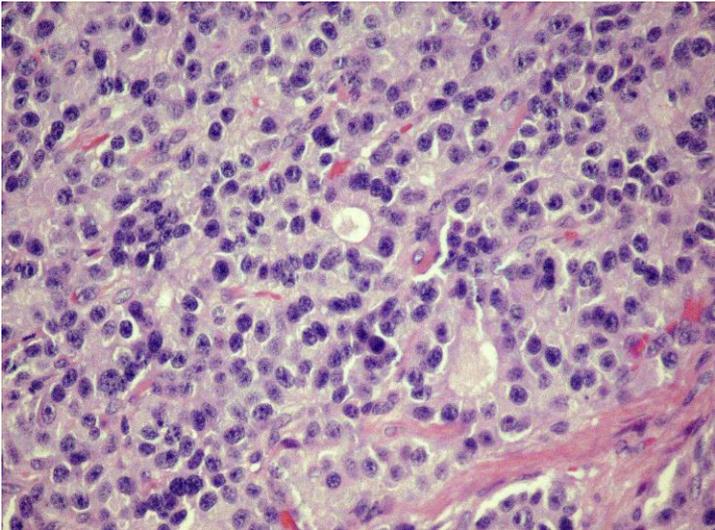
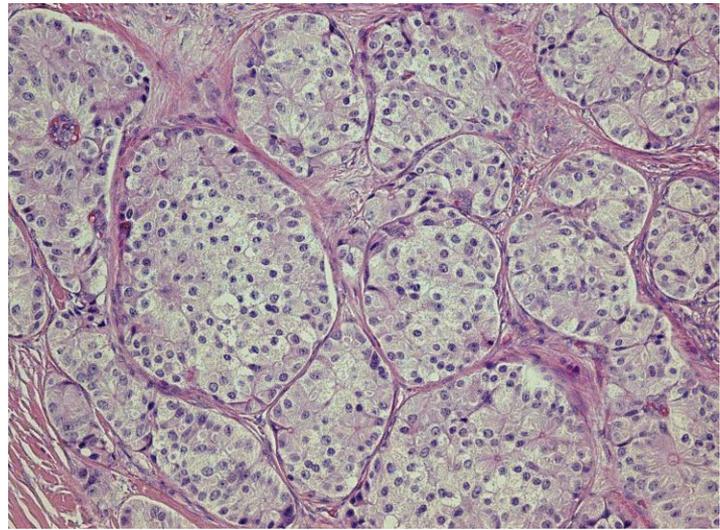
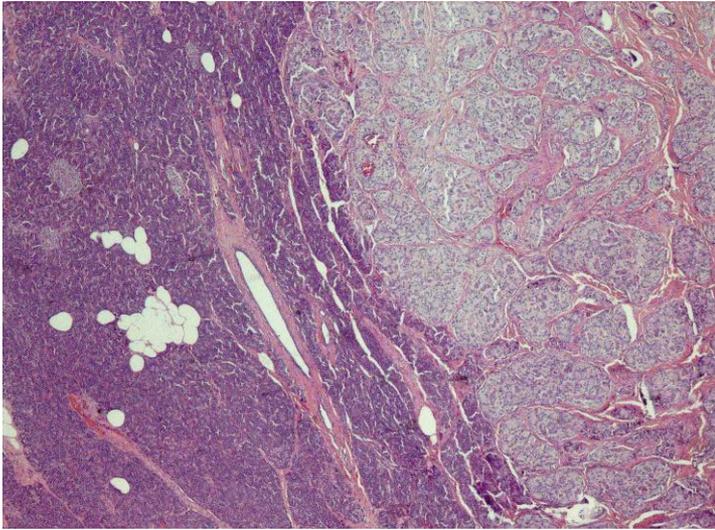
carcinoma neuroendocrino (NEC) G3
a grandi cellule e a piccole cellule

ca misto adenoneuroendocrino (MANEC)

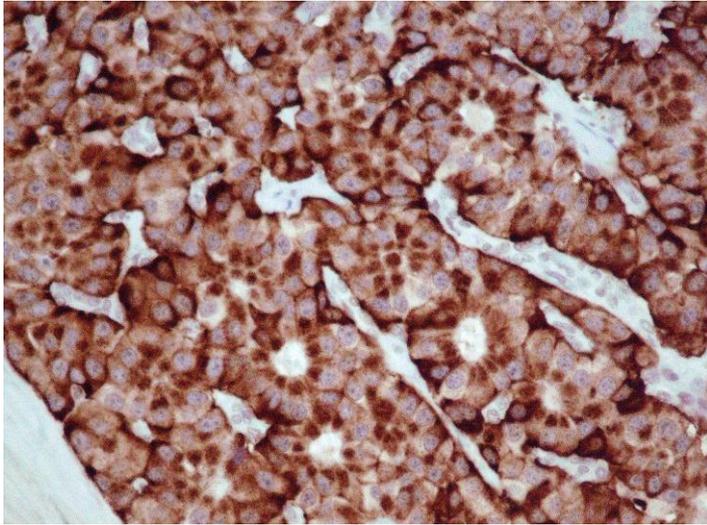
lesioni iperplastiche e preneoplasie



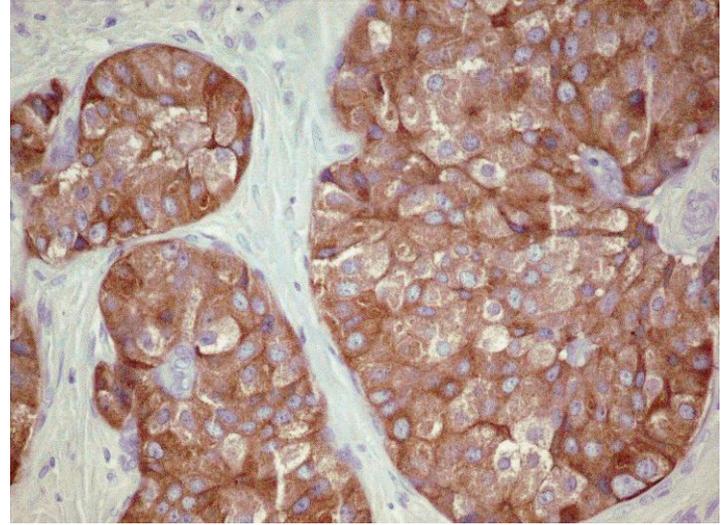
Pancreas: tumori neuroendocrini



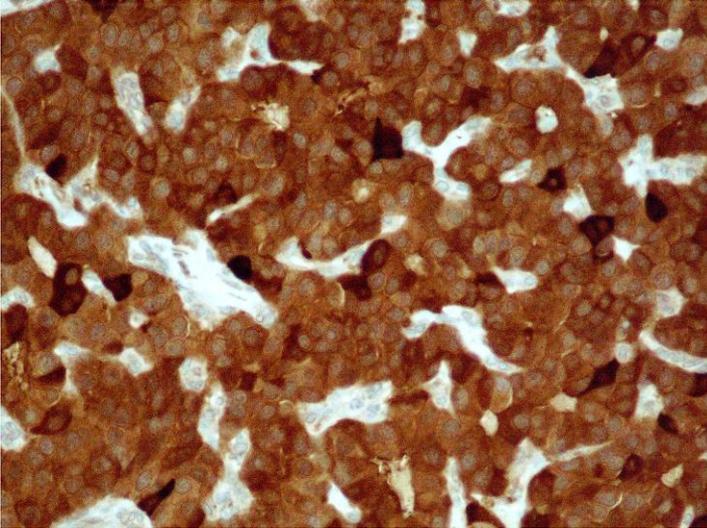
Tumore endocrino pancreatico bene differenziato G1 (insulinoma)



