FACULTAD DE MEDICINA

PONTIFICIA UNIVERSIDAD
CATÓLICA DE CHILE

Tumores neuroendocrinos del aparato digestivo

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Facultad de Medicina
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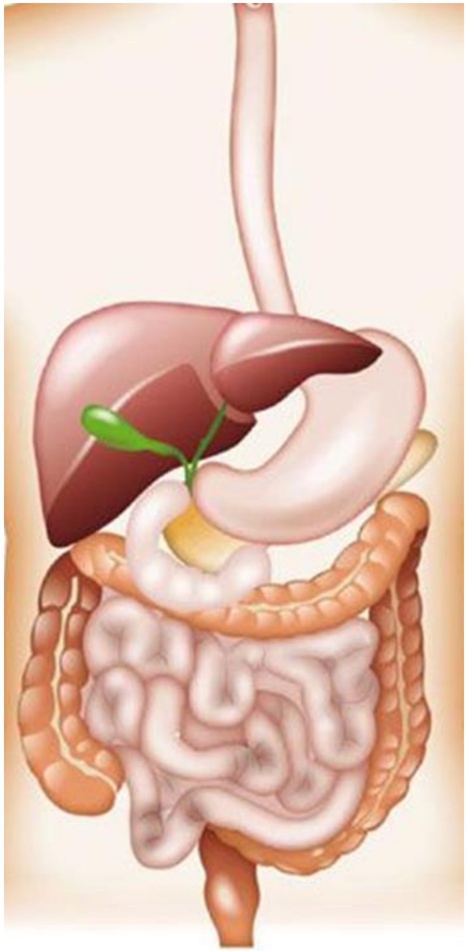
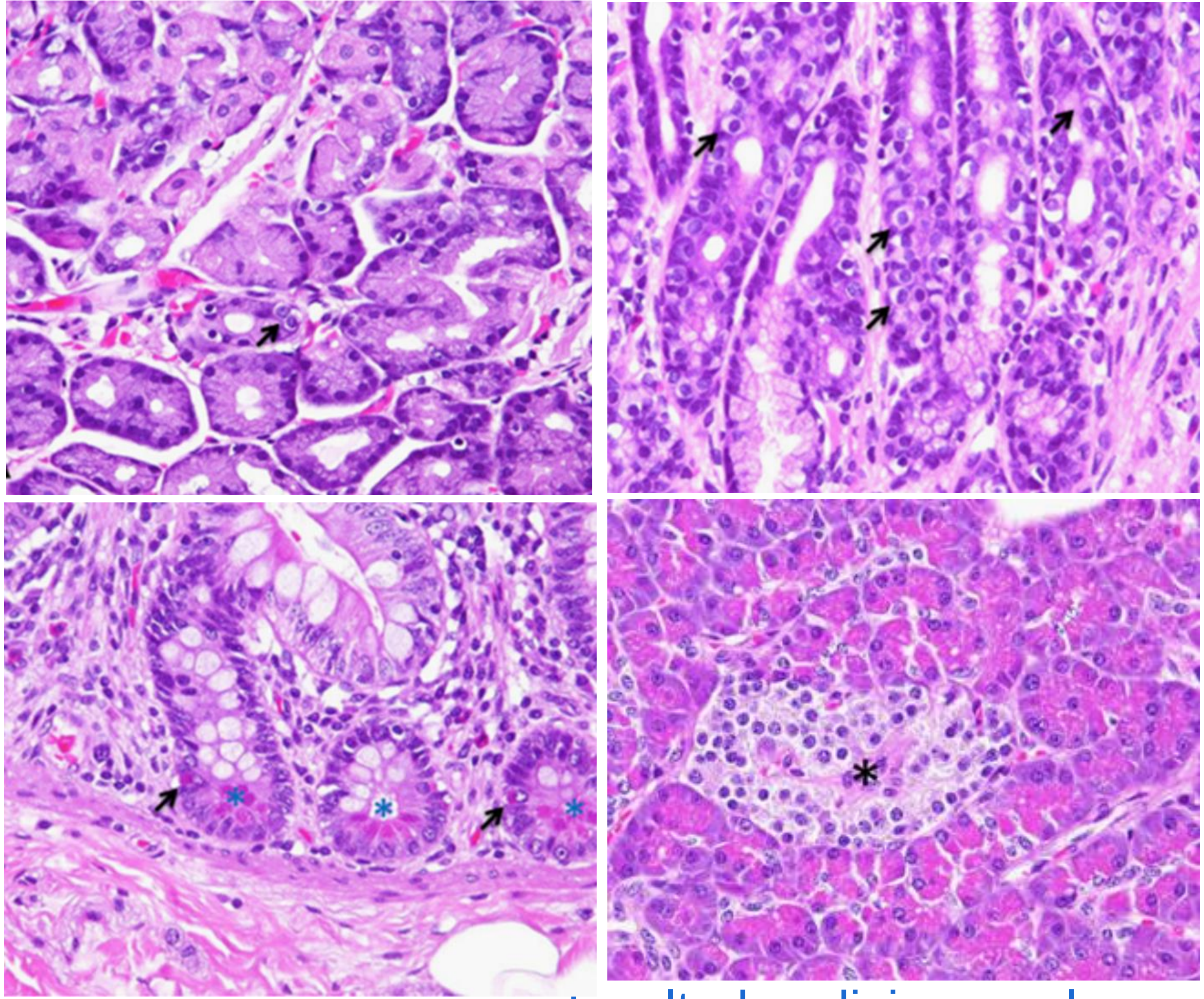
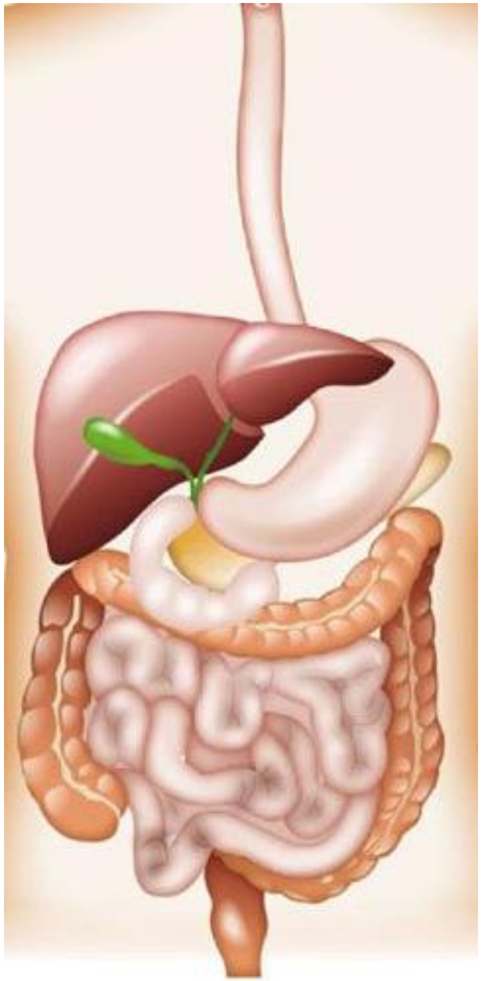
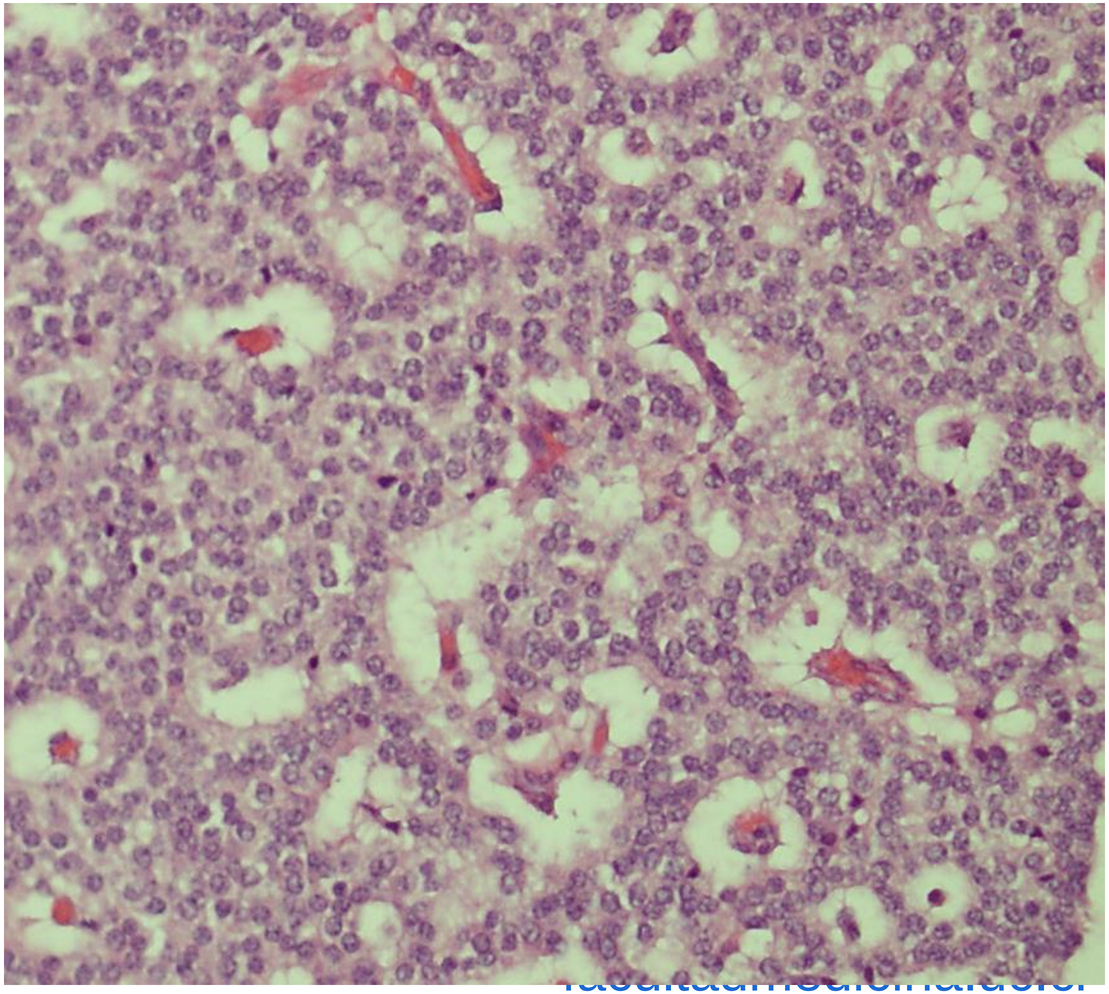
Sistema neuroendocrino



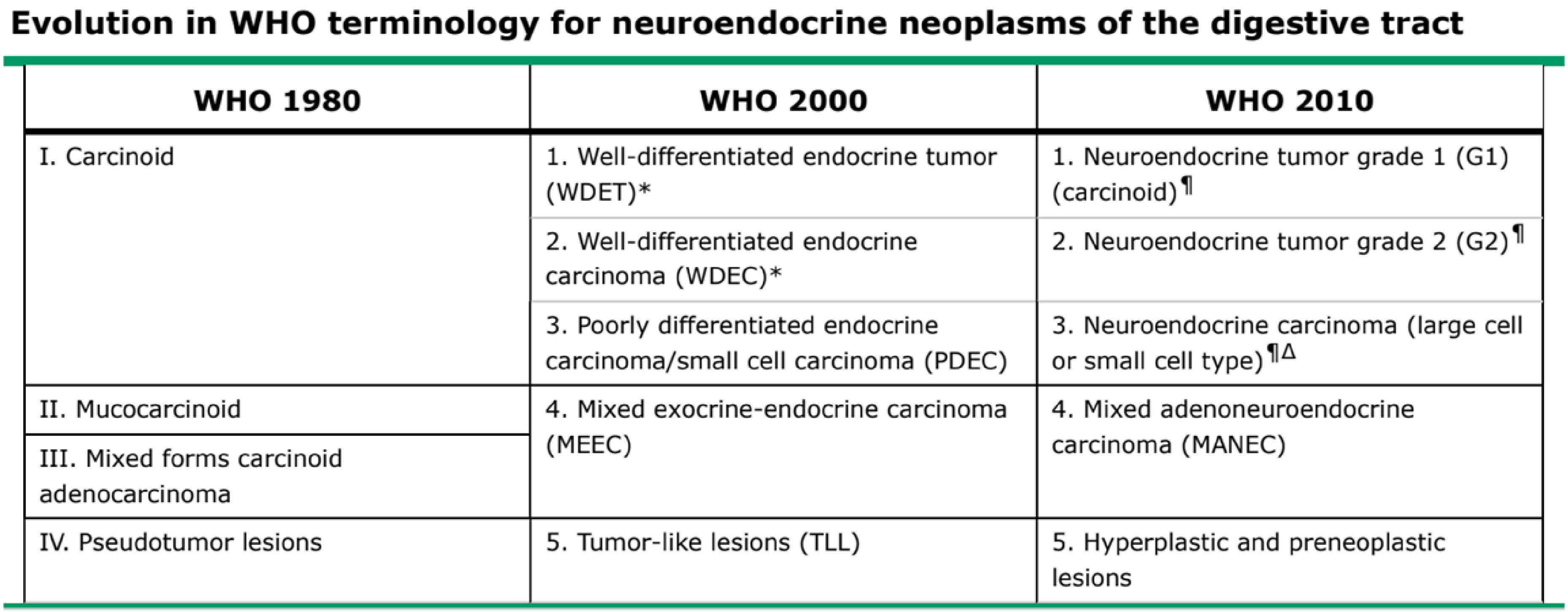


Tumores neuroendocrinos





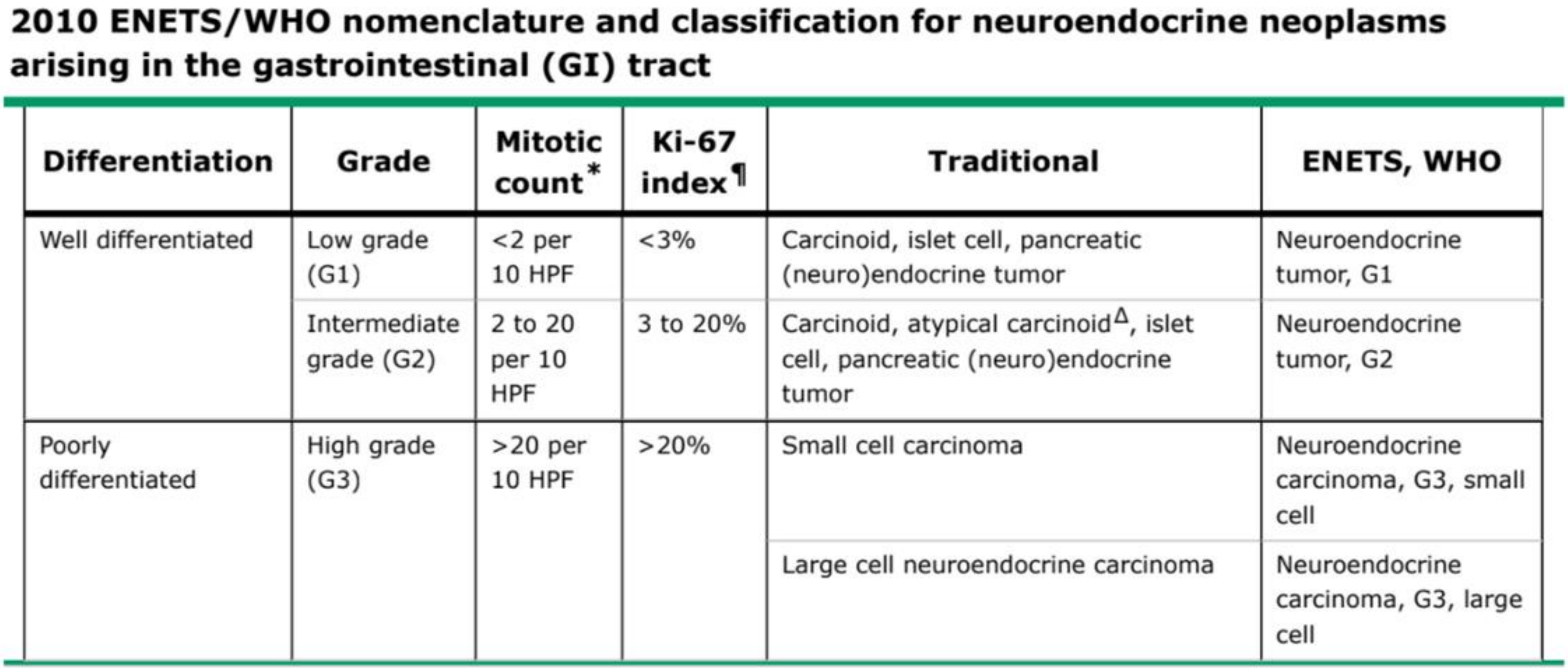
Clasificación de los Tumores Neuroendocrinos



Evolution in WHO terminology for neuroendocrine neoplasms of the digestive tract

WHO 1980	WHO 2000	WHO 2010
I. Carcinoid	1. Well-differentiated endocrine tumor (WDET)*	1. Neuroendocrine tumor grade 1 (G1) (carcinoid)[¶]
	2. Well-differentiated endocrine carcinoma (WDEC)*	2. Neuroendocrine tumor grade 2 (G2)[¶]
	3. Poorly differentiated endocrine carcinoma/small cell carcinoma (PDEC)	3. Neuroendocrine carcinoma (large cell or small cell type)[¶Δ]
II. Mucocarcinoid	4. Mixed exocrine-endocrine carcinoma (MEEC)	4. Mixed adenoneuroendocrine carcinoma (MANEC)
III. Mixed forms carcinoid adenocarcinoma		
IV. Pseudotumor lesions	5. Tumor-like lesions (TLL)	5. Hyperplastic and preneoplastic lesions