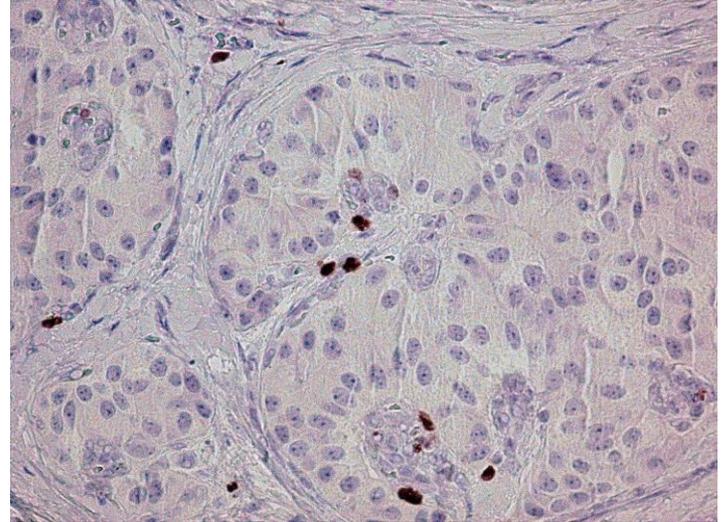
cromogranina A



sinaptofisina

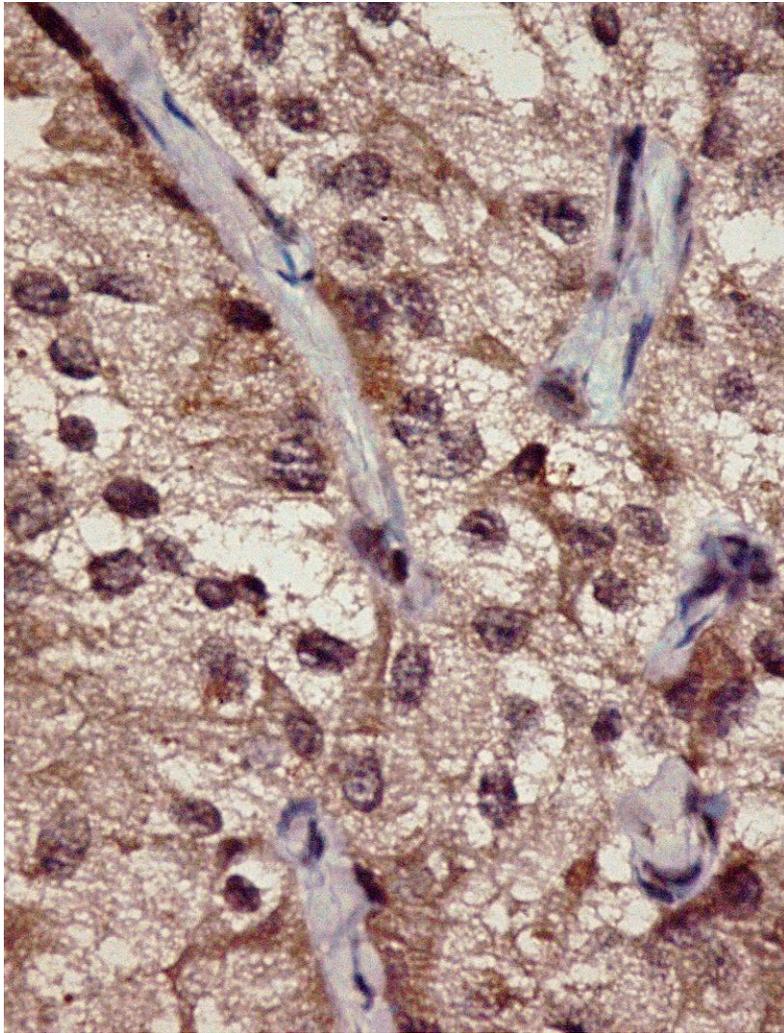


NSE

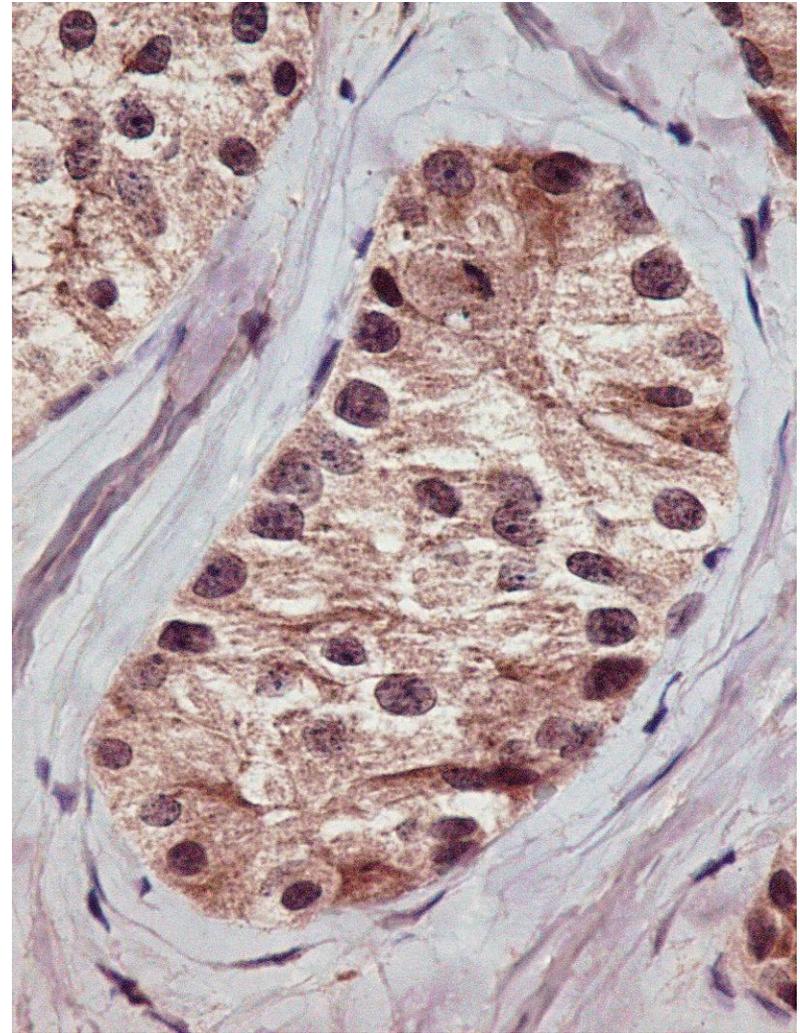


Mib-1

Tumore endocrino pancreatico bene differenziato G1 (insulinoma)



SSTR2

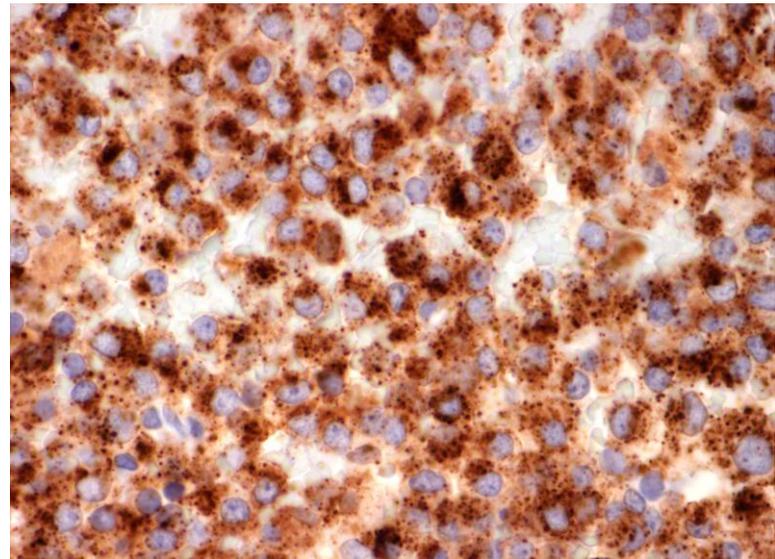
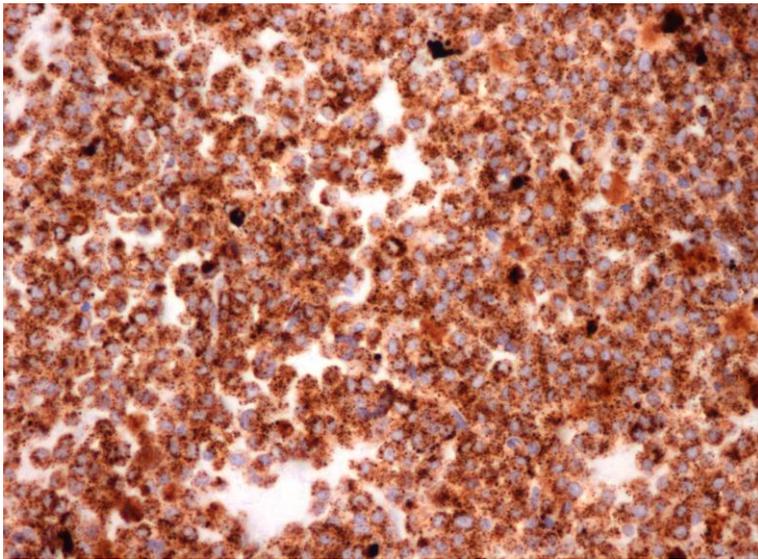
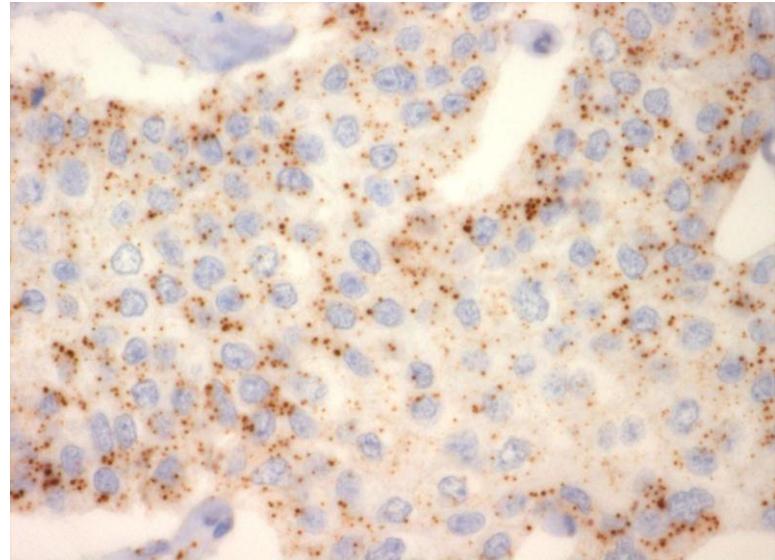
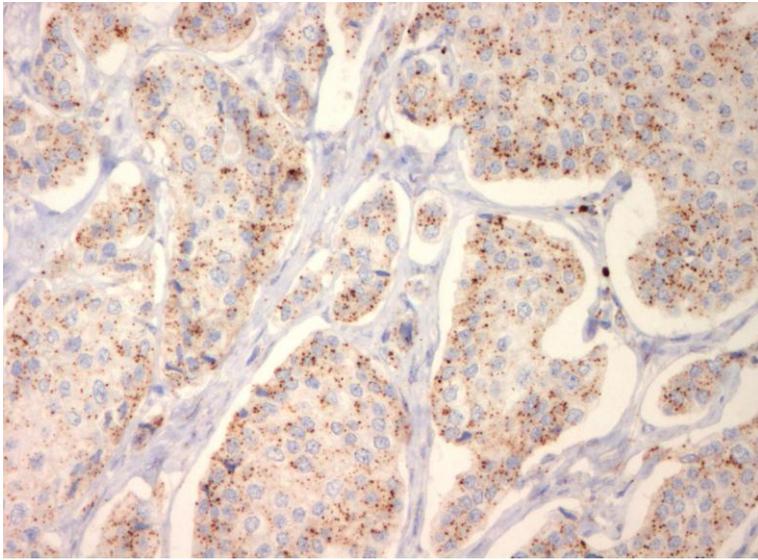


SSTR5

Tumore endocrino pancreatico bene differenziato: recettori della somatostatina

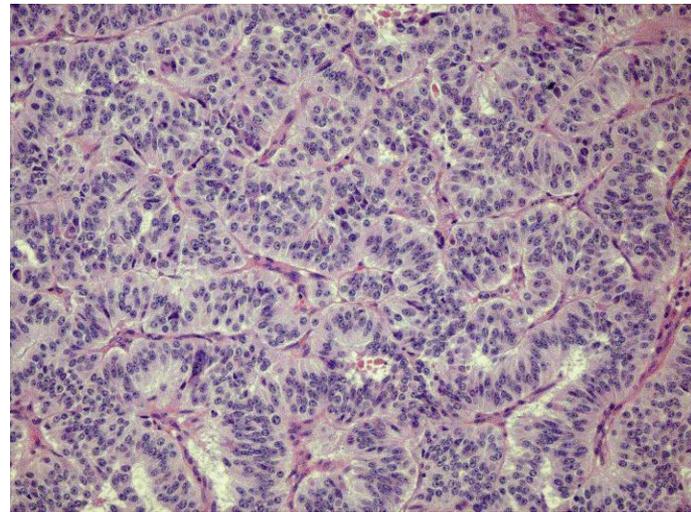
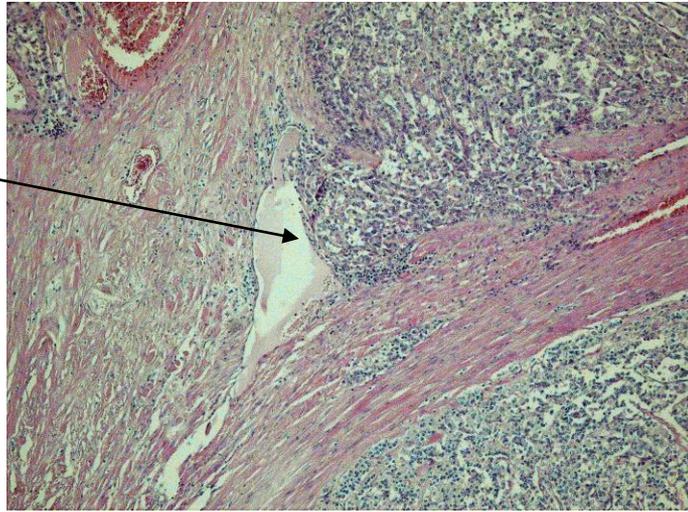
Inhibitory effect	Receptor subtype				
	<i>sst</i> 1	<i>sst</i> 2	<i>sst</i> 3	<i>sst</i> 4	<i>sst</i> 5
Hormone secretion					
Growth hormone	+	+			+
Adrenocorticotropic hormone		+			+
Thyroid-stimulating hormone		+			+
Insulin		+			+
Glucagon		+			
Exocrine secretion					
Gastric acid		+			
Amylase					+
Intestinal GI secretion	+	+			
Cell proliferation					
Induction of G ₁ cell cycle arrest	+	+		+	+
Induction of apoptosis		+	+		