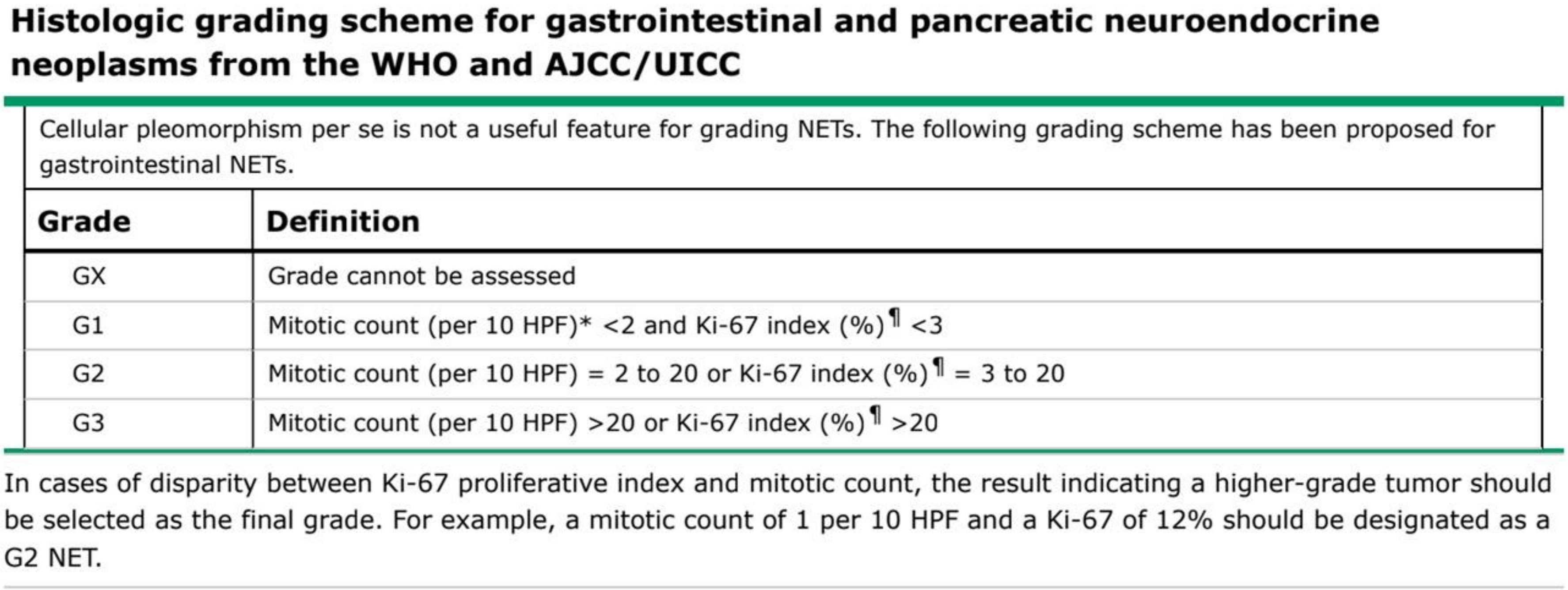
Clasificación de los Tumores Neuroendocrinos



2010 ENETS/WHO nomenclature and classification for neuroendocrine neoplasms arising in the gastrointestinal (GI) tract

Differentiation	Grade	Mitotic count[*]	Ki-67 index[¶]	Traditional	ENETS, WHO
Well differentiated	Low grade (G1)	<2 per 10 HPF	<3%	Carcinoid, islet cell, pancreatic (neuro)endocrine tumor	Neuroendocrine tumor, G1
	Intermediate grade (G2)	2 to 20 per 10 HPF	3 to 20%	Carcinoid, atypical carcinoid[Δ], islet cell, pancreatic (neuro)endocrine tumor	Neuroendocrine tumor, G2
Poorly differentiated	High grade (G3)	>20 per 10 HPF	>20%	Small cell carcinoma	Neuroendocrine carcinoma, G3, small cell
				Large cell neuroendocrine carcinoma	Neuroendocrine carcinoma, G3, large cell

Clasificación de los Tumores Neuroendocrinos



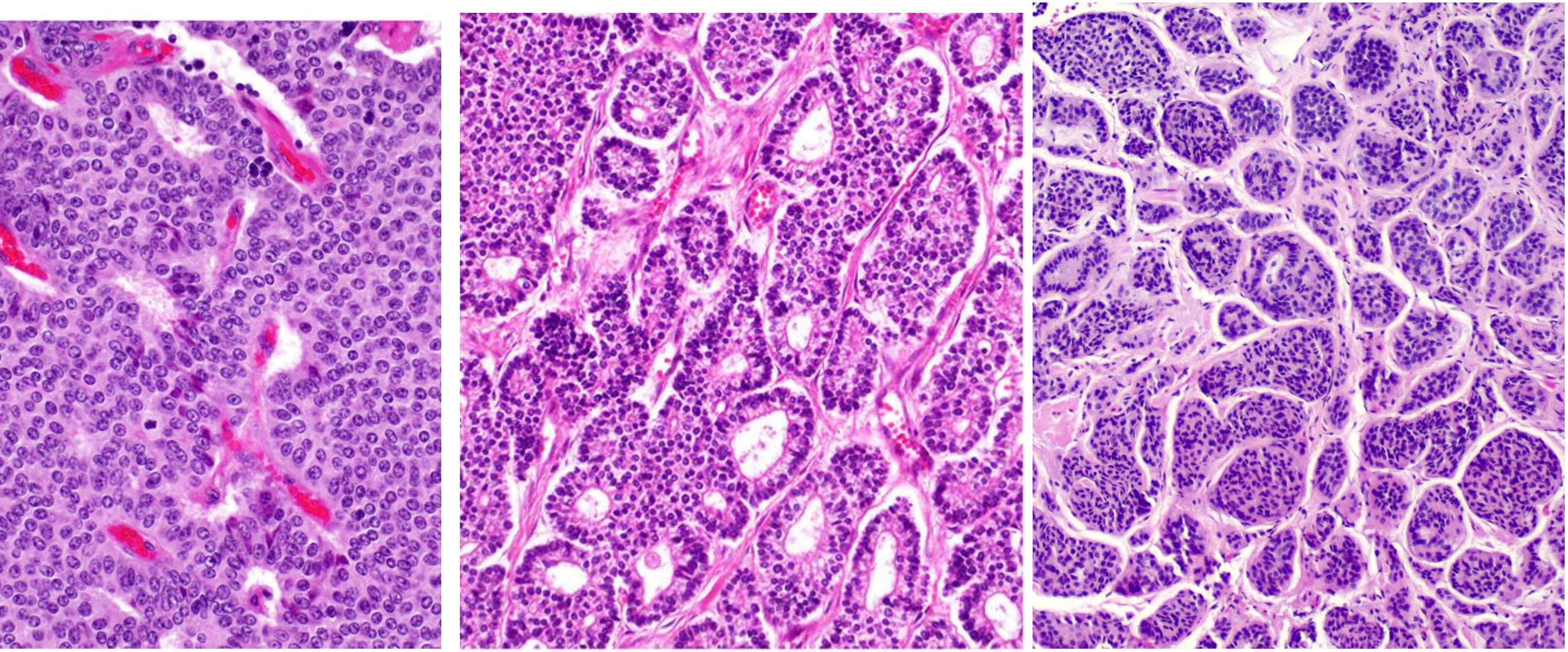
Histologic grading scheme for gastrointestinal and pancreatic neuroendocrine neoplasms from the WHO and AJCC/UICC

Cellular pleomorphism per se is not a useful feature for grading NETs. The following grading scheme has been proposed for gastrointestinal NETs.

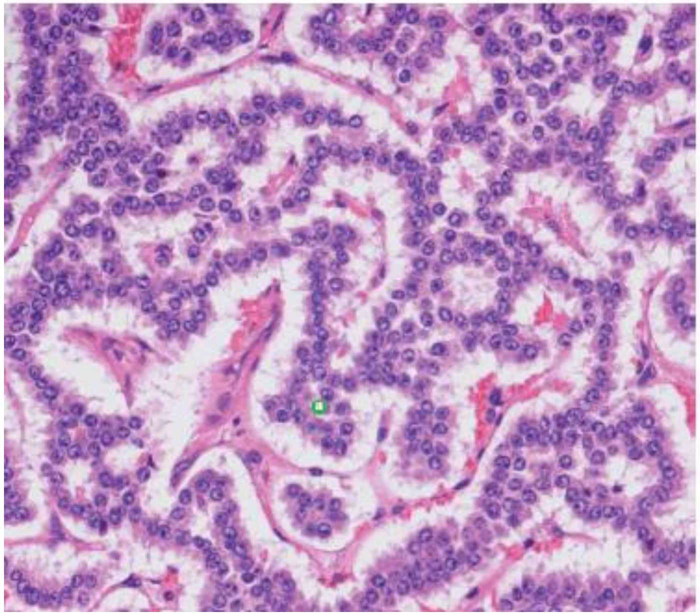
Grade	Definition
GX	Grade cannot be assessed
G1	Mitotic count (per 10 HPF)* <2 and Ki-67 index (%)¶ <3
G2	Mitotic count (per 10 HPF) = 2 to 20 or Ki-67 index (%)¶ = 3 to 20
G3	Mitotic count (per 10 HPF) >20 or Ki-67 index (%)¶ >20

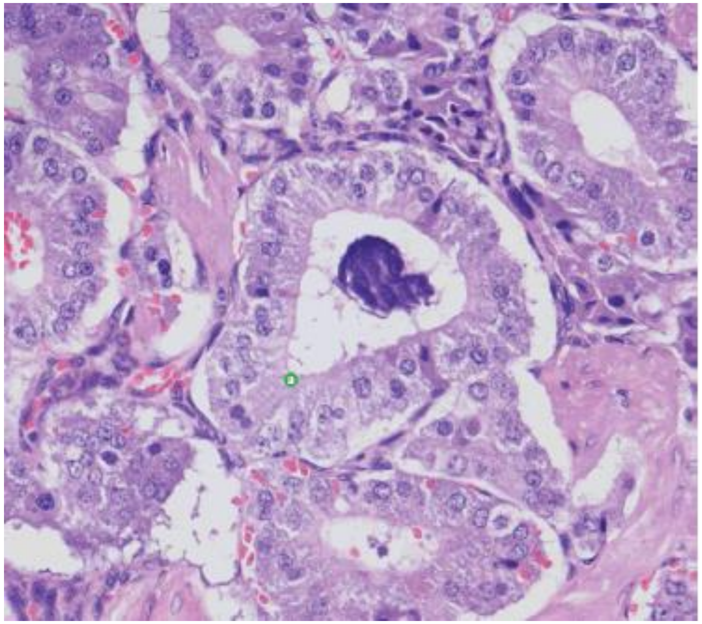
In cases of disparity between Ki-67 proliferative index and mitotic count, the result indicating a higher-grade tumor should be selected as the final grade. For example, a mitotic count of 1 per 10 HPF and a Ki-67 of 12% should be designated as a G2 NET.

Tumores neuroendocrinos bien diferenciados

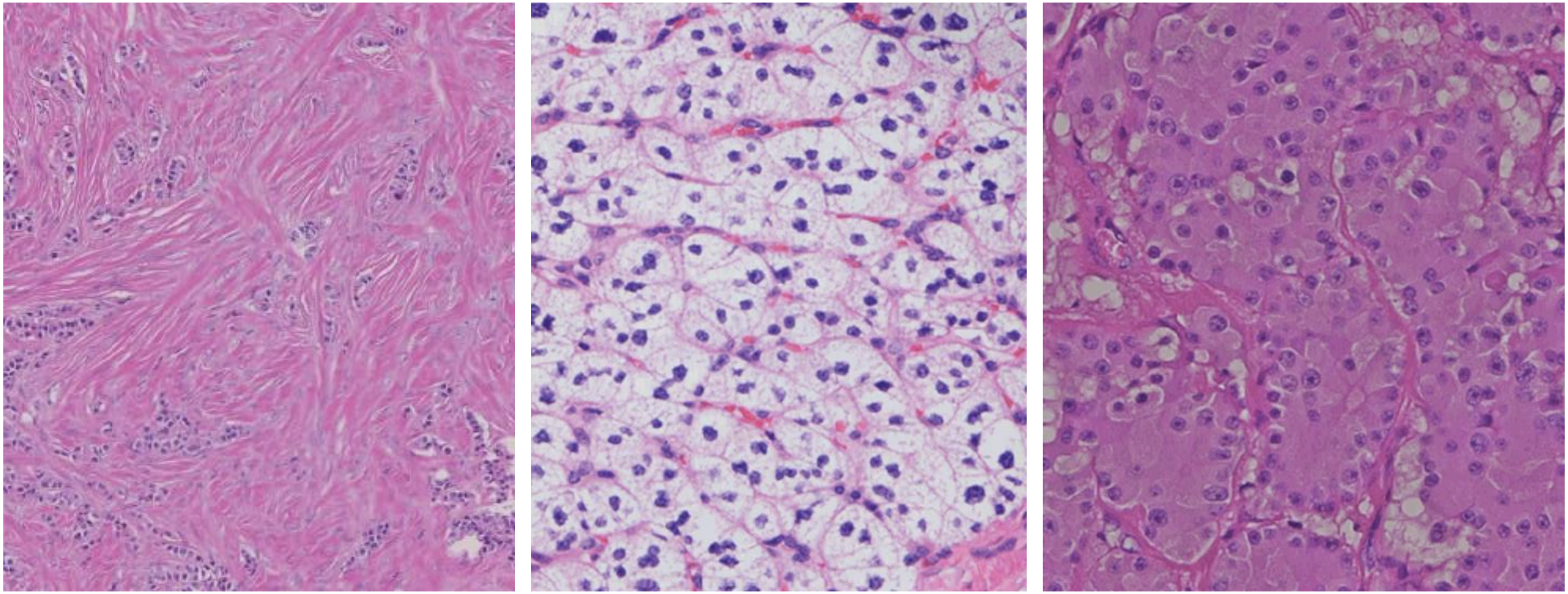


Tumores neuroendocrinos bien diferenciados

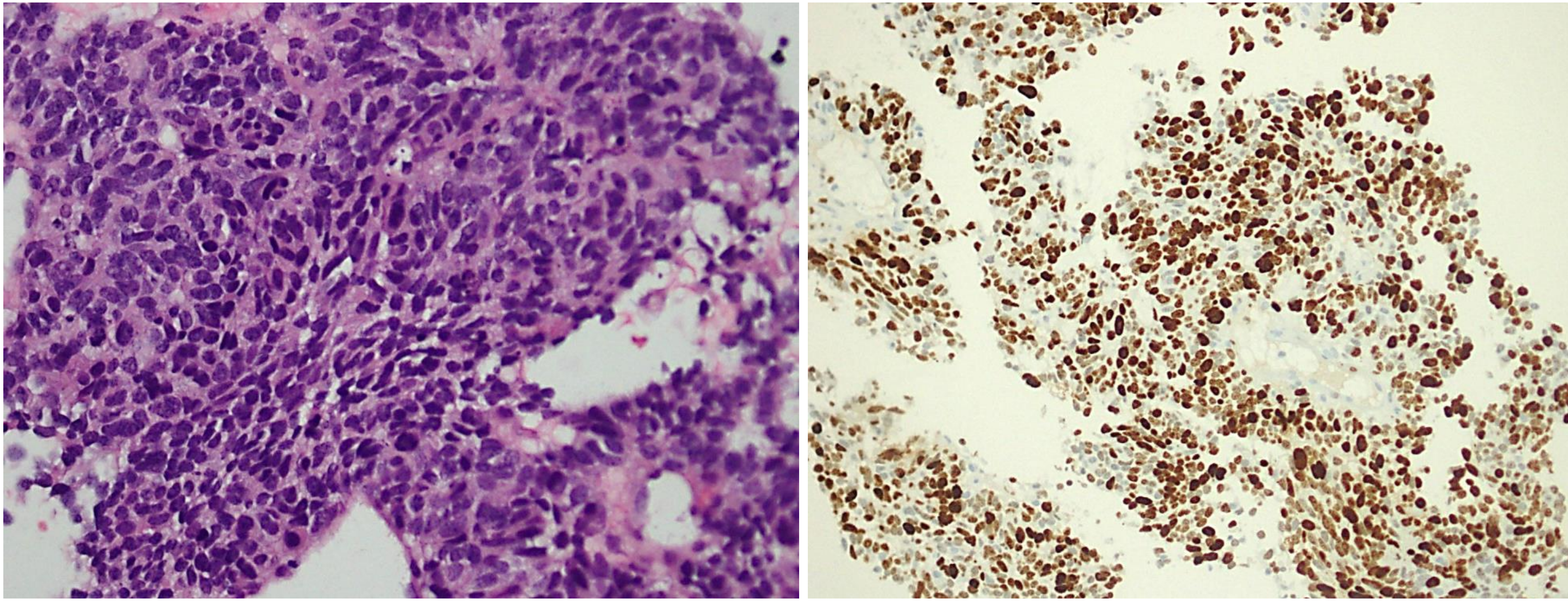




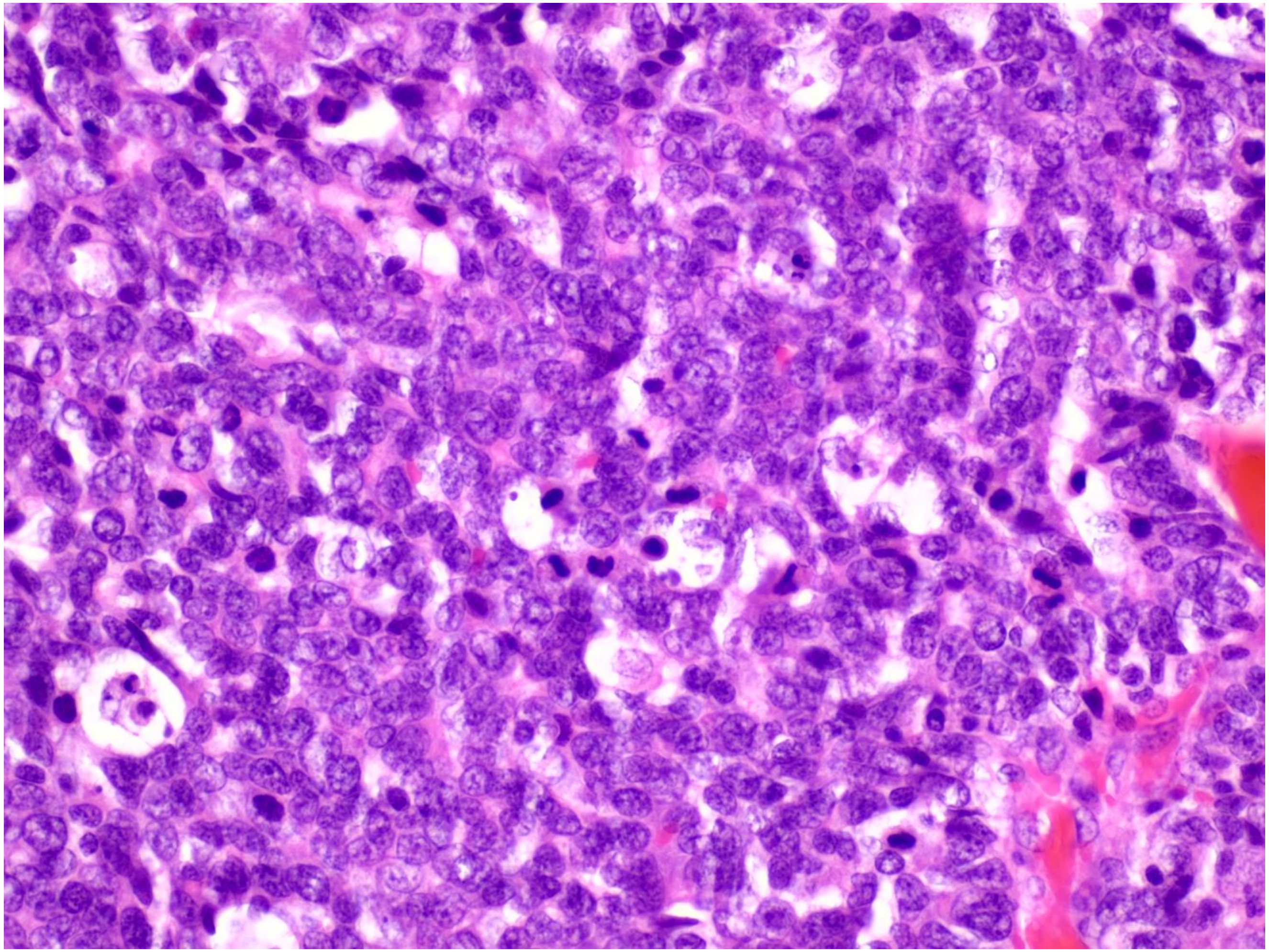
Tumores neuroendocrinos bien diferenciados



Tumores neuroendocrinos poco diferenciados



Tumores neuroendocrinos poco diferenciados



Tumores neuroendocrinos poco diferenciados

- Presentación clínica agresiva.
- Todos de alto grado por definición.
- Genéticamente presentan mutación de *TP53 y RB1*.
- Uniformes independiente del sitio de origen.
- Molecularmente se asemejan más a su contraparte maligna no neuroendocrina que a los tumores neuroendocrinos.