Effetti inibitori dei sottotipi dei recettori della somatostatina

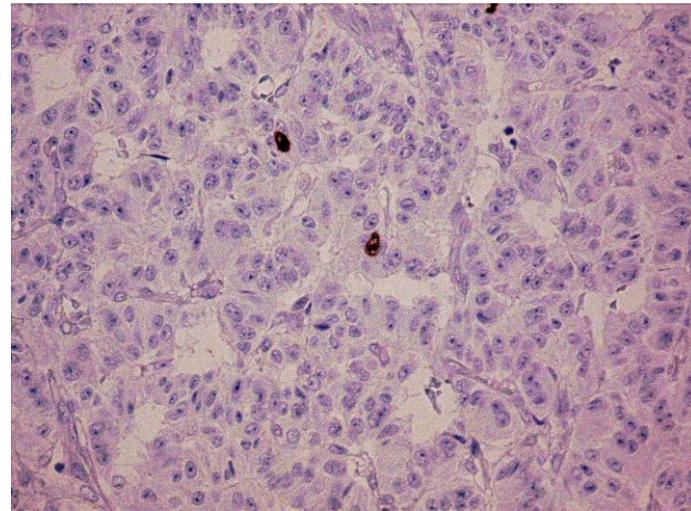
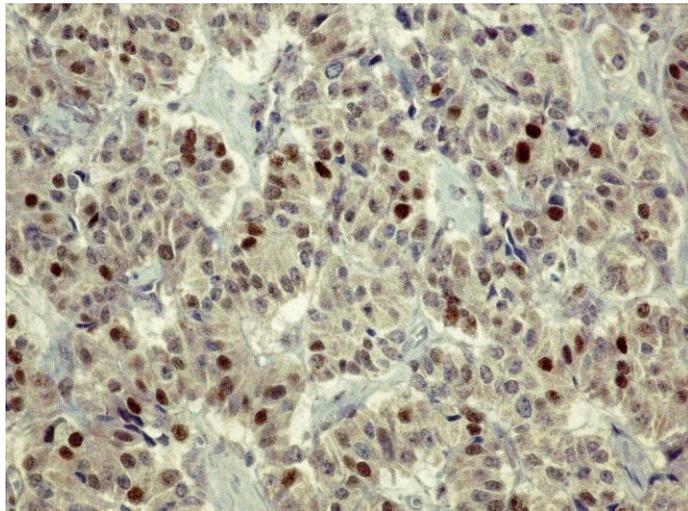


Tumore endocrino pancreatico: espressione recettore DR2 della dopamina

sospetta
angioinvasività

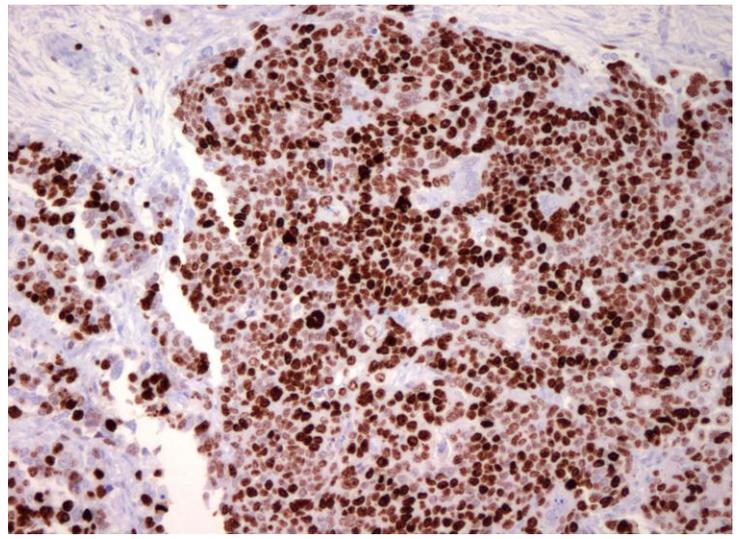
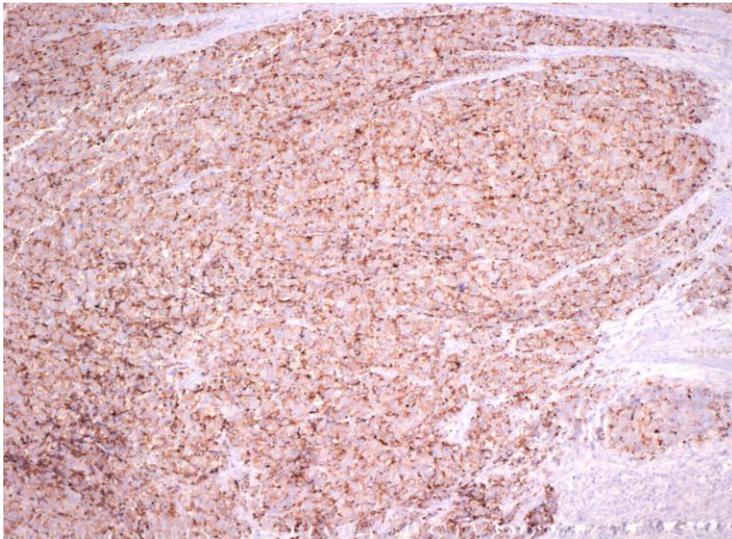
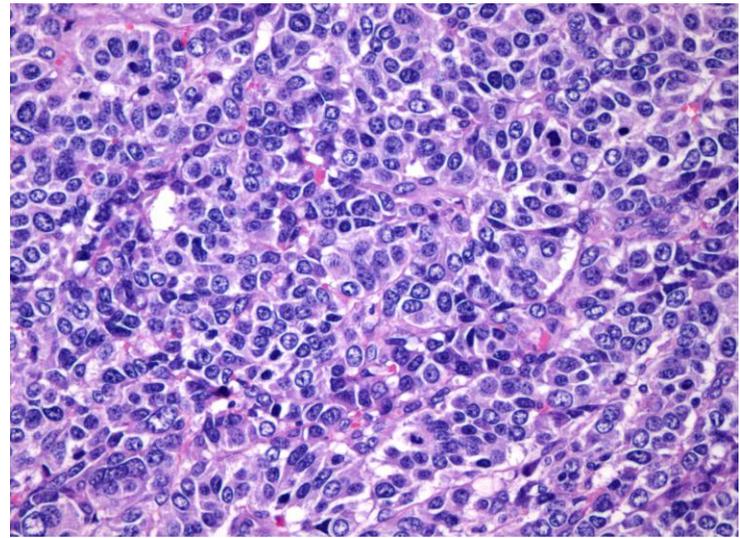
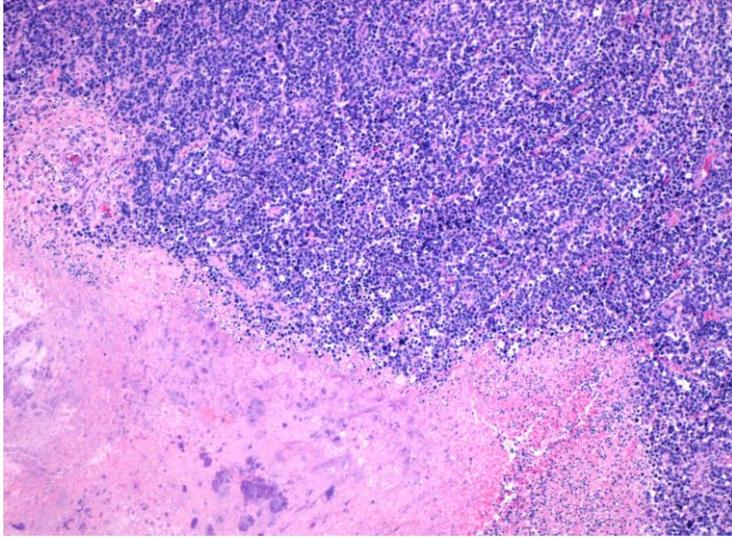


p53



Mib-1 (<2%)

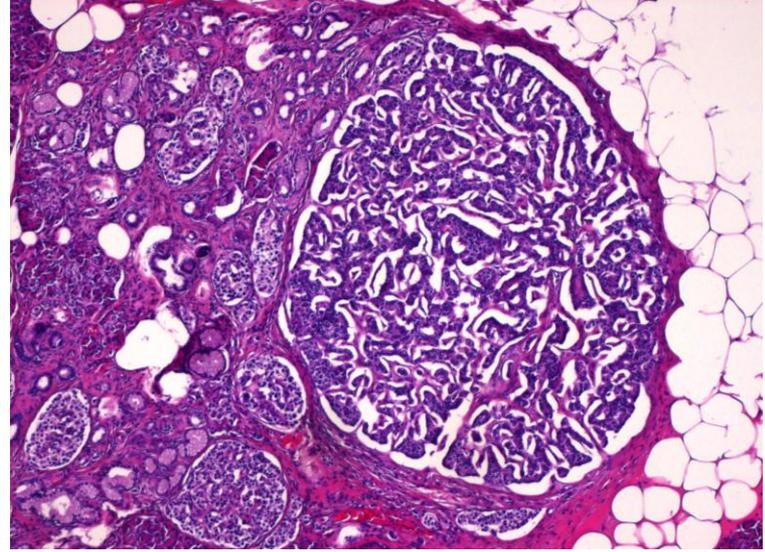
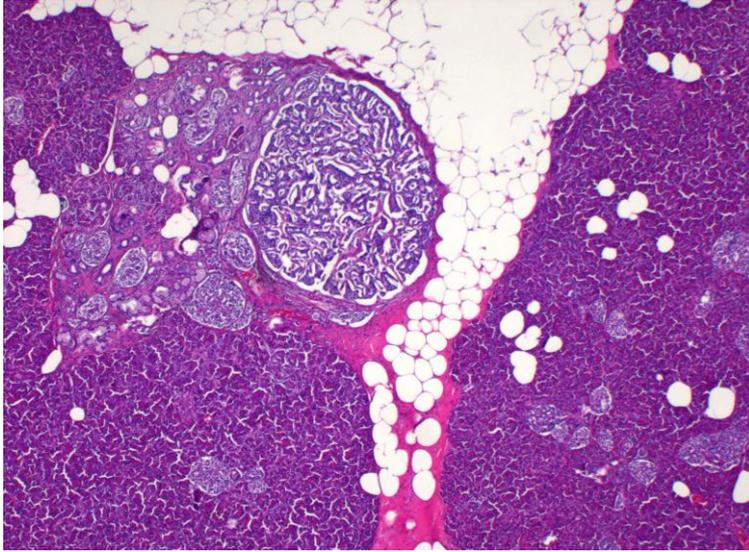
Carcinoma endocrino pancreatico bene differenziato (basso grado) WHO 2000
Tumore neuroendocrino pancreatico G1 WHO 2010



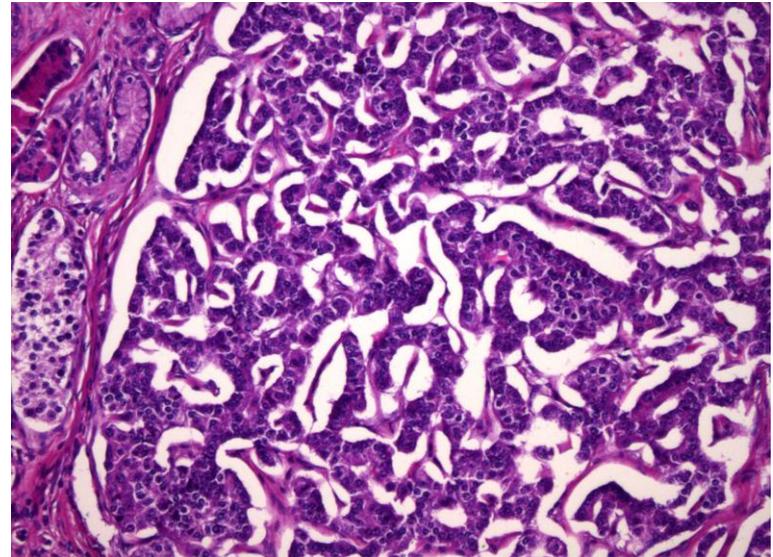
Mib-1 (>20%)