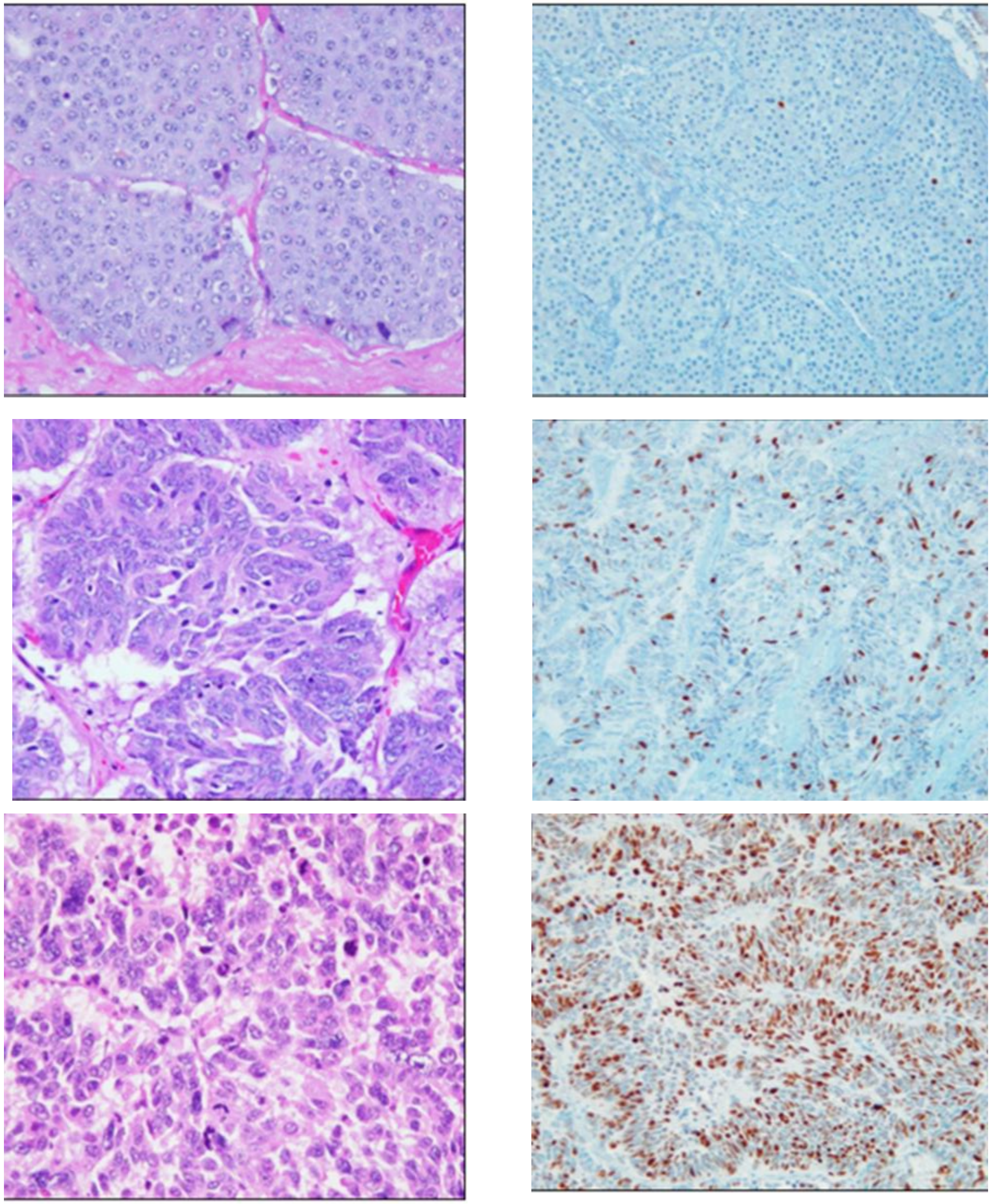


Fig. 3 – Neuroendocrine neoplasms of different histologic grades based on 2010 WHO criteria. (A and D) Low-grade (G1) NET with low mitotic rate (0.6/10 HPF) and Ki67 index (0.8%). (B and E) Intermediate-grade (G2) NET with moderate mitotic rate (3.5/10 HPF) and Ki67 index (9.6%). (C and F) High-grade NEC (G3) with high mitotic rate (64/10 HPF) and Ki67 index (38%). [(A–C) H&E staining, original magnification ×400; (D–F) immunohistochemical staining for Ki67, original magnification ×200.]

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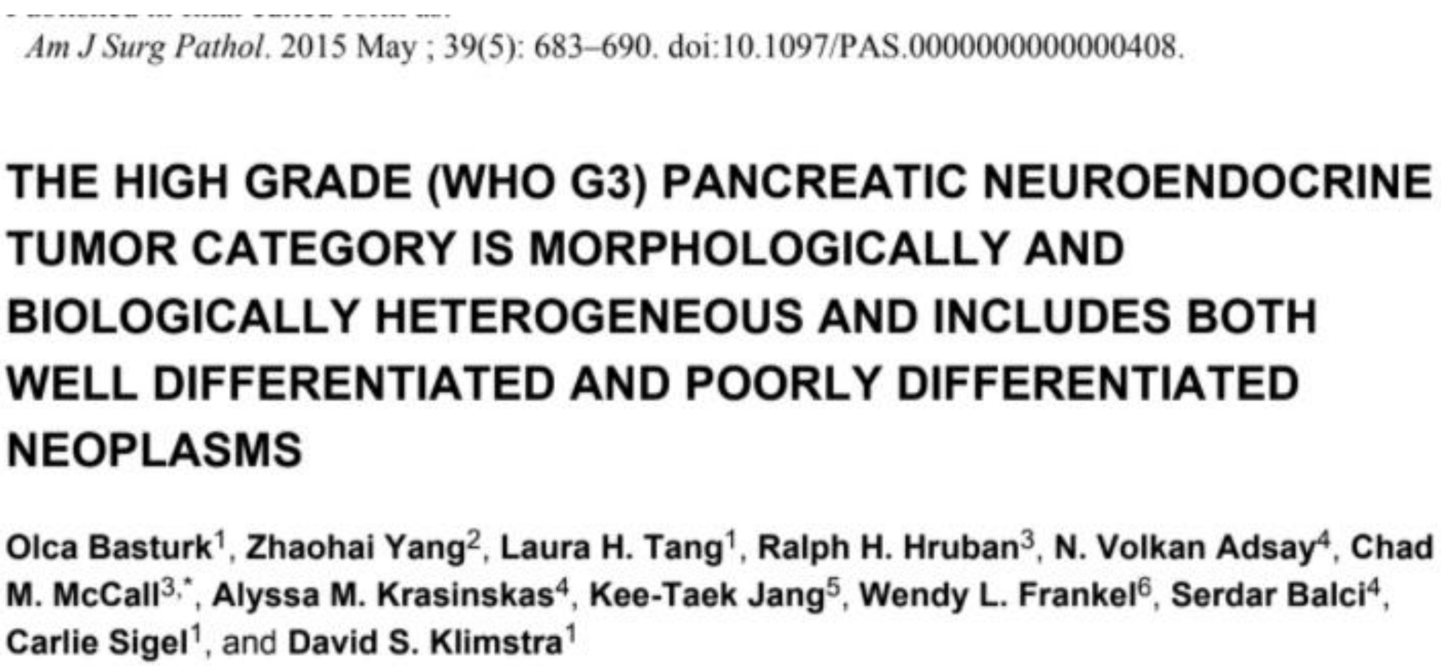

Am J Surg Pathol. 2015 May ; 39(5): 683–690. doi:10.1097/PAS.0000000000000408.

THE HIGH GRADE (WHO G3) PANCREATIC NEUROENDOCRINE TUMOR CATEGORY IS MORPHOLOGICALLY AND BIOLOGICALLY HETEROGENEOUS AND INCLUDES BOTH WELL DIFFERENTIATED AND POORLY DIFFERENTIATED NEOPLASMS

Olca Basturk[1], Zhaohai Yang[2], Laura H. Tang[1], Ralph H. Hruban[3], N. Volkan Adsay[4], Chad M. McCall[3,*], Alyssa M. Krasinskas[4], Kee-Taek Jang[5], Wendy L. Frankel[6], Serdar Balci[4], Carlie Sigel[1], and **David S. Klimstra[1]**

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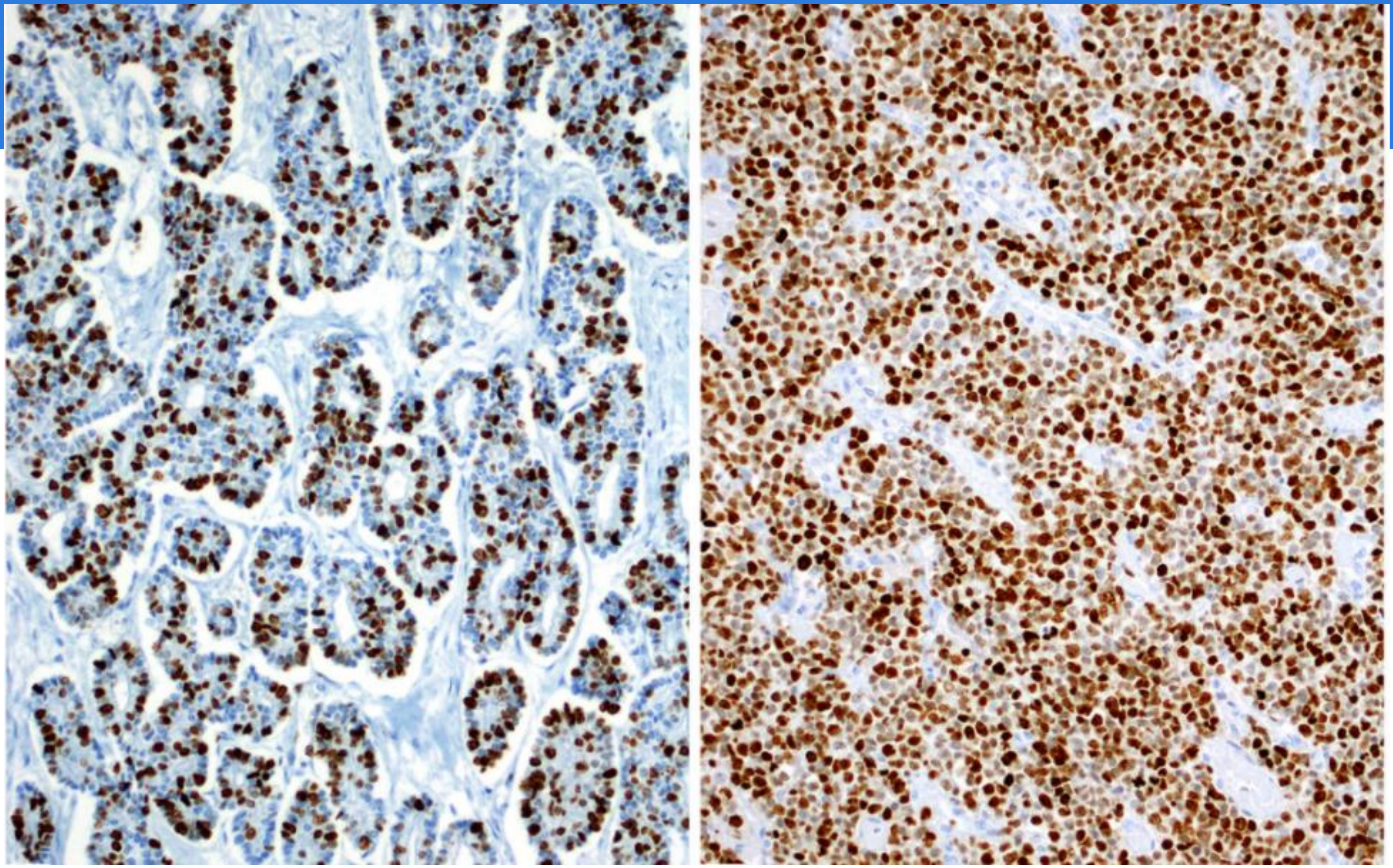

Average Ki67 proliferation index of grade-discordant pancreatic neuroendocrine tumors was 40% (as opposed to 74% of small cell type and 66% of large cell type poorly differentiated neuroendocrine carcinomas). (b) A small cell carcinoma with Ki67 proliferation index of >95% is depicted here.

Am J Surg Pathol. 2015 May ; 39(5): 683–690.

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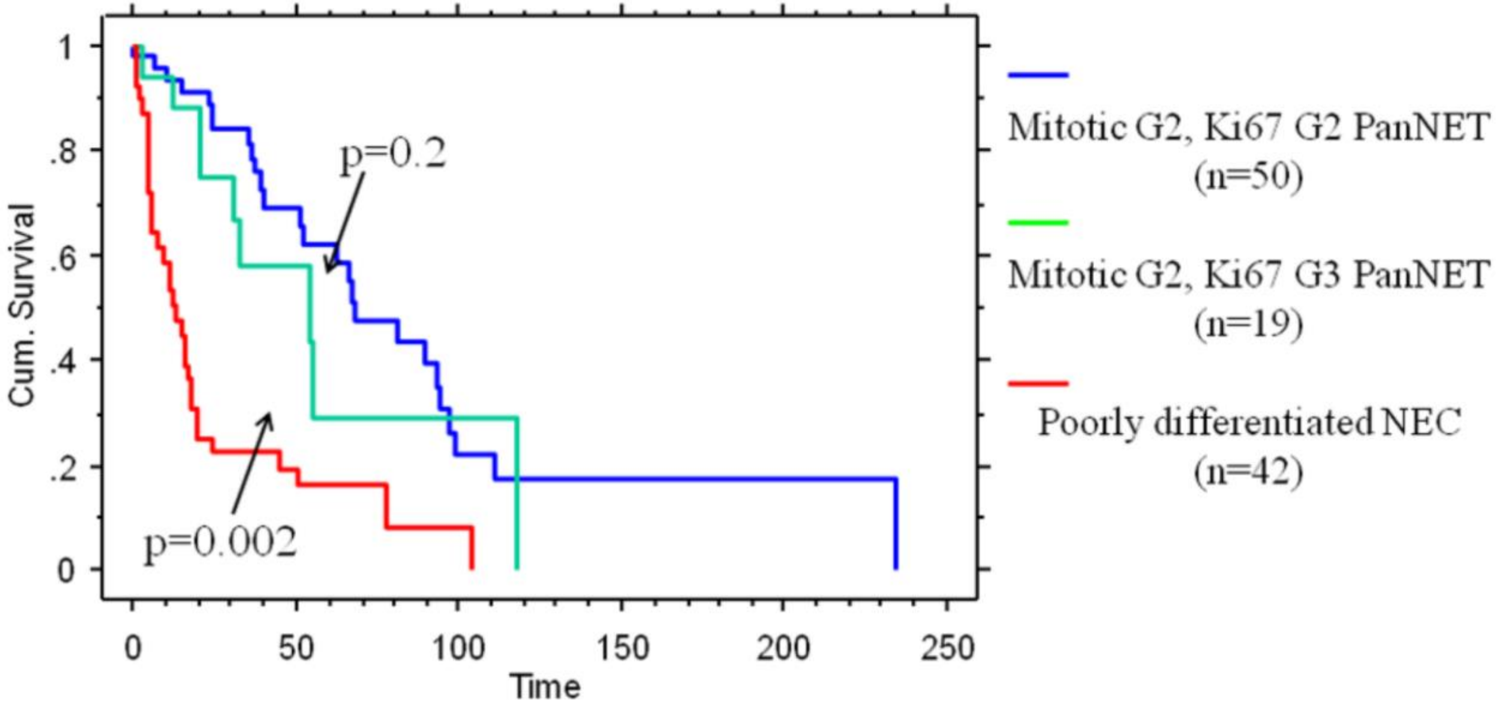

The Kaplan-Meier analysis comparing the overall disease-specific survivals of all grade-concordant pancreatic neuroendocrine tumors, grade-discordant pancreatic neuroendocrine tumors, and poorly differentiated neuroendocrine carcinomas (All cases)

Am J Surg Pathol. 2015 May ; 39(5): 683–690

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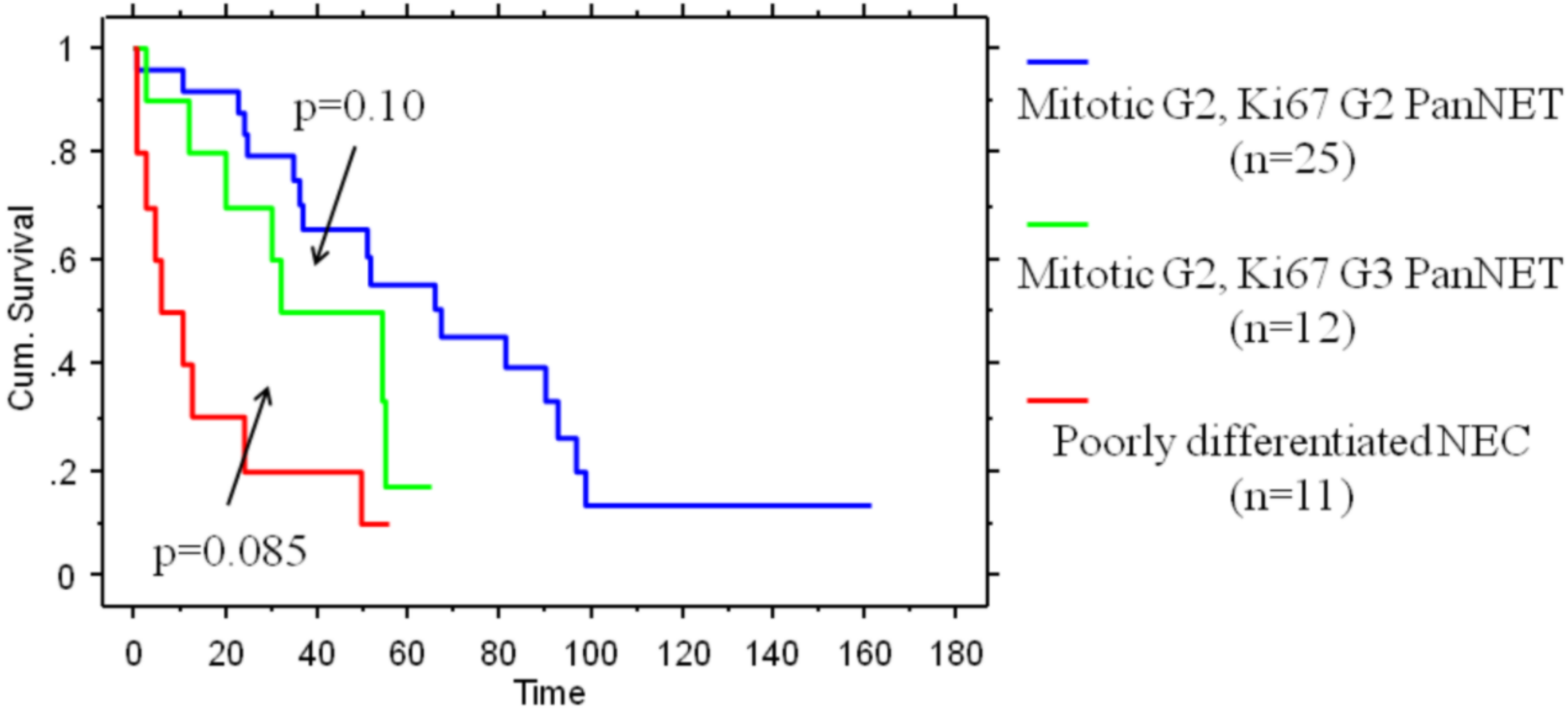