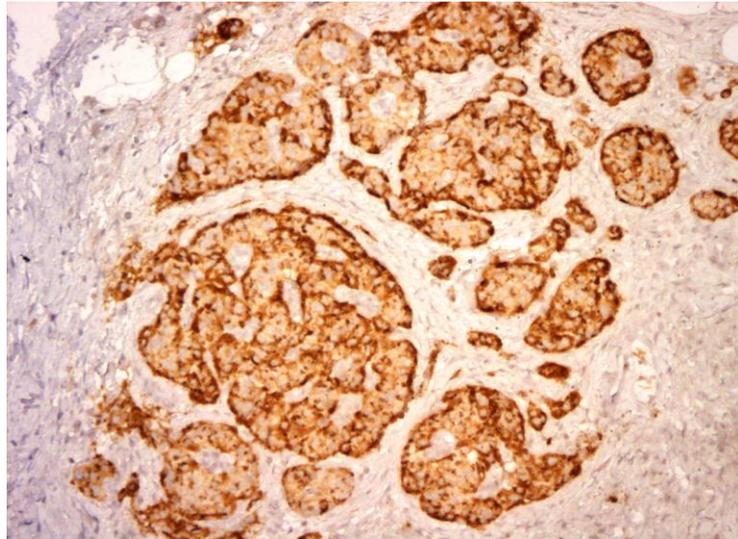
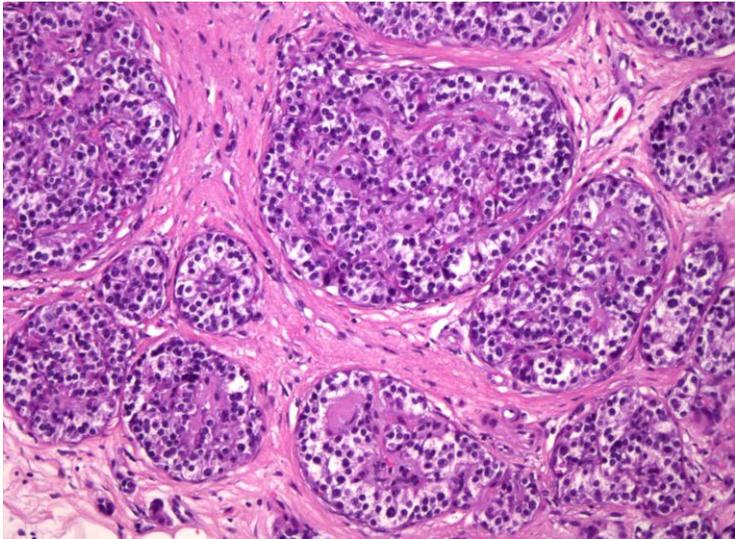
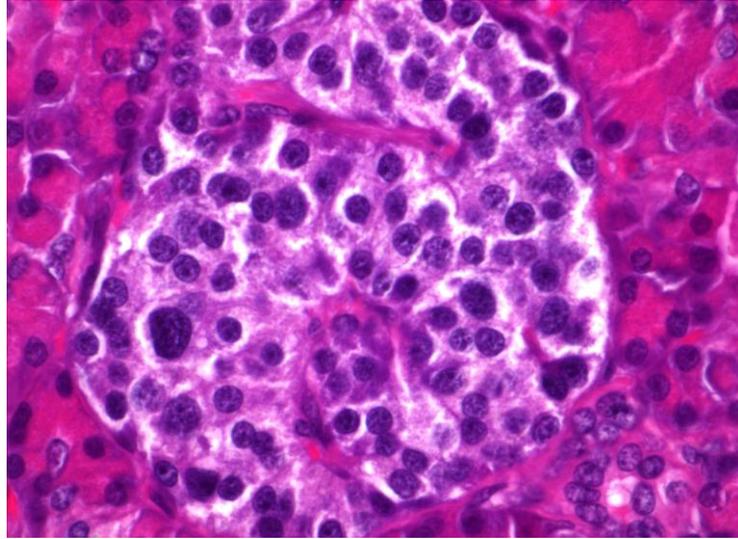
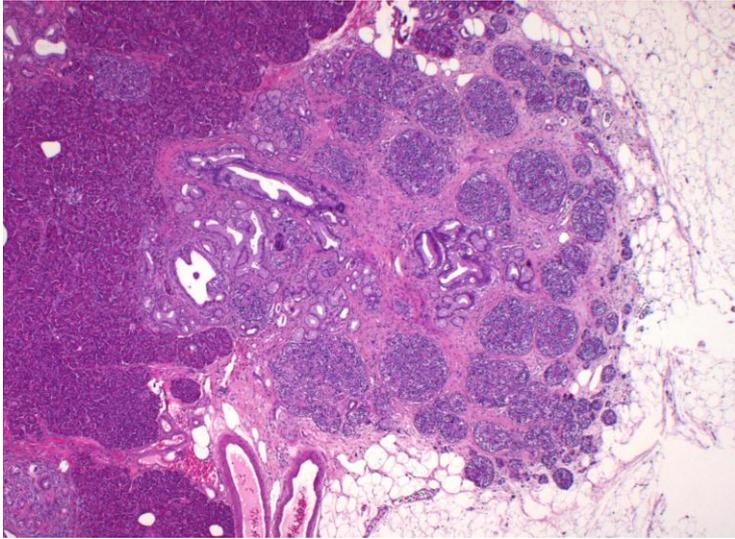
Carcinoma endocrino scarsamente differenziato (alto grado) WHO 2000
Carcinoma neuroendocrino G3 WHO 2010

cromogranina A



Microadenoma endocrino pancreatico





Nesidioblastosi focale (displasia insulare)

TUMORI DEL PANCREAS Classificazione TNM 2010

La classificazione si applica sia ai carcinomi del pancreas esocrino che ai **tumori neoendocrini** pancreatici

T – Primary tumour
 TX Primary tumour cannot be assessed
 T0 No evidence of primary tumour
 Tis Carcinoma *in situ*, includes PanIN-3
 T1 Tumour limited to the pancreas, 2 cm or less in greatest dimension
 T2 Tumour limited to the pancreas, more than 2 cm in greatest dimension
 T3 Tumour extends beyond pancreas
 T4 Tumour involves coeliac axis or superior mesenteric artery

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
 M0 No distant metastasis
 M1 Distant metastasis

Stage grouping

Stage	T	N	M
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1, T2, T3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

Neoplasie neuroendocrine pancreatiche: TNM 2010

Staging

- **T1** Tumor limited to the pancreas, < 2 cm
- **T2** Tumor limited to the pancreas, > 2 cm
- **T3** Tumor extends beyond the pancreas but no involvement of the celiac axis or the SMA
- **T4** Tumor involves the celiac axis or the SMA (unresectable)

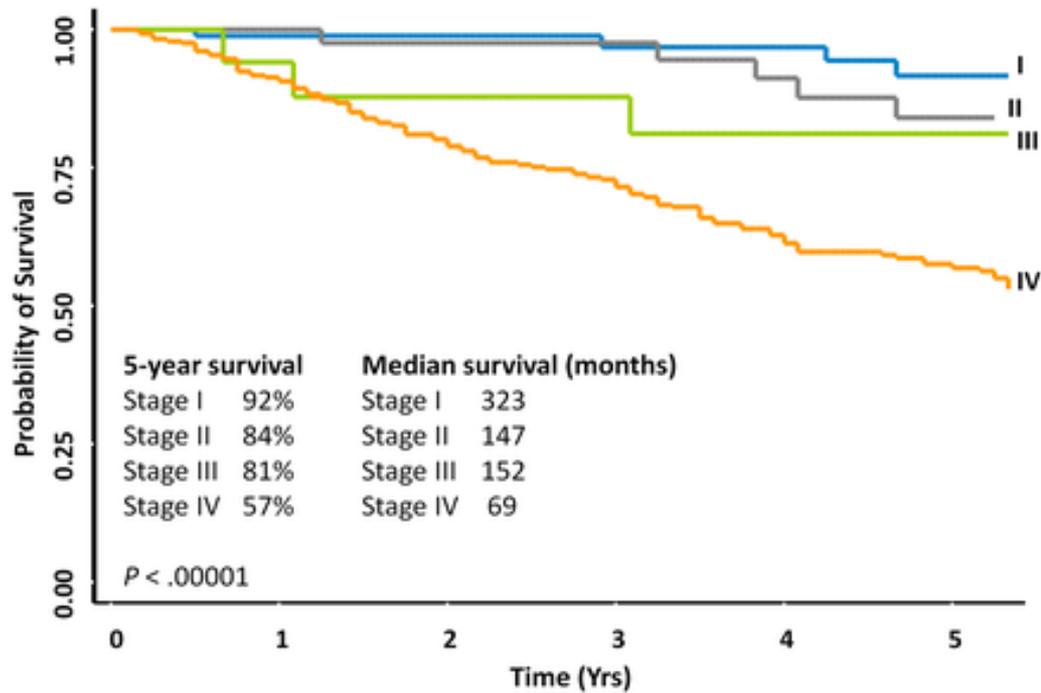
- **N0** No regional LN metastasis
- **N1** Regional LN metastasis