The Kaplan-Meier analysis comparing the overall disease-specific survivals of grade-concordant pancreatic neuroendocrine tumors, grade-discordant pancreatic neuroendocrine tumors, and poorly differentiated neuroendocrine carcinomas (Cases with distant metastasis only)

Am J Surg Pathol. 2015 May ; 39(5): 683–690

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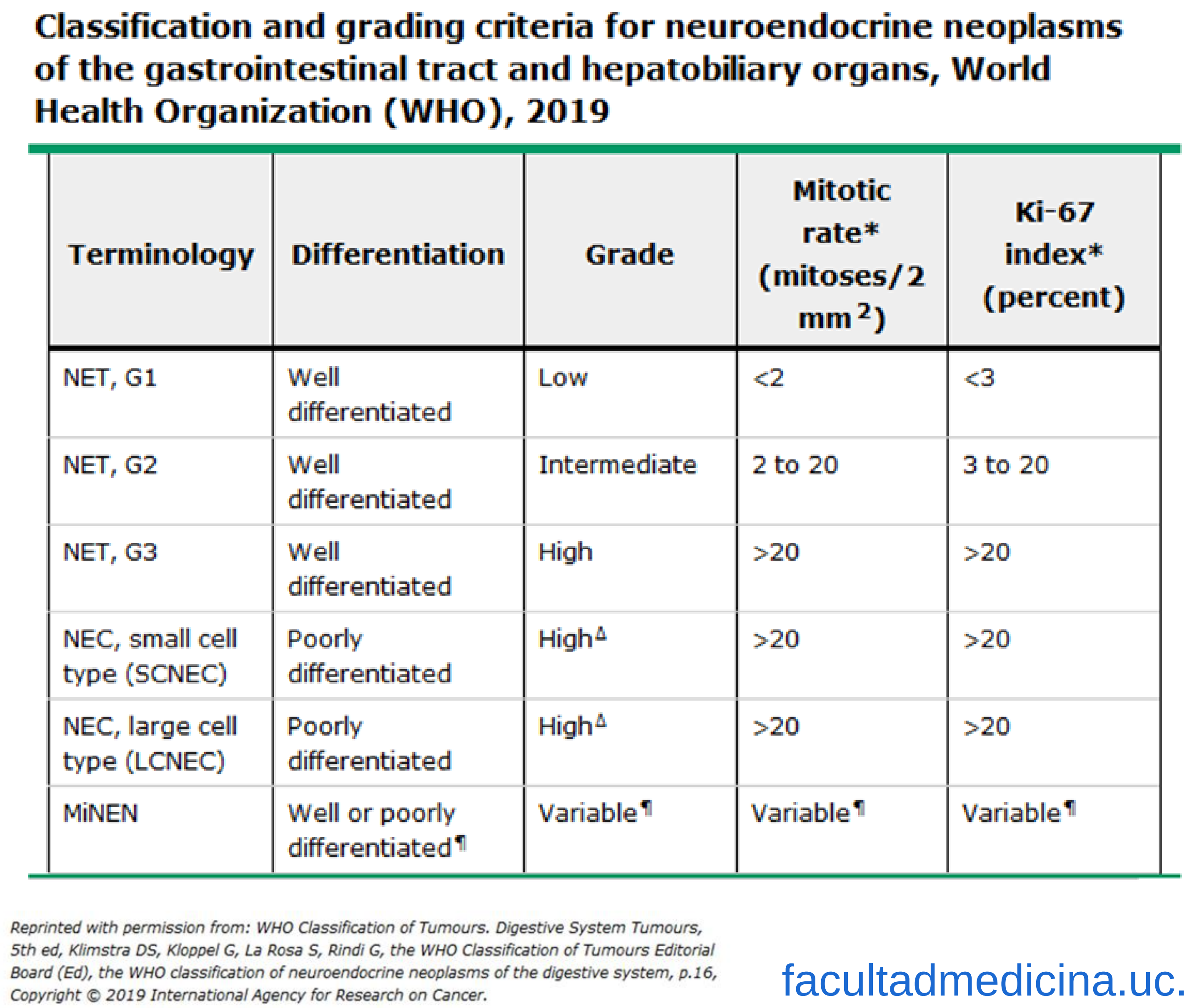


Classification and grading criteria for neuroendocrine neoplasms of the gastrointestinal tract and hepatobiliary organs, World Health Organization (WHO), 2019

Terminology	Differentiation	Grade	Mitotic rate* (mitoses/2 mm ^{2})	Ki-67 index* (percent)
NET, G1	Well differentiated	Low	<2	<3
NET, G2	Well differentiated	Intermediate	2 to 20	3 to 20
NET, G3	Well differentiated	High	>20	>20
NEC, small cell type (SCNEC)	Poorly differentiated	High[Δ]	>20	>20
NEC, large cell type (LCNEC)	Poorly differentiated	High[Δ]	>20	>20
MiNEN	Well or poorly differentiated[¶]	Variable[¶]	Variable[¶]	Variable[¶]

Reprinted with permission from: WHO Classification of Tumours. Digestive System Tumours, 5th ed, Klimstra DS, Kloppel G, La Rosa S, Rindi G, the WHO Classification of Tumours Editorial Board (Ed), the WHO classification of neuroendocrine neoplasms of the digestive system, p.16, Copyright © 2019 International Agency for Research on Cancer.

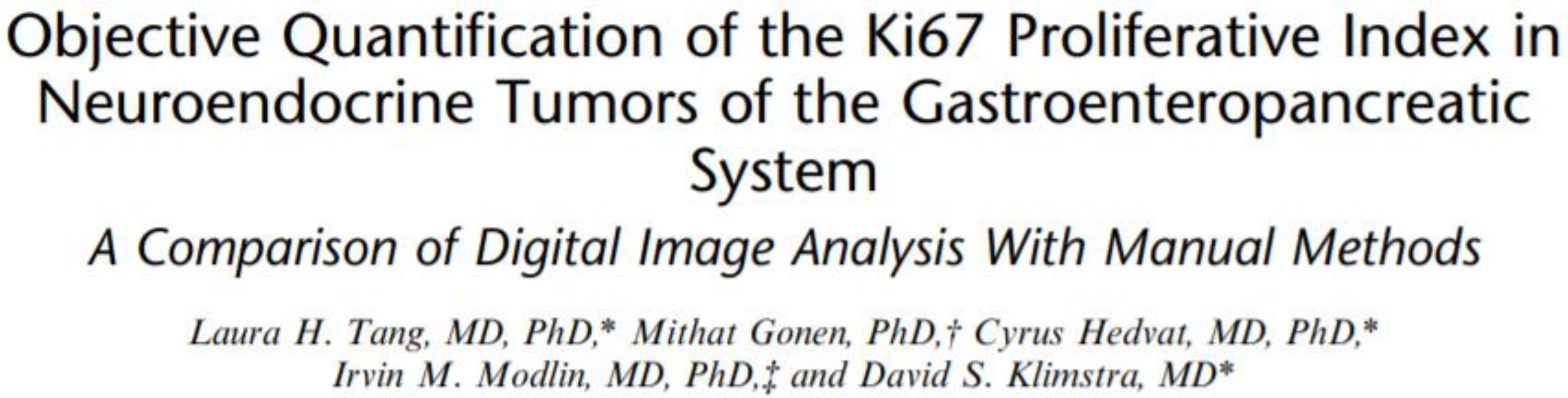
Clasificación de la WHO 2019

- Recuento mitótico expresado en número de mitosis en 2 mm cuadrados (para los microscopios convencionales corresponde a 10 campos de aumento mayor 40x y un diámetro del ocular de 0.5 mm).

- Recomendación hacer conteo en 50 campos de aumento mayor (en total una superficie de 10 mm cuadrados).

- Índice de proliferación medido con Ki-67 debe ser determinado al menos en 500 células (hotspot), recomendable 2000 células.

Evaluación de Ki-67 en tumores neuroendocrinos



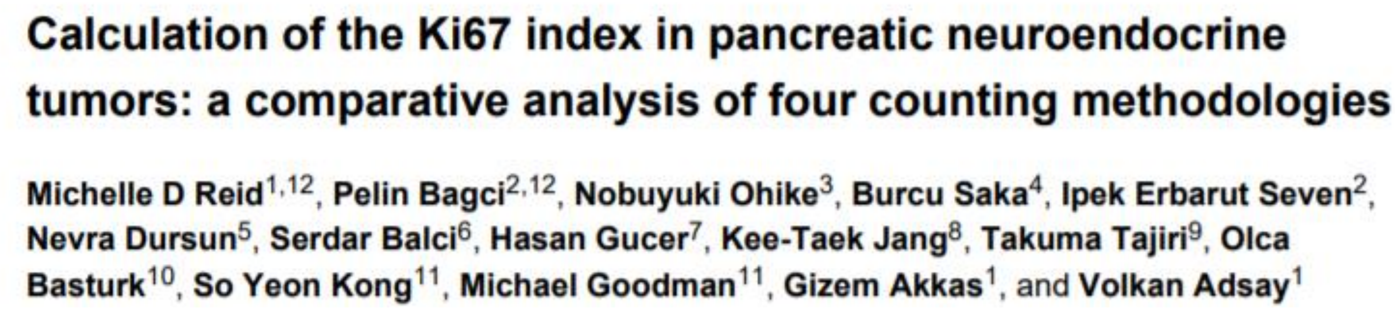
Objective Quantification of the Ki67 Proliferative Index in Neuroendocrine Tumors of the Gastroenteropancreatic System

A Comparison of Digital Image Analysis With Manual Methods

Laura H. Tang, MD, PhD, Mithat Gonen, PhD,† Cyrus Hedvat, MD, PhD,**
*Irvin M. Modlin, MD, PhD,‡ and David S. Klimstra, MD**

Am J Surg Pathol Volume 36, Number 12, December 2012

Evaluación de Ki-67 en tumores neuroendocrinos

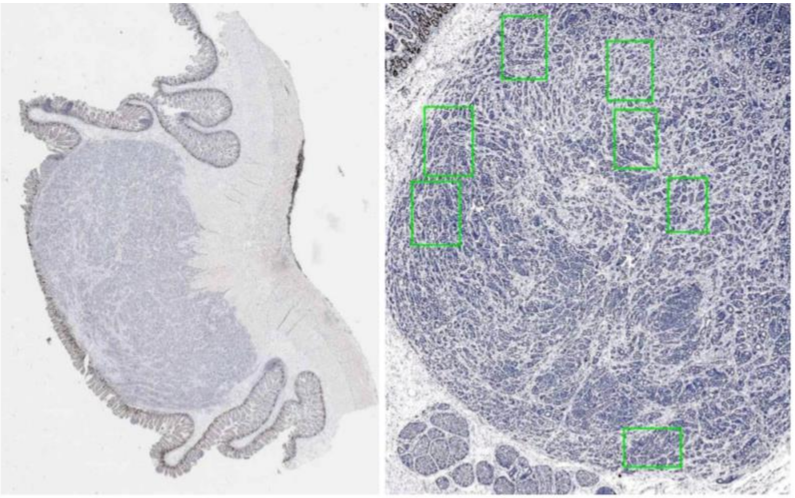


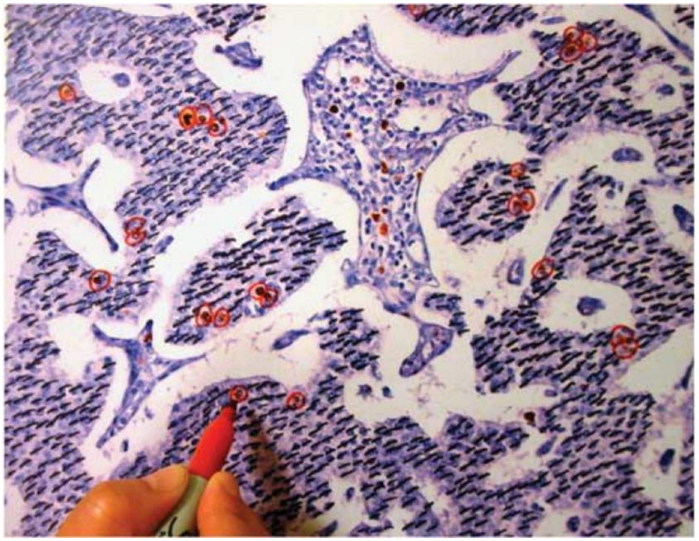
Calculation of the Ki67 index in pancreatic neuroendocrine tumors: a comparative analysis of four counting methodologies

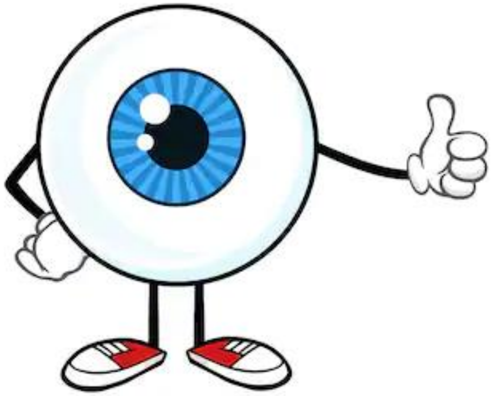
Michelle D Reid[1,12], **Pelin Bagci**[2,12], **Nobuyuki Ohike**[3], **Burcu Saka**[4], **Ipek Erbarut Seven**[2], **Nevra Dursun**[5], **Serdar Balci**[6], **Hasan Gucer**[7], **Kee-Taek Jang**[8], **Takuma Tajiri**[9], **Olca Basturk**[10], **So Yeon Kong**[11], **Michael Goodman**[11], **Gizem Akkas**[1], and **Volkan Adsay**[1]

Mod Pathol. 2015 May ; 28(5): 686–694.

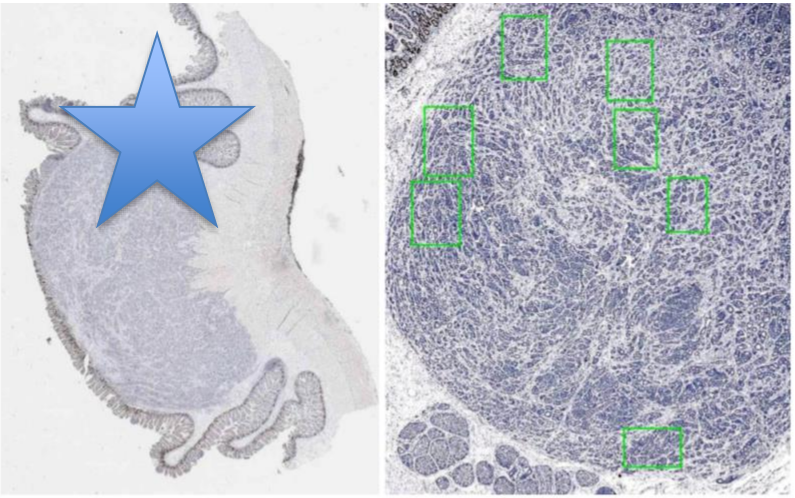
Evaluación de Ki-67 en tumores neuroendocrinos

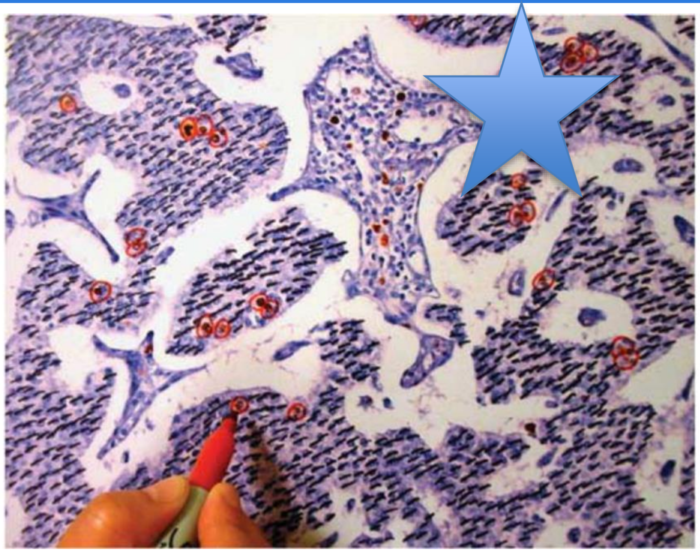


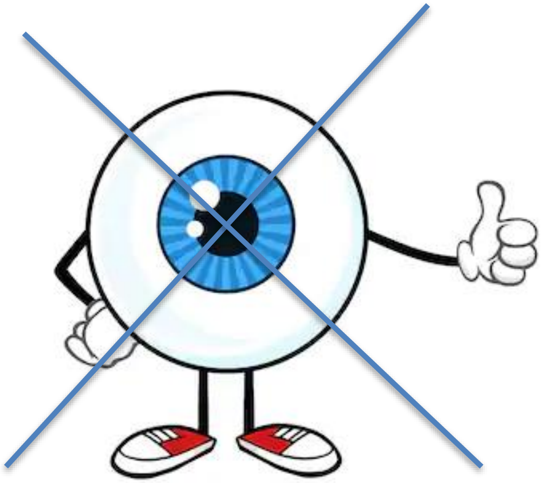




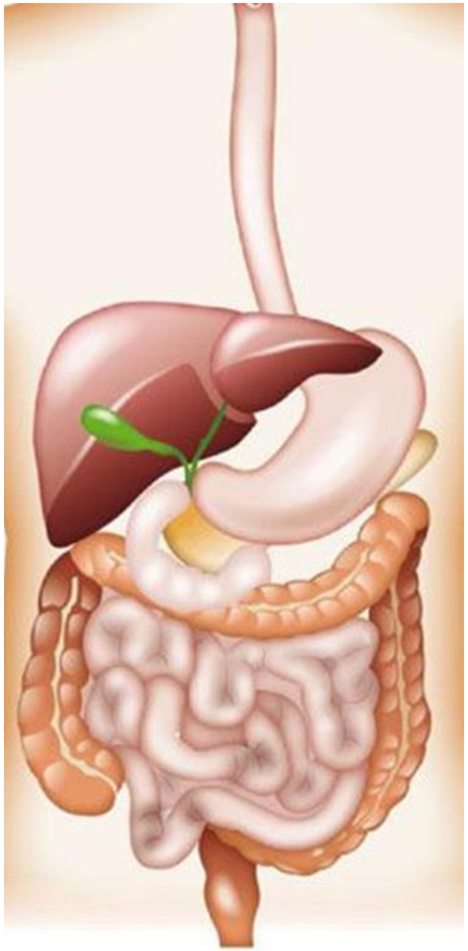
Evaluación de Ki-67 en tumores neuroendocrinos





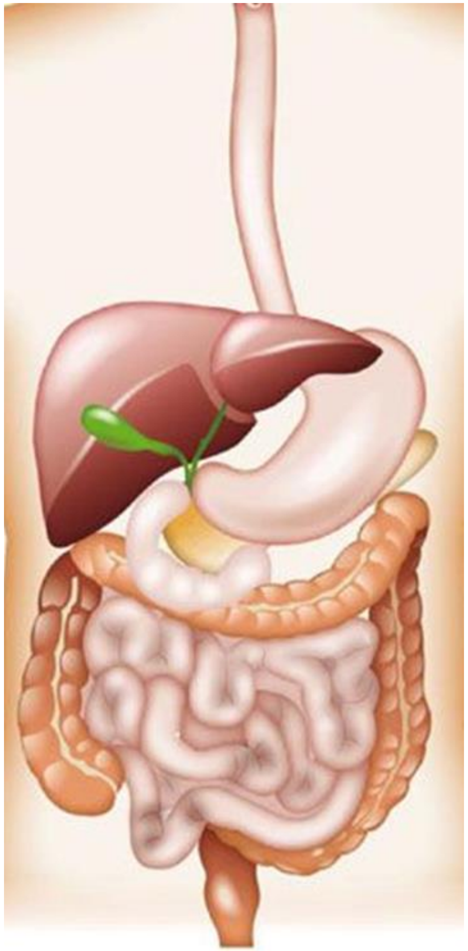


Tumores neuroendocrino en el tracto digestivo



- Esófago.
- Estómago.
- Intestino delgado: Duodeno, ampolla de Vater e íleon.
- Colon y recto.
- Páncreas.
- Hígado.

Tumores neuroendocrino en el tracto digestivo



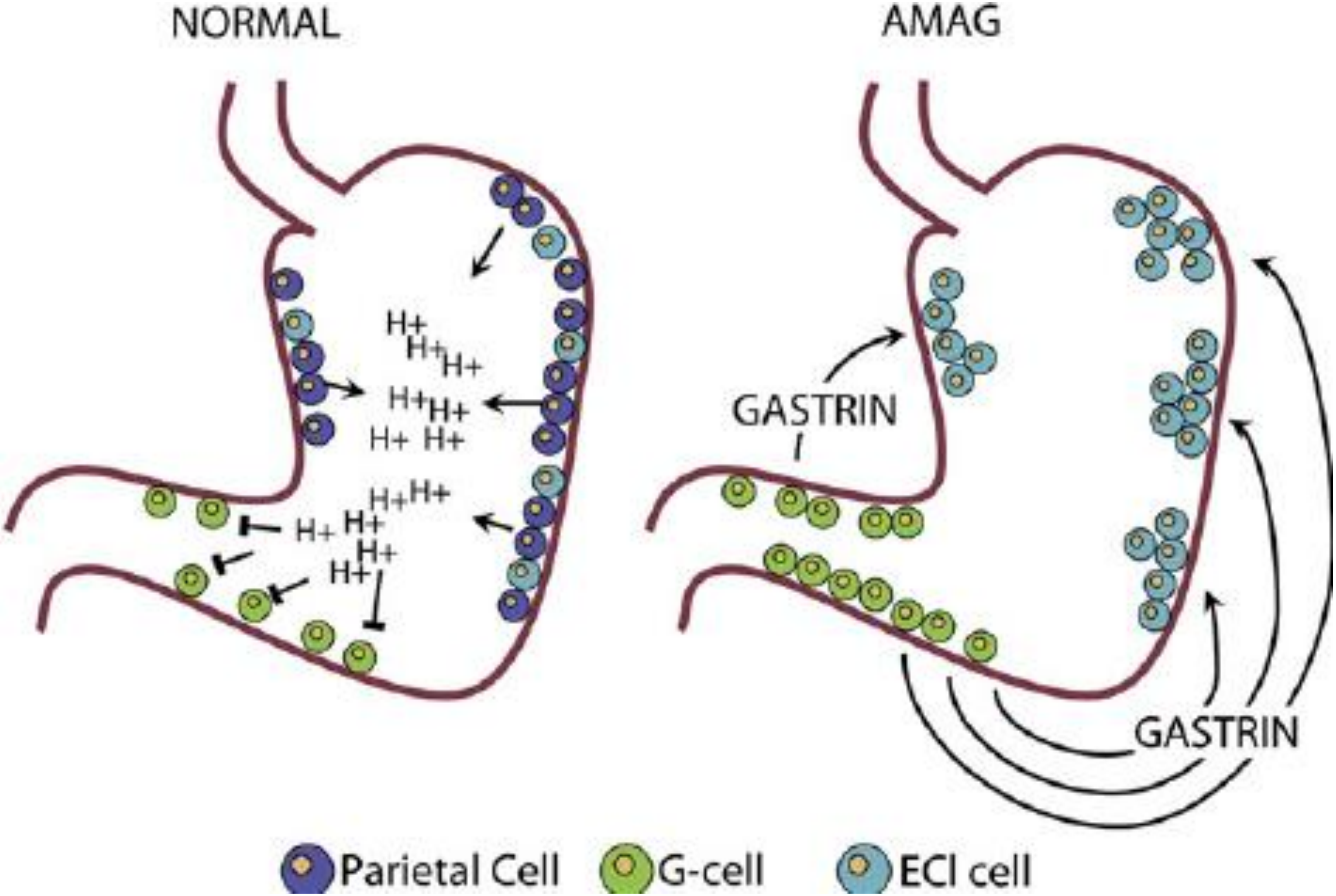
- Esófago.
- Estómago.
- Intestino delgado: Duodeno, ampolla de Vater e íleon.
- Colon y recto.
- Páncreas.
- Hígado.

Tumores neuroendocrinos gástricos

- Tumores no funcionantes.

- A diferencia de otros NET se dan en el contexto enfermedades definidas o bien caracterizadas.

- Se clasifican igual que el resto de los NET de acuerdo a la WHO, pero además tienen una segunda clasificación.


NORMAL
AMAG
H+
H+
H+
H+
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H+ H+
H+
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H+ H+
H+
H+
GASTRIN
GASTRIN
Parietal Cell
G-cell
ECl cell

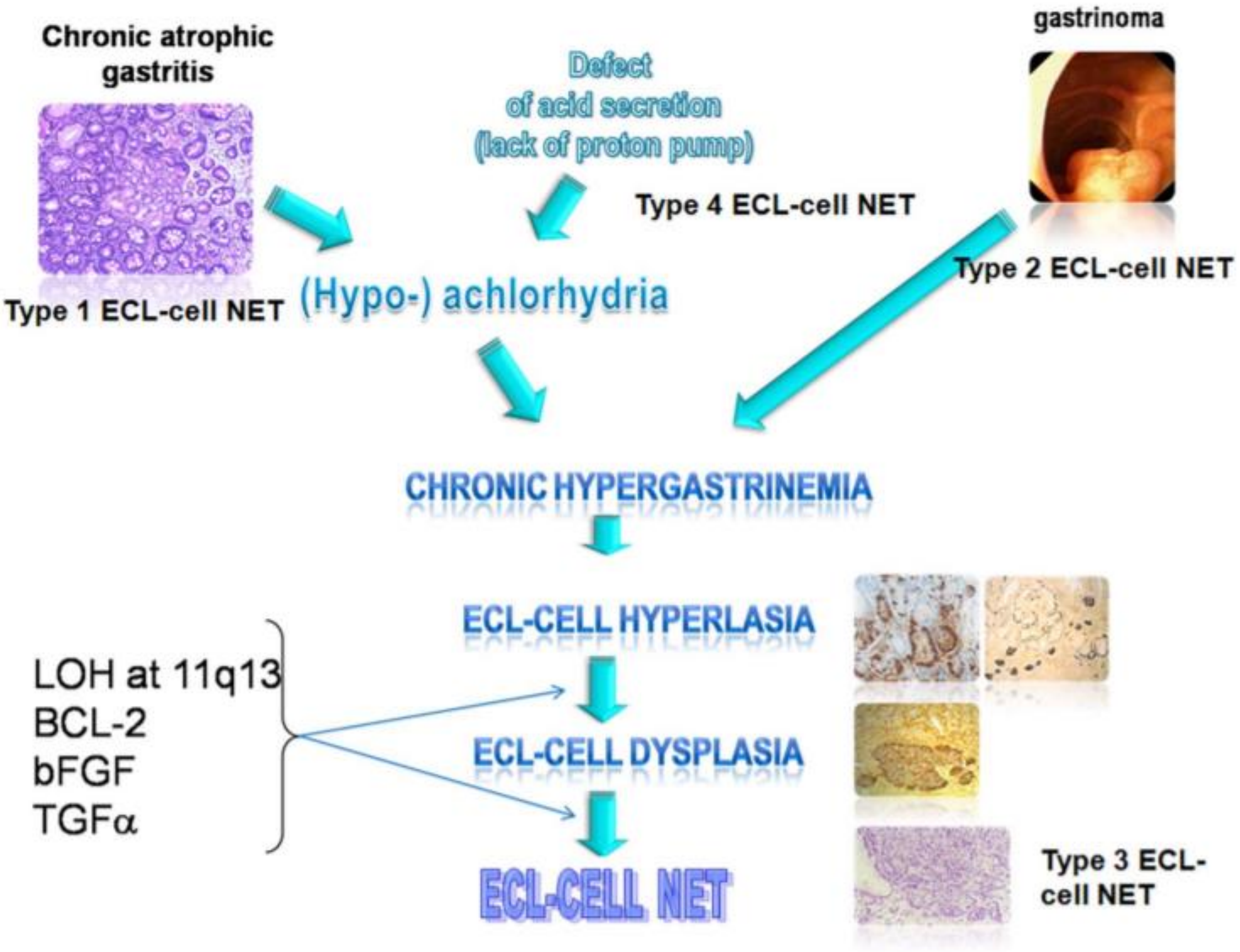
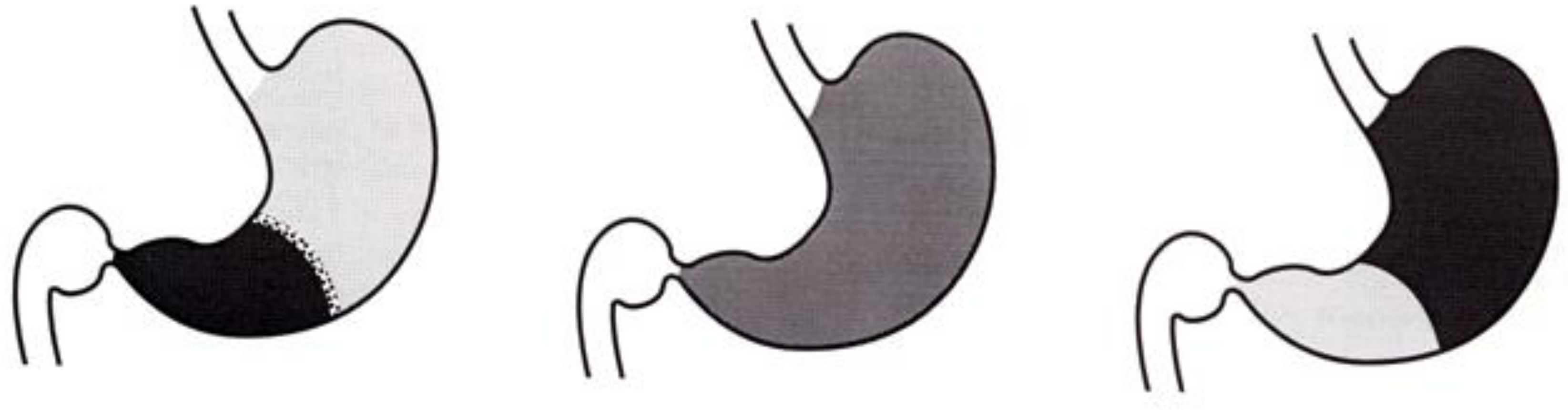

Chronic atrophic gastritis
Defect of acid secretion (lack of proton pump)
gastrinoma
Type 4 ECL-cell NET
Type 2 ECL-cell NET
Type 1 ECL-cell NET
(Hypo-) achlorhydria
CHRONIC HYPERGASTRINEMIA
ECL-CELL HYPERLASIA
LOH at 11q13
BCL-2
bFGF
TGFα
ECL-CELL DYSPLASIA
ECL-CELL NET
Type 3 ECL-cell NET

Figure 5 Schematic pathogenetic mechanism of ECL-cell neuroendocrine tumours (NETs). Types 1, 2 and 4 arise in a background of long-standing hypergastrinemia due to gastric body atrophic gastritis, to gastrinoma in the setting of multiple endocrine neoplasia type 1 (MEN1) or to a defect of the proton pump, respectively. Type 3 ECL-cell NETs are sporadic arising in normal oxyntic mucosa with an unknown pathogenetic mechanism not depending on hypergastrinemia.

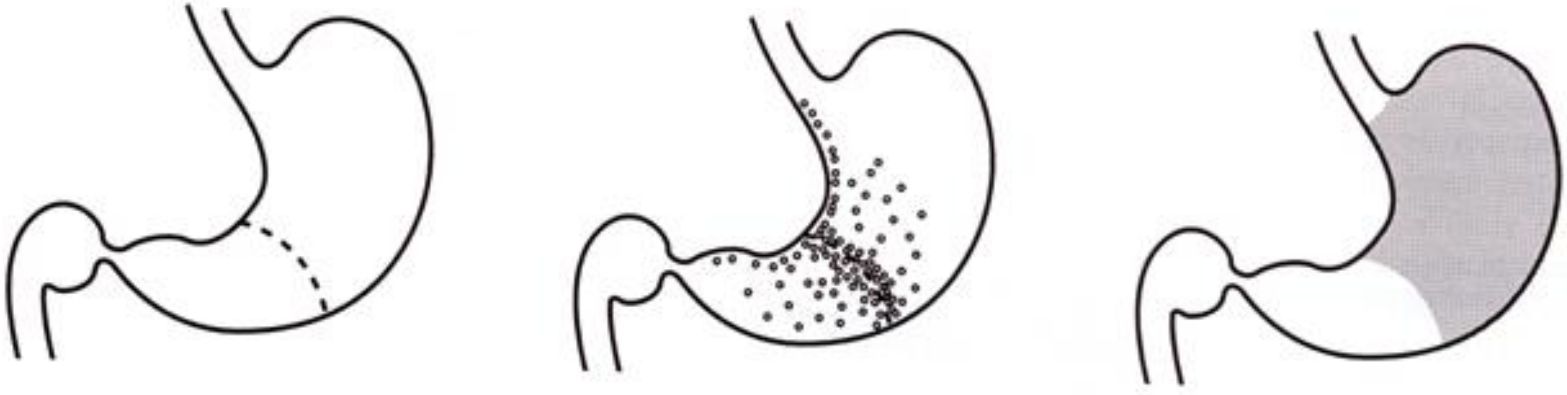
La Rosa S, et al. J Clin Pathol 2014;67:938–948. doi:10.1136/jclinpath-2014-202515

Representación esquemática de la distribución de inflamación y atrofia en los diferentes tipos de gastritis crónica atrófica y no-atrófica

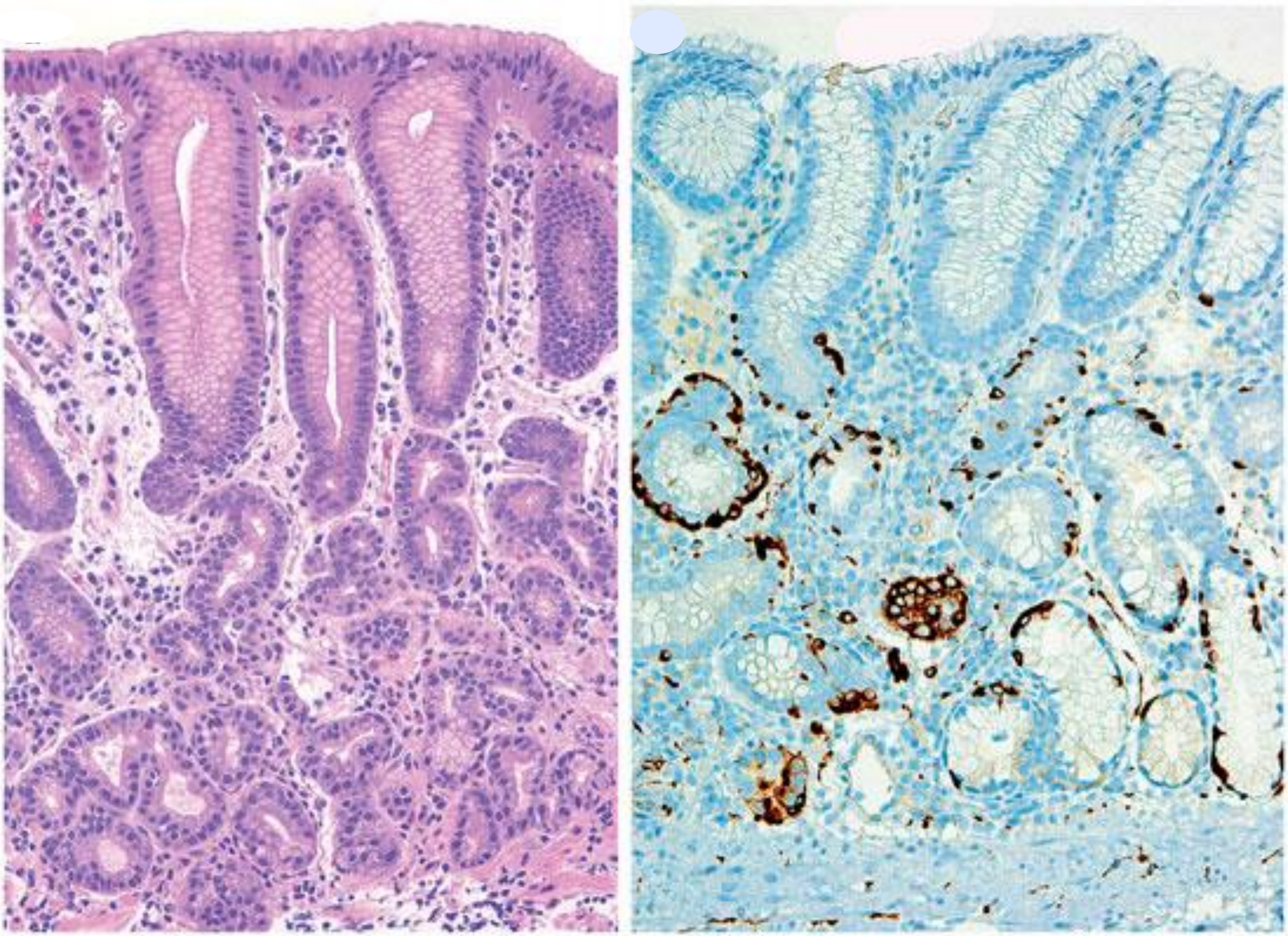
No-atrófica **Multifocal** **Autoinmune**