- **M0** No distant metastasis
- **M1** Distant metastasis

Stage	T	N	M
IA	T1	N0	M0
IB	T2	N0	M0
IIA	T3	N0	M0
IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
III	T4	Any N	M0
IV	Any T	Any N	M1

Tumori neuroendocrini pancreatici

Overall Survival by AJCC Staging

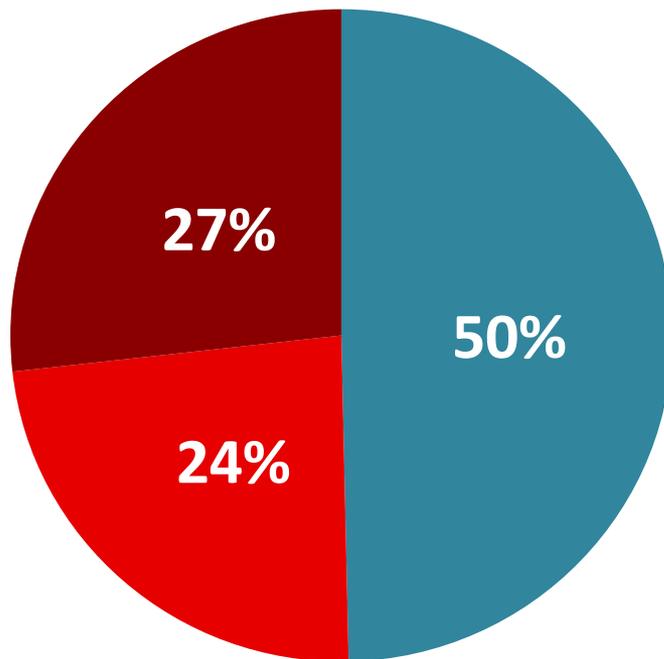


Strosberg J, et al. ISGIO 2010.

OS neoplasie neuroendocrine in rapporto allo stadio

■ Localized ■ Regional

■ Distant



Median survival (1988 – 2004)

- Localized 203 months
- Regional 114 months
- Distant 39 months

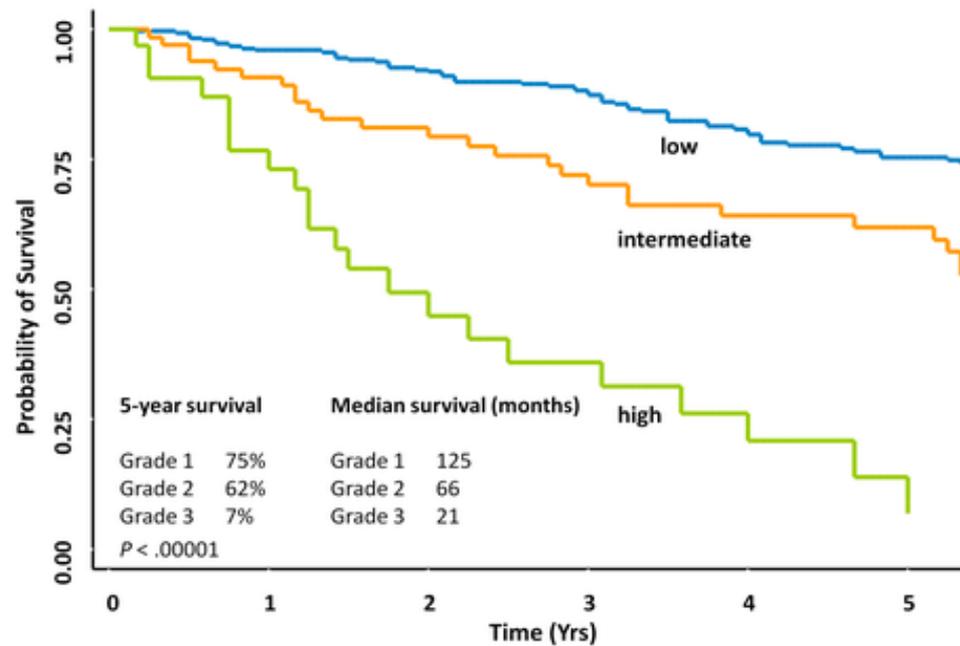
Neoplasie neuroendocrine pancreatiche:

Grade/Differentiation

Differentiation	Grade	Mitotic Rate	Ki-67 Index	
Well Differentiated	Low Grade	Grade 1	< 2	< 5%
Moderately Differentiated	Intermediate Grade	Grade 2	2-10	5%-20%
Poorly Differentiated	High Grade	Grade 3	> 10	> 20%

Tumori neuroendocrini pancreatici

Overall Survival by Grade



Strosberg J, et al. ISGIO 2010.

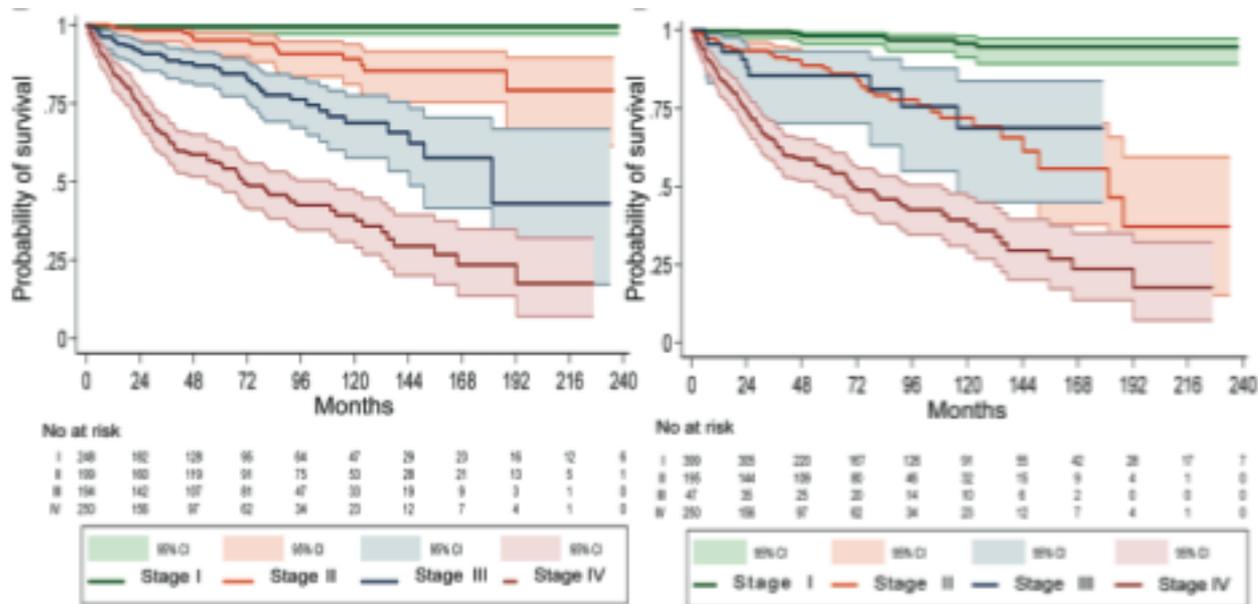
Table 1. T and stage definitions in the European Neuroendocrine Tumor Society (ENETS) and the International Union for Cancer Control/American Joint Cancer Committee/World Health Organization (UICC/AJCC/WHO) 2010 TNM staging systems (3–6)*

Definitions	ENETS TNM	UICC/AJCC/WHO 2010 TNM
T definition		
T1	Limited to the pancreas, <2 cm	Limited to the pancreas, ≤2 cm in greatest dimension
T2	Limited to the pancreas, 2–4 cm	Limited to the pancreas, >2 cm in greatest dimension
T3	Limited to the pancreas, >4 cm or invading duodenum or bile duct	Beyond the pancreas but without involvement of the superior mesenteric artery
T4	Tumor invading adjacent organs (stomach, spleen, colon, adrenal gland) or the wall of large vessels (celiac axis or the superior mesenteric artery)	Involvement of celiac axis or the superior mesenteric artery (unresectable tumor)
Stage definition		
Stage I	T1, N0, M0	NA
Stage IIa	T2, N0, M0	NA
Stage IIb	T3, N0, M0	NA
Stage IIIa	T4, N0, M0	NA
Stage IIIb	Any T, N1, M0	NA
Stage IV	Any T, any N, M1	NA
Stage IA	NA	T1, N0, M0
Stage IB	NA	T2, N0, M0
Stage IIA	NA	T3, N0, M0
Stage IIB	NA	T1–T3, N1, M0
Stage III	NA	T4, any N, M0
Stage IV	NA	Any T, any N, M1

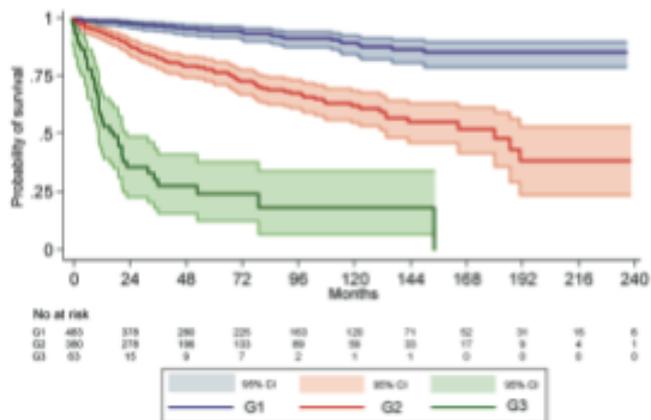
* NA = not applicable.

Rindi G, Falconi M, Klersy C *et al*: TNM staging of neoplasms of the endocrine pancreas: results from a large international cohort study. *J Natl Cancer Inst* 2012; 104: 764-777

Stadiazione TNM delle neoplasie del pancreas endocrino



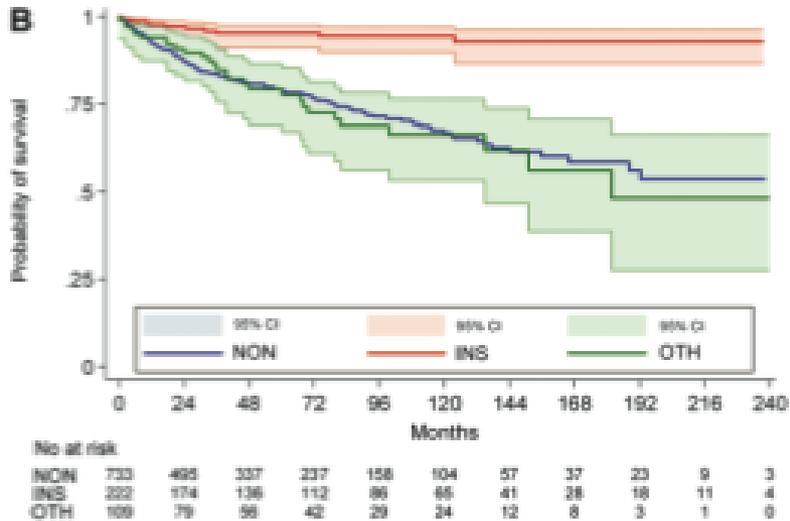
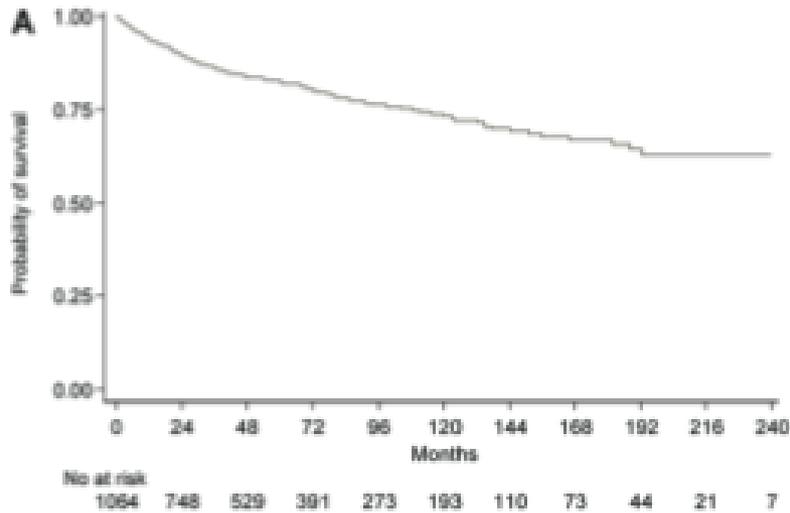
Curve di sopravvivenza (Kaplan-Meier) di 891 pazienti per **stadio** ENETS e UICC/WHO



Curve di sopravvivenza (Kaplan-Meier) di 926 pazienti per **grado** ENETS/UICC/WHO

Rindi G, Falconi M, Klersy C *et al*: TNM staging of neoplasms of the endocrine pancreas: results from a large international cohort study. *J Natl Cancer Inst* 2012; 104: 764-777

Stadiazione TNM delle neoplasie del pancreas endocrino



KM curva di sopravvivenza per neoplasie neuroendocrine pancreatiche in 1064 pazienti (A) raggruppate per stato funzionale (B)

NON non funzionanti
 INS insulinomi
 OTH altre sindromi funzionali

Rindi G, Falconi M, Klersy C *et al*: TNM staging of neoplasms of the endocrine pancreas: results from a large international cohort study. *J Natl Cancer Inst* 2012; 104: 764-777

REFERTO PATOLOGICO (Raccomandazioni WHO 2010)

Descrizione macroscopica

sede anatomica
distanza dai margini di resezione
dimensioni della lesione
lesione solitaria/multipla (sindromi familiari)
a confini netti o male definiti
consistenza, colore

Descrizione microscopica

struttura istologica
bene differenziata (organoide): a nidi solidi, trabecolare, ghiandolare, tubulo-acinare, mista, cistico-papillare, angiomatosa
poco differenziata
indifferenziata (a grandi o a piccole cellule)
presenza di: fibrosi, amiloidosi (*insulinomi*), calcificazioni (*corpi psammomatosi nei somatostatiniomi*), necrosi (indice di malignità)
interessamento dei margini
reattività immunoistochimica
numero di mitosi per 10HPF (2mmq) basato sul conteggio delle mitosi in almeno 50 HPF
indice di attività proliferativa (Ki67/Mib-1) sulle aree di maggiore attività (500-2000 cellule)
stato linfonodale

Diagnosi istologica

NET / NEC
grado (G1, G2, G3)
componente cellulare nei casi funzionalmente attivi
stadio TNM