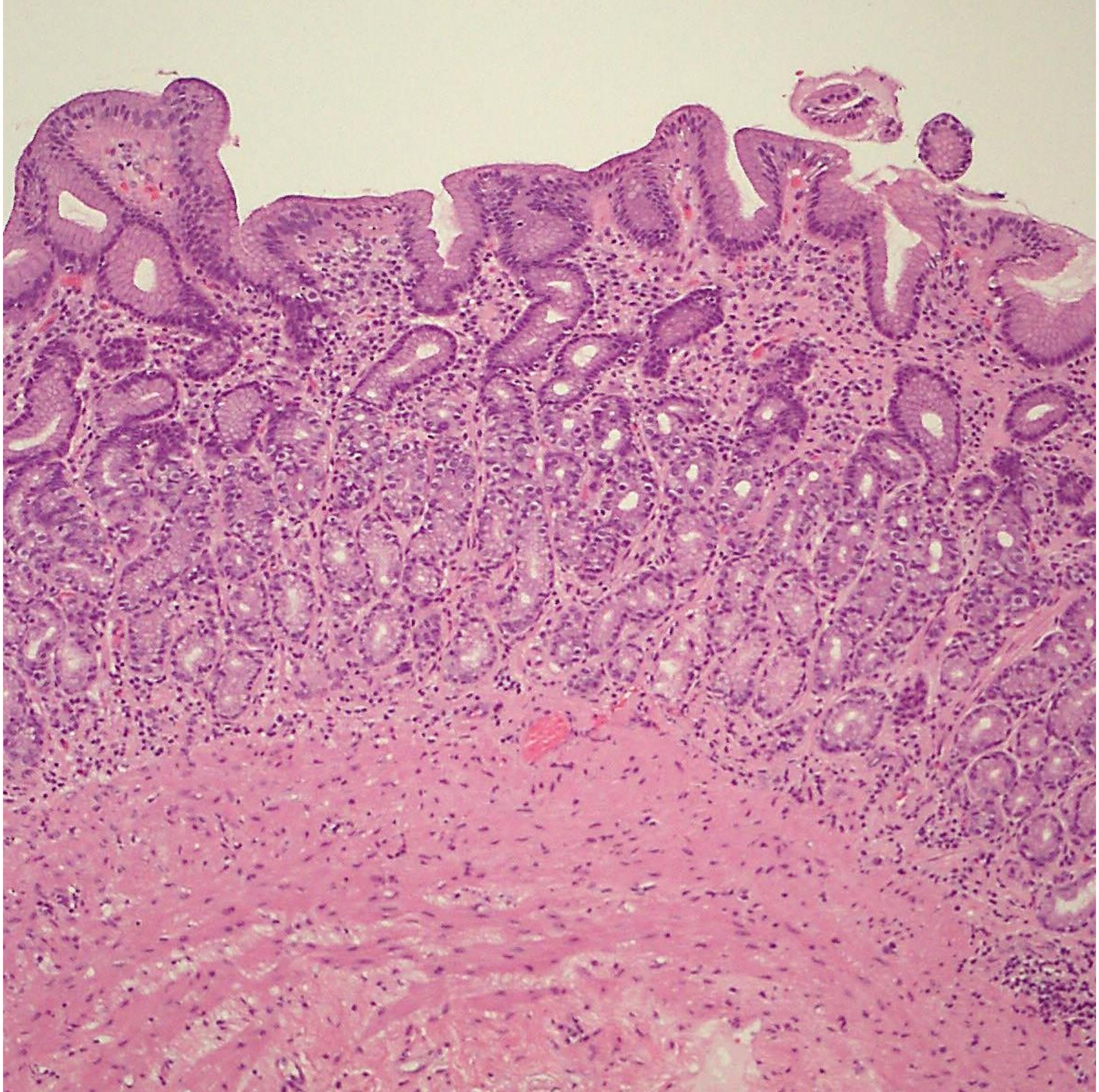


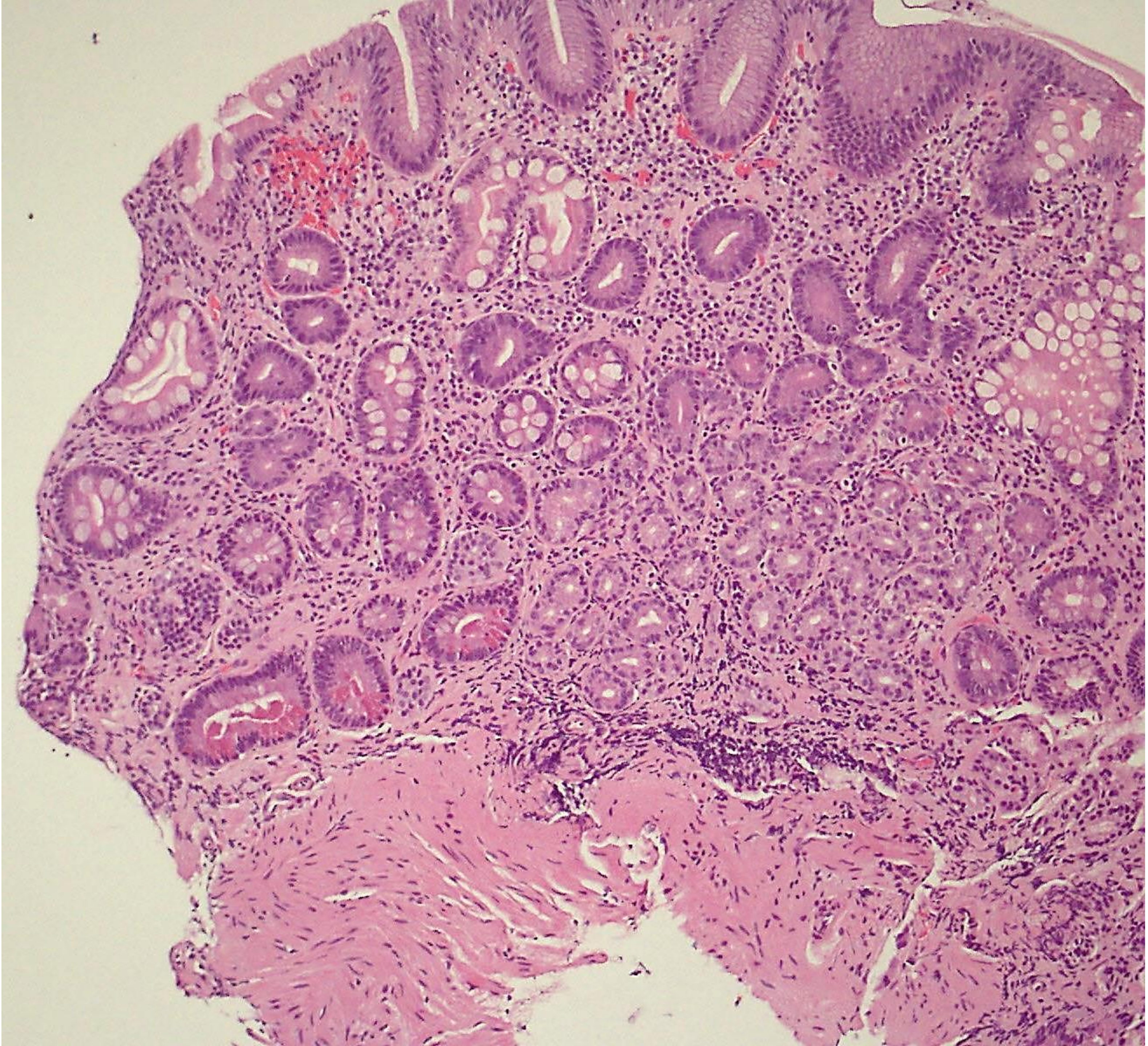
Inflamación

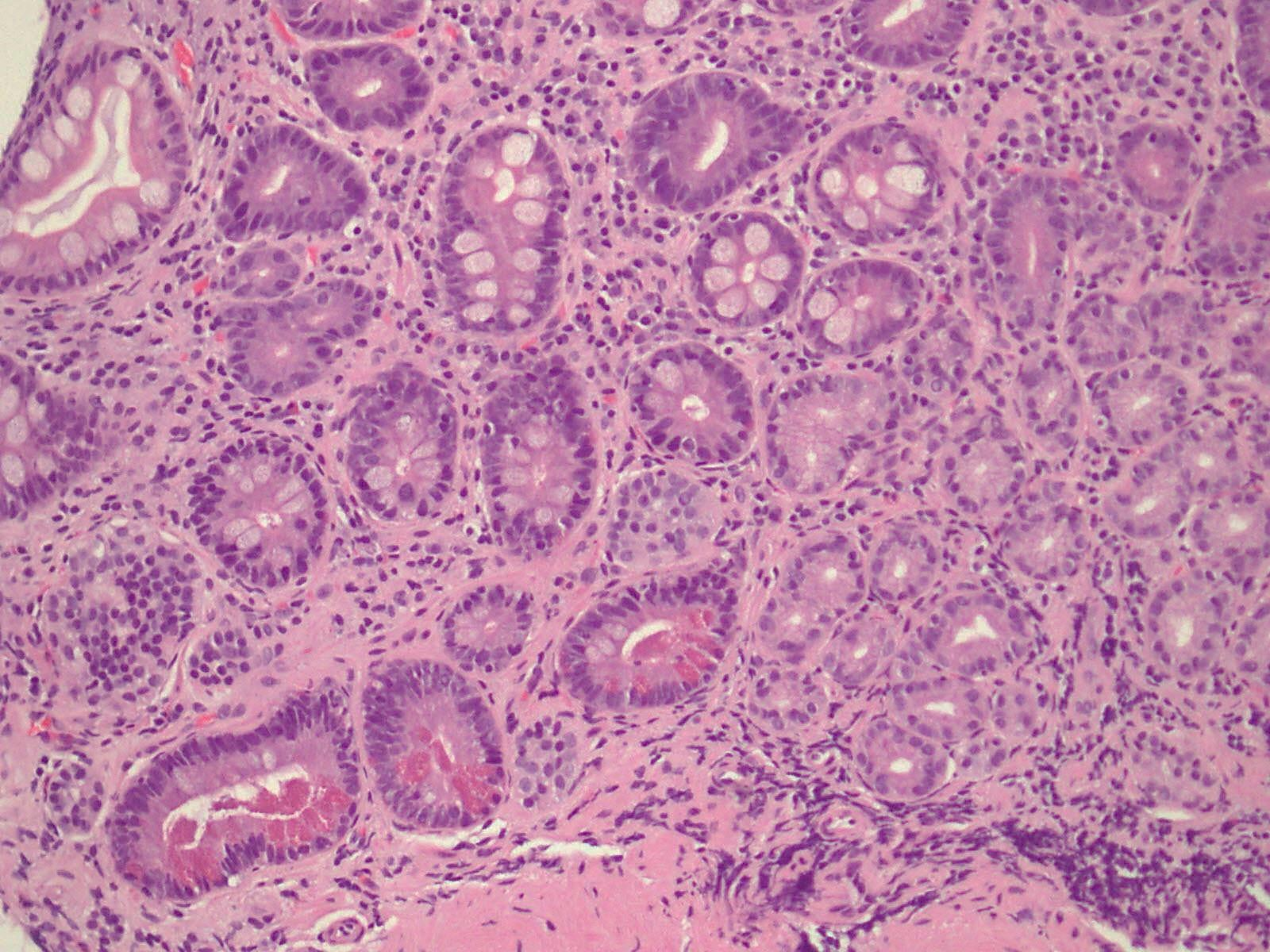


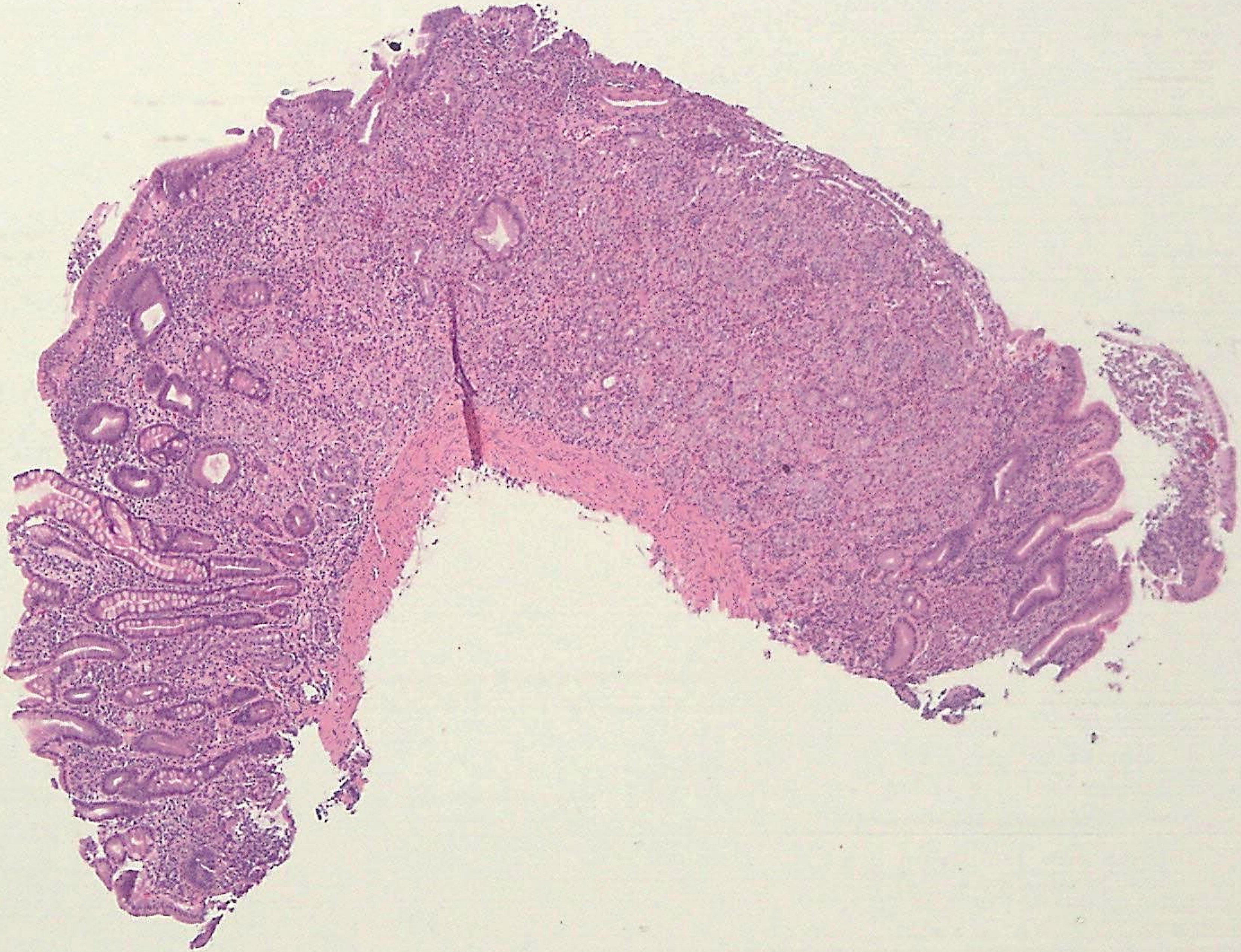
Atrofia y Metaplasia

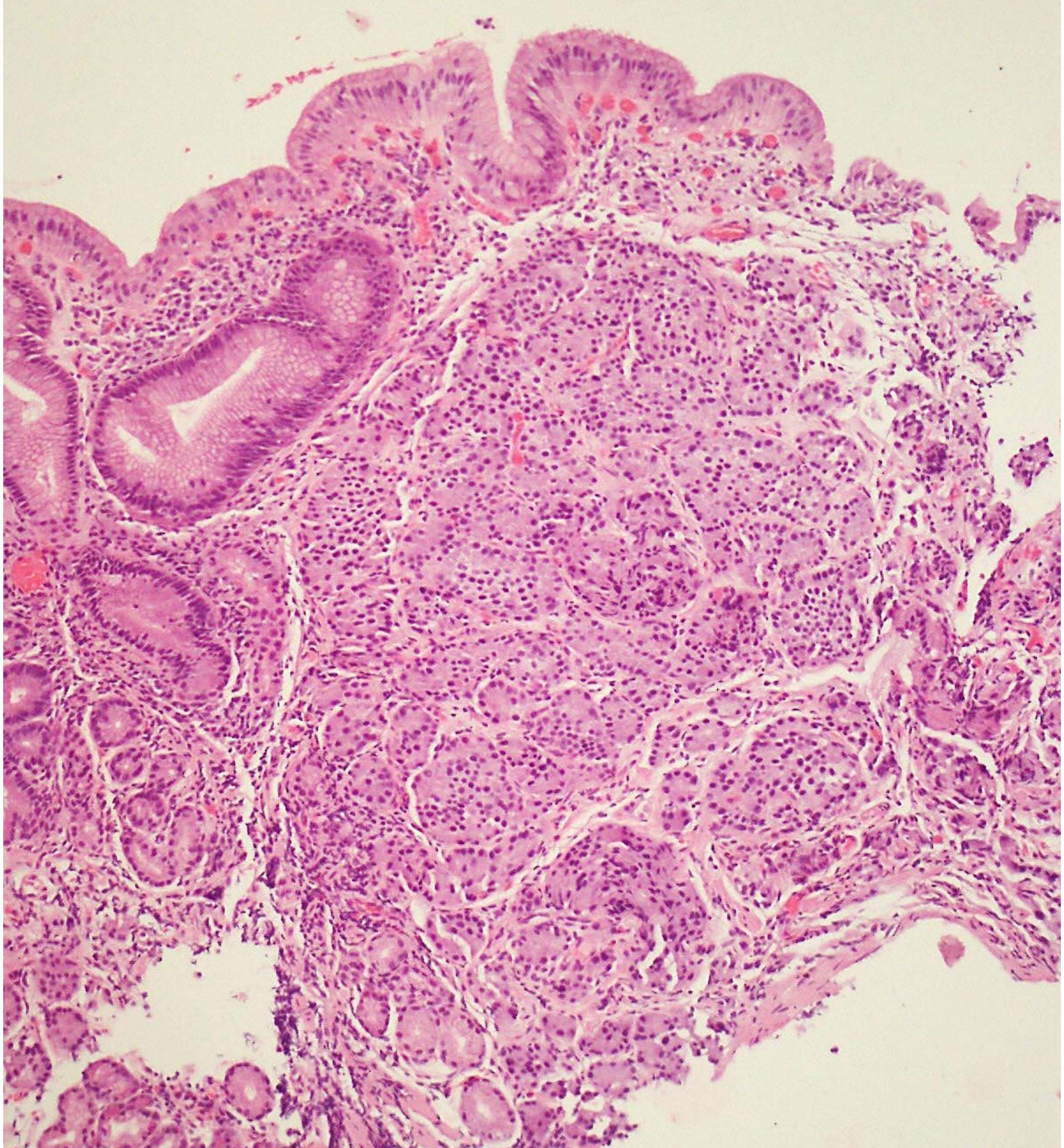


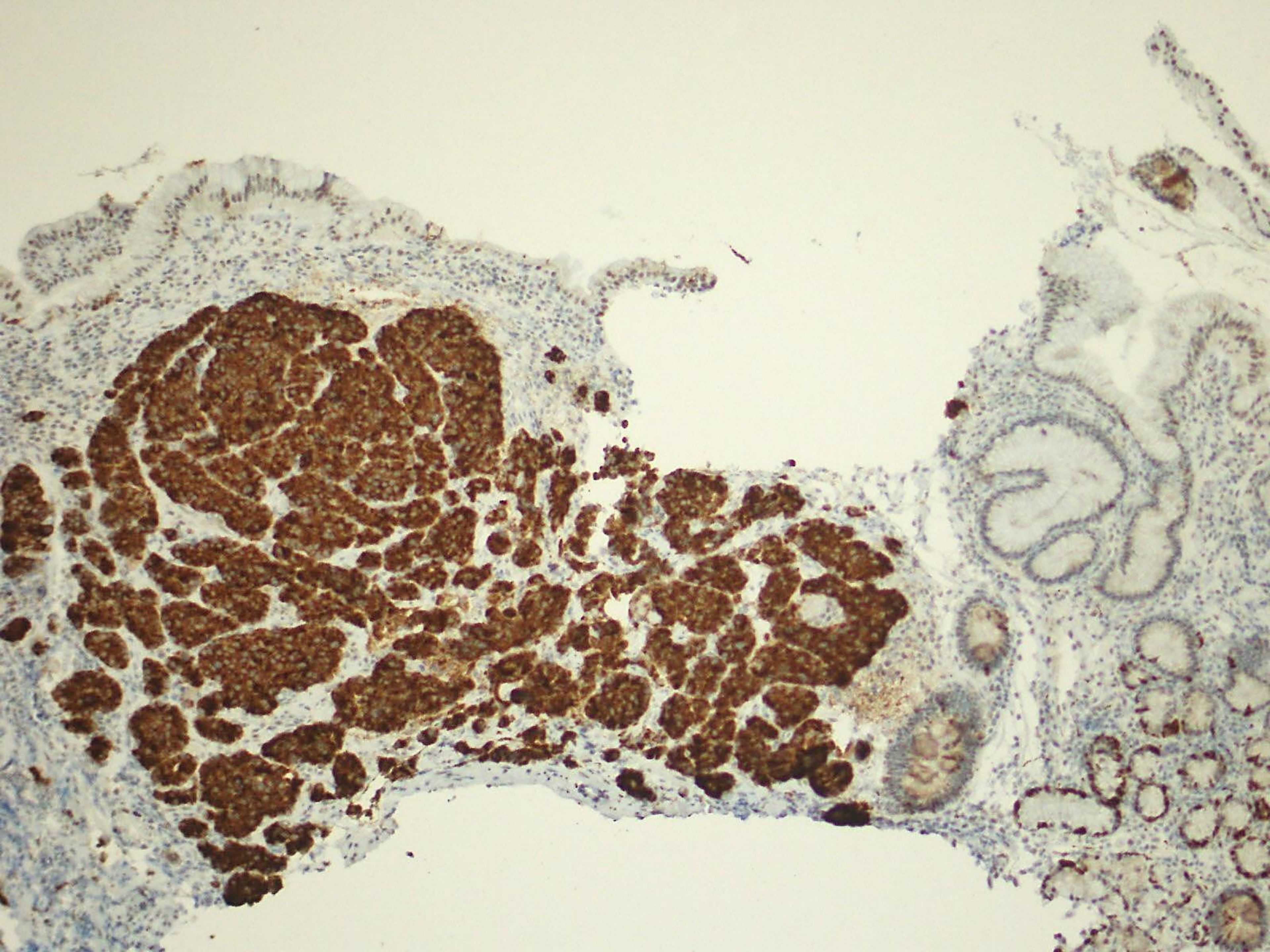




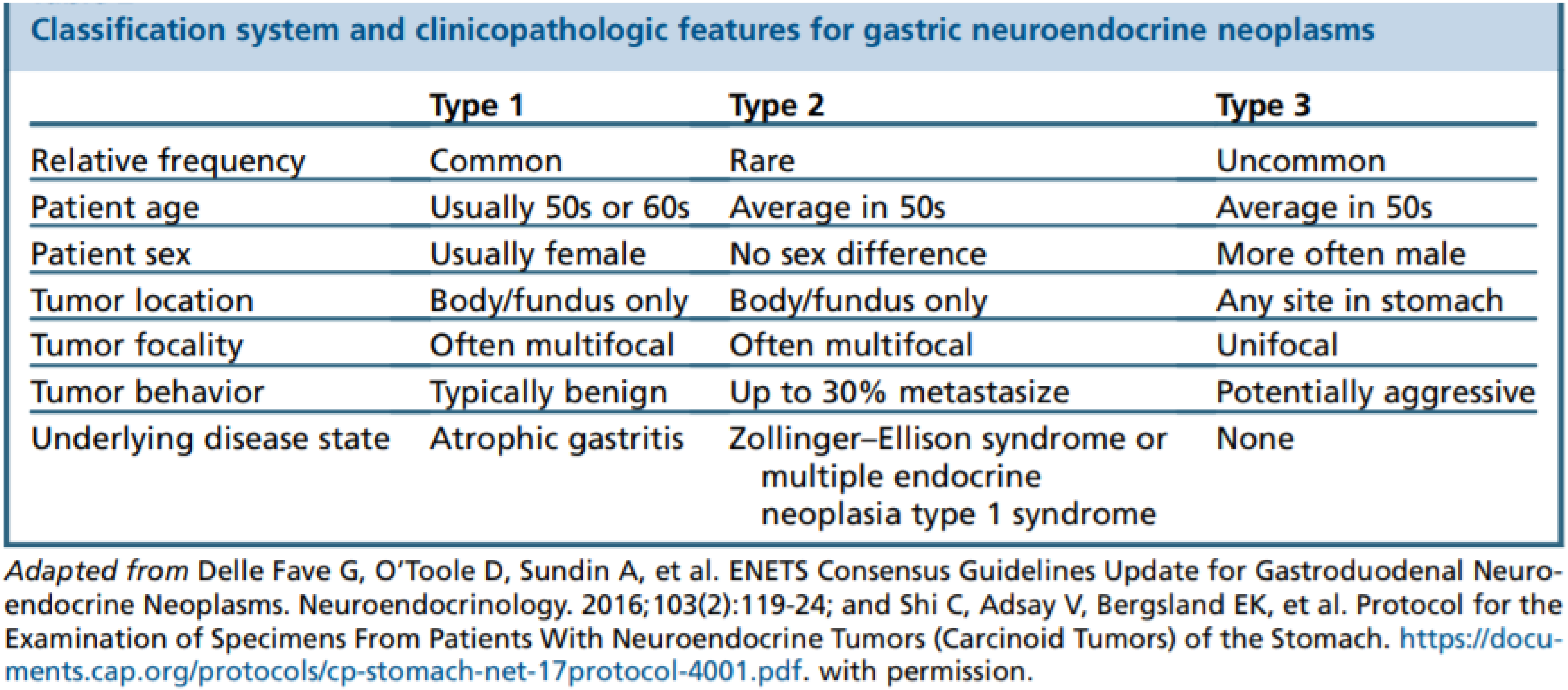








Tumores neuroendocrinos gástricos



Classification system and clinicopathologic features for gastric neuroendocrine neoplasms

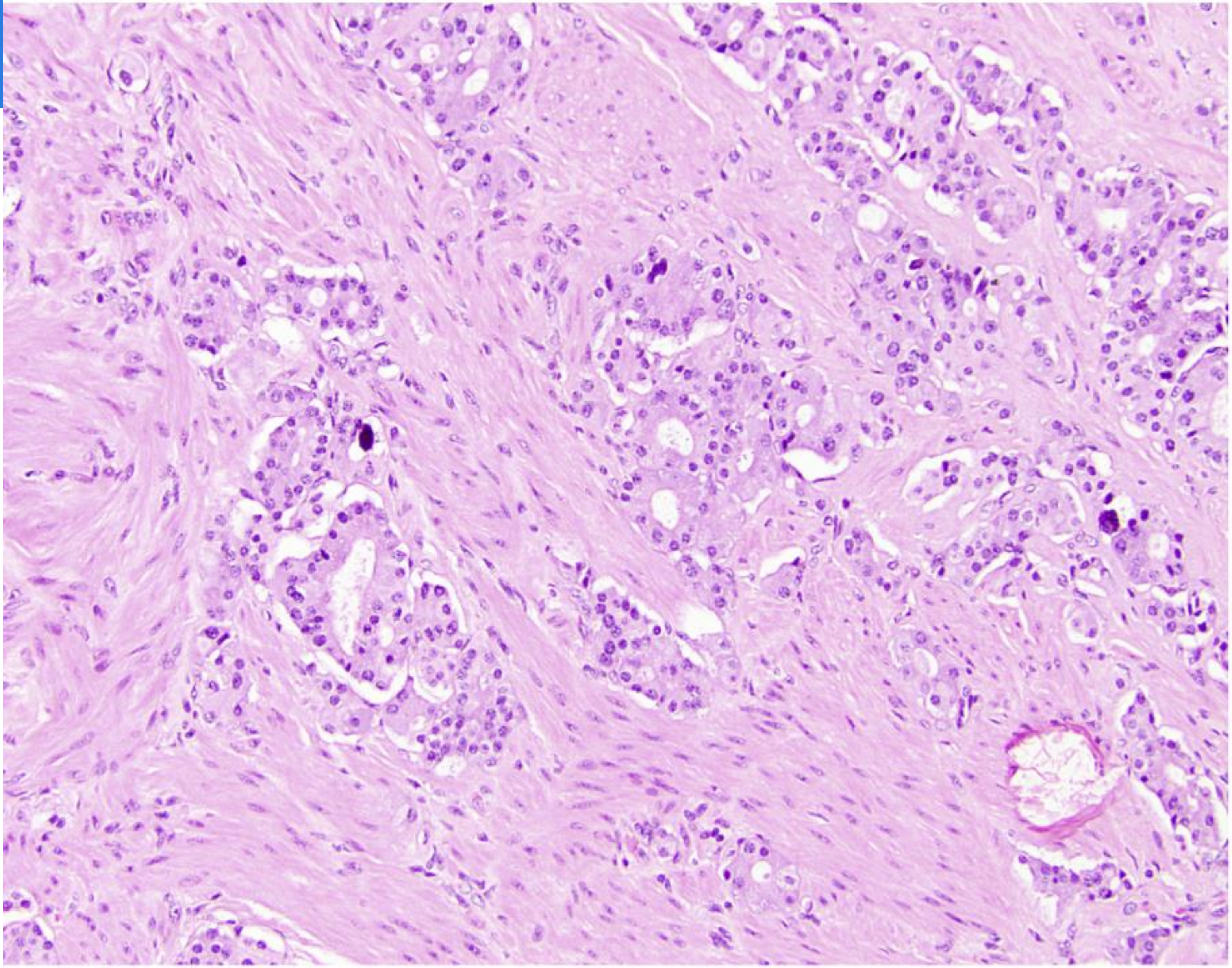
	Type 1	Type 2	Type 3
Relative frequency	Common	Rare	Uncommon
Patient age	Usually 50s or 60s	Average in 50s	Average in 50s
Patient sex	Usually female	No sex difference	More often male
Tumor location	Body/fundus only	Body/fundus only	Any site in stomach
Tumor focality	Often multifocal	Often multifocal	Unifocal
Tumor behavior	Typically benign	Up to 30% metastasize	Potentially aggressive
Underlying disease state	Atrophic gastritis	Zollinger–Ellison syndrome or multiple endocrine neoplasia type 1 syndrome	None

Adapted from Delle Fave G, O'Toole D, Sundin A, et al. ENETS Consensus Guidelines Update for Gastroduodenal Neuroendocrine Neoplasms. Neuroendocrinology. 2016;103(2):119-24; and Shi C, Adsay V, Bergsland EK, et al. Protocol for the Examination of Specimens From Patients With Neuroendocrine Tumors (Carcinoid Tumors) of the Stomach. https://documents.cap.org/protocols/cp-stomach-net-17protocol-4001.pdf. with permission.

Tumores neuroendocrinos del duodeno y Ampolla de Vater

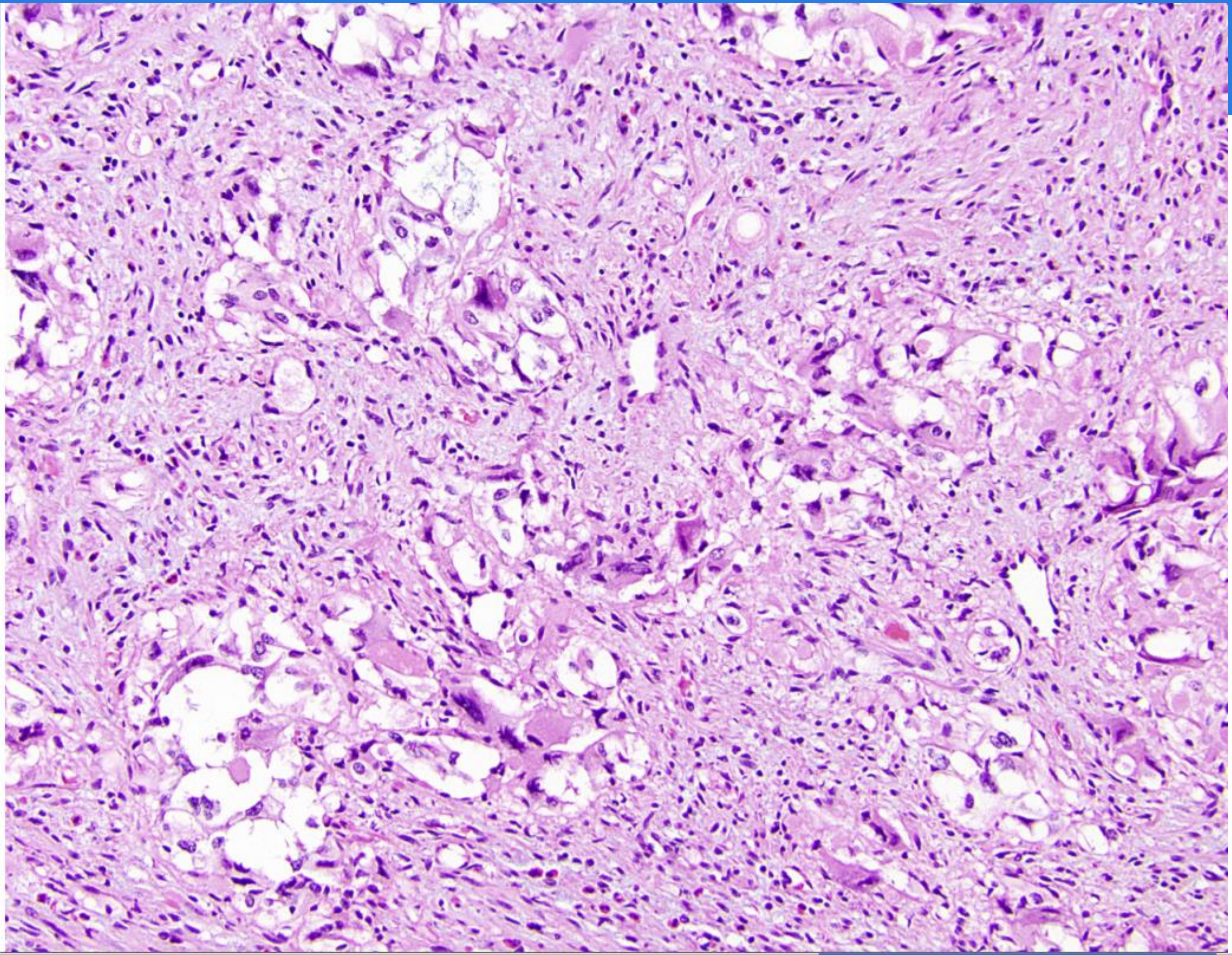
- Raros.
- Pueden ser funcionantes: Gastrinomas o somatostatinoma.
- Gastrinomas: duodeno, puede o no estar asociado a MEN1.
- Somatostatinoma: Ampular, pacientes con NF tipo 1.

Ampolla de Vater: Somatostatinoma.



Surgical Pathology 13 (2020) 377–397

Ampolla de Vater: Paraganglioma gangliocítico.



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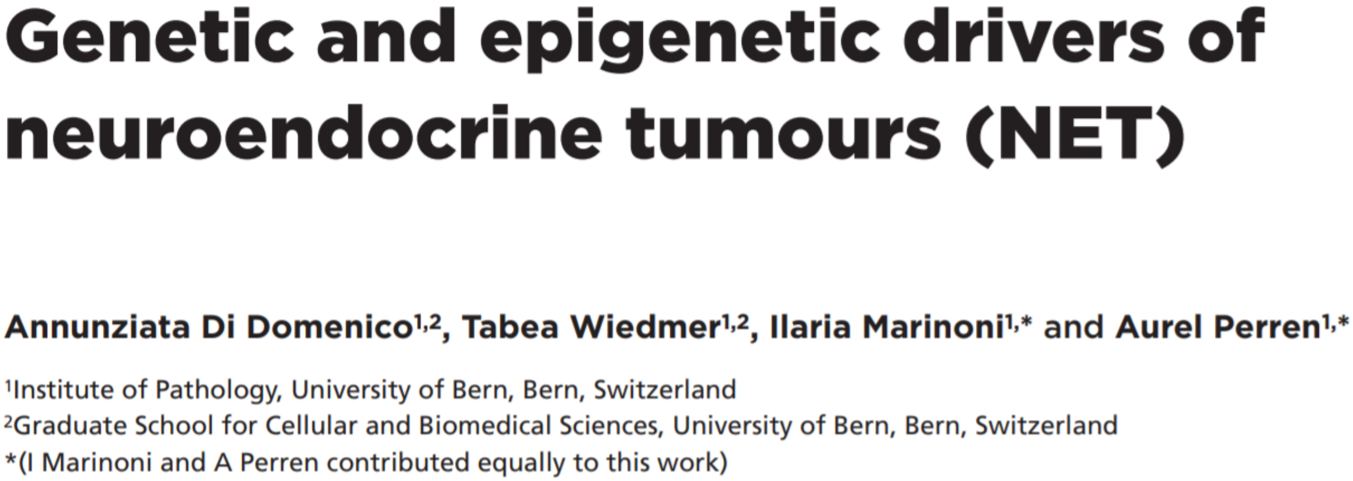
Tumores neuroendocrinos del íleon

- El íleon corresponde al segundo lugar en frecuencia de NET del tracto gastrointestinal, siendo la neoplasia maligna más frecuente en esa ubicación.
- Inducen fibrosis en las metástasis al mesenterio, generando mayor morblidad y mortalidad por isquemia.
- Frecuentemente son multifocales (30%).
- Metástasis a linfonodos e hígado.
- Metástasis a partes blandas en el mesenterio en forma de depósitos tumorales.
- Los depósitos tumorales varían en tamaño y pueden tener contorno redondeado.

Tumores neuroendocrinos del íleon



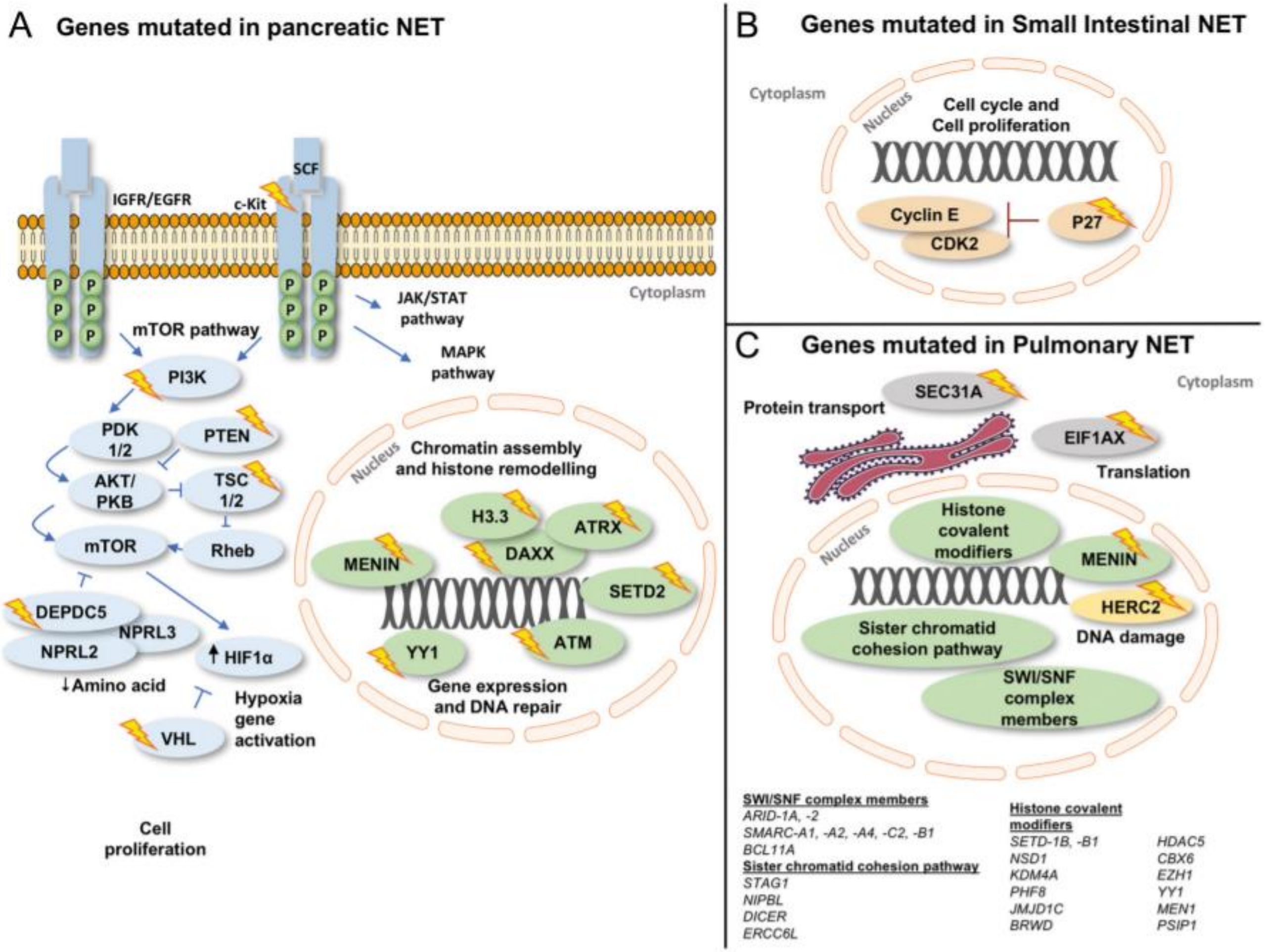
Genetic and epigenetic drivers of neuroendocrine tumours (NET)

Annunziata Di Domenico[1,2], Tabea Wiedmer[1,2], Ilaria Marinoni[1,*] and Aurel Perren[1,*]

[1]Institute of Pathology, University of Bern, Bern, Switzerland
[2]Graduate School for Cellular and Biomedical Sciences, University of Bern, Bern, Switzerland
*(I Marinoni and A Perren contributed equally to this work)

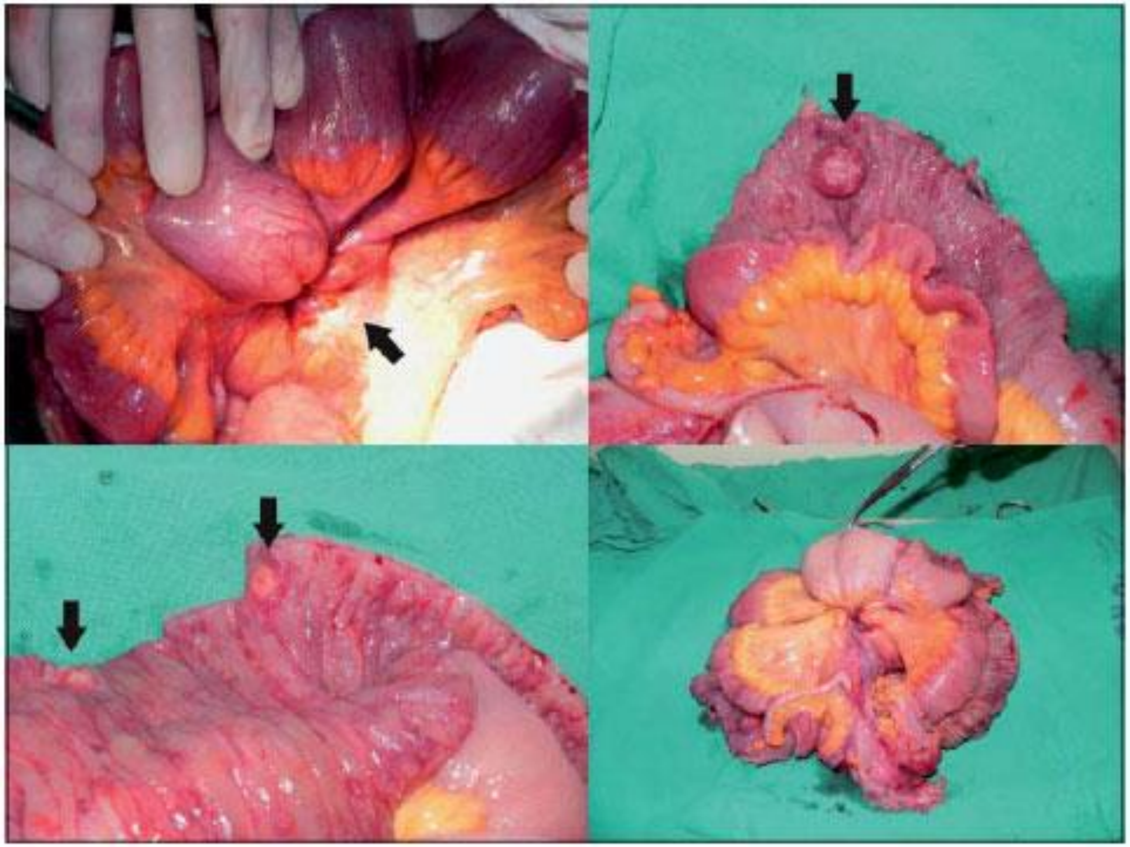
Endocrine-Related Cancer (2017) 24, R315–R334

Tumores neuroendocrinos del íleon


A
Genes mutated in pancreatic NET
IGFR/EGFR
SCF
c-Kit
P
Cytoplasm
JAK/STAT pathway
MAPK pathway
mTOR pathway
PI3K
PDK 1/2
PTEN
AKT/ PKB
TSC 1/2
mTOR
Rheb
DEPDC5
NPRL3
NPRL2
↑HIF1α
↓Amino acid
Hypoxia gene activation
VHL
Cell proliferation
Nucleus
Chromatin assembly and histone remodelling
H3.3
ATRX
DAXX
MENIN
SETD2
YY1
ATM
Gene expression and DNA repair
B
Genes mutated in Small Intestinal NET
Cytoplasm
Nucleus
Cell cycle and Cell proliferation
Cyclin E
CDK2
P27
C
Genes mutated in Pulmonary NET
Cytoplasm
SEC31A
Protein transport
EIF1AX
Translation
Nucleus
Histone covalent modifiers
MENIN
HERC2
DNA damage
Sister chromatid cohesion pathway
SWI/SNF complex members
SWI/SNF complex members
ARID-1A, -2
SMARC-A1, -A2, -A4, -C2, -B1
BCL11A
Sister chromatid cohesion pathway
STAG1
NIPBL
DICER
ERCC6L
Histone covalent modifiers
SETD-1B, -B1
NSD1
KDM4A
PHF8
JMJD1C
BRWD
HDAC5
CBX6
EZH1
YY1
MEN1
PSIP1

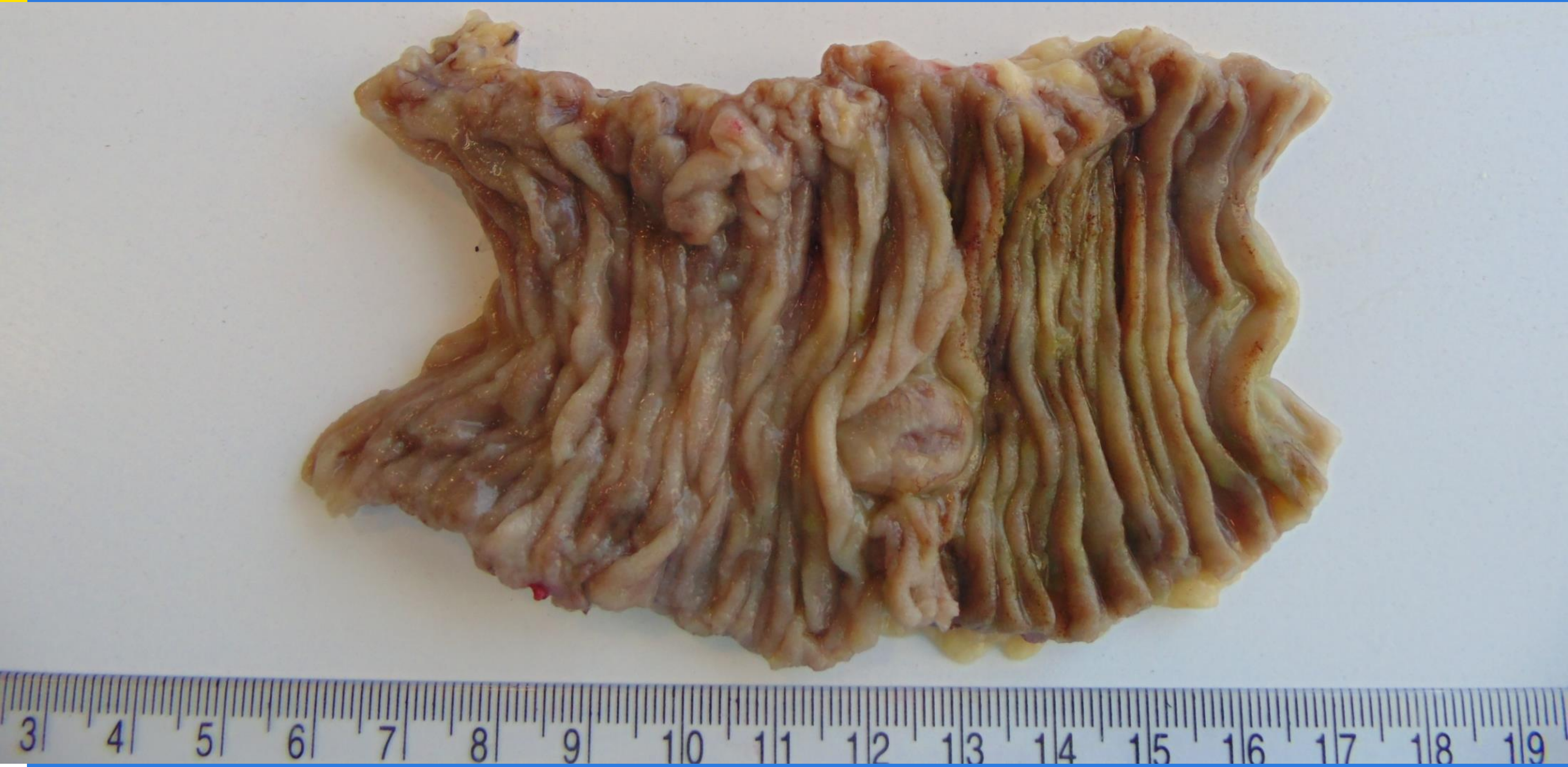
Endocrine-Related Cancer 2017) 24, R315–R334

Tumores neuroendocrinos del íleon



Rev. Chilena de Cirugía. Vol 64 - N° 3, Junio 2012; pág. 264-273

Tumores neuroendocrinos del íleon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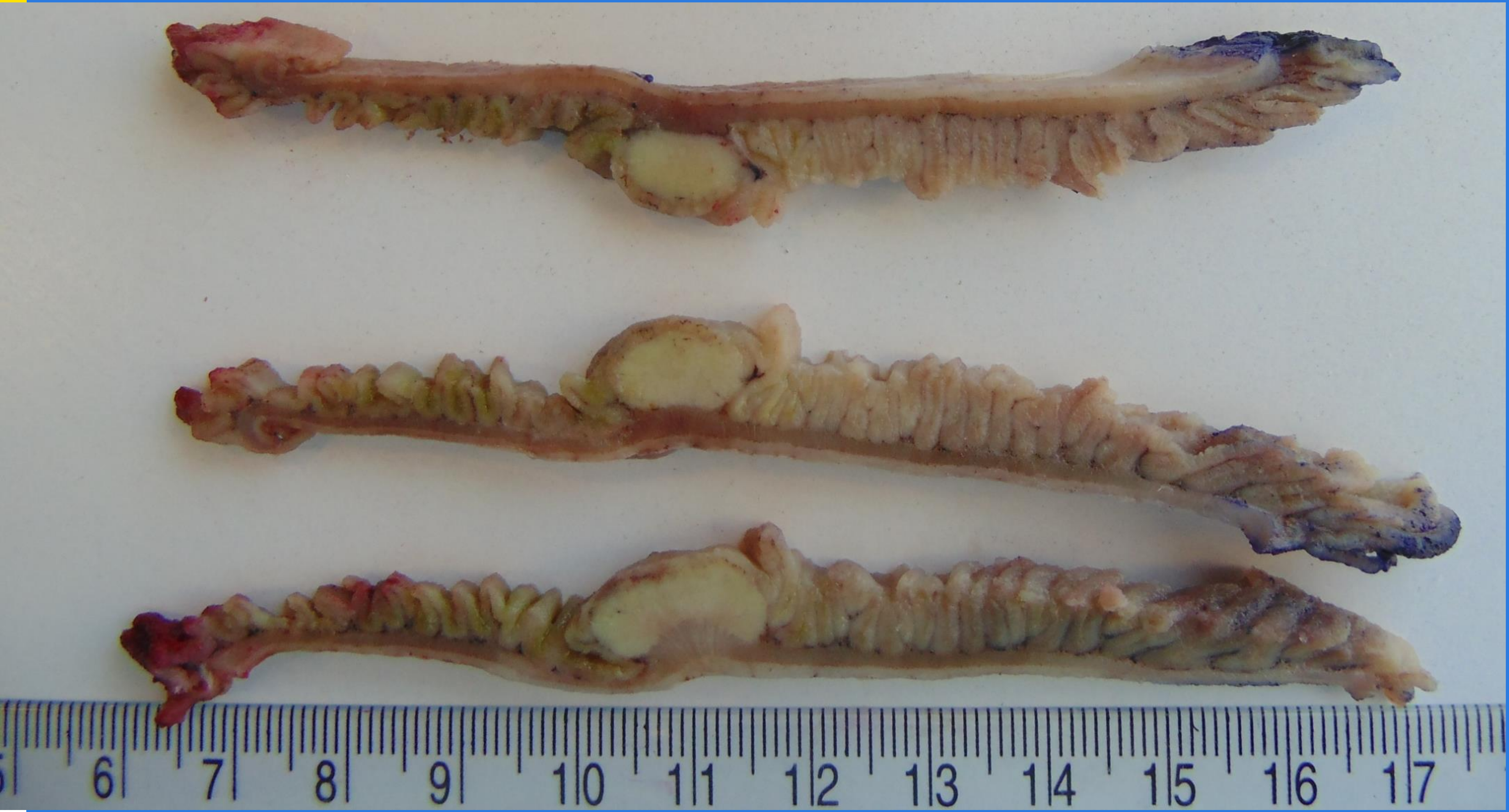
Tumores neuroendocrinos del íleon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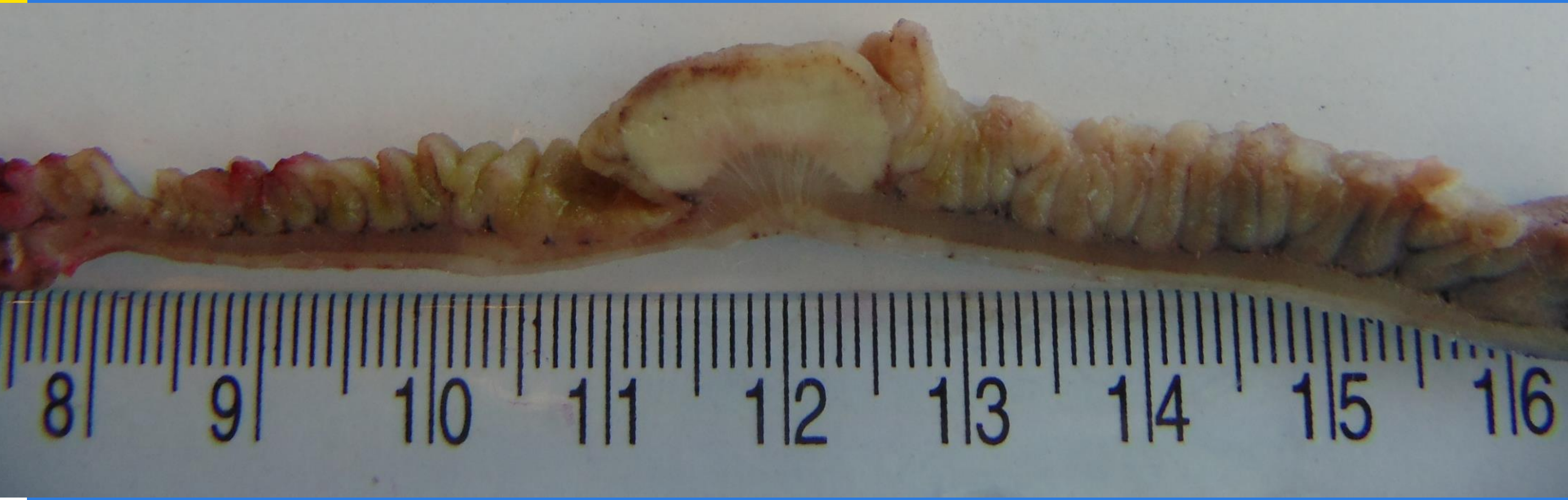
Tumores neuroendocrinos del íleon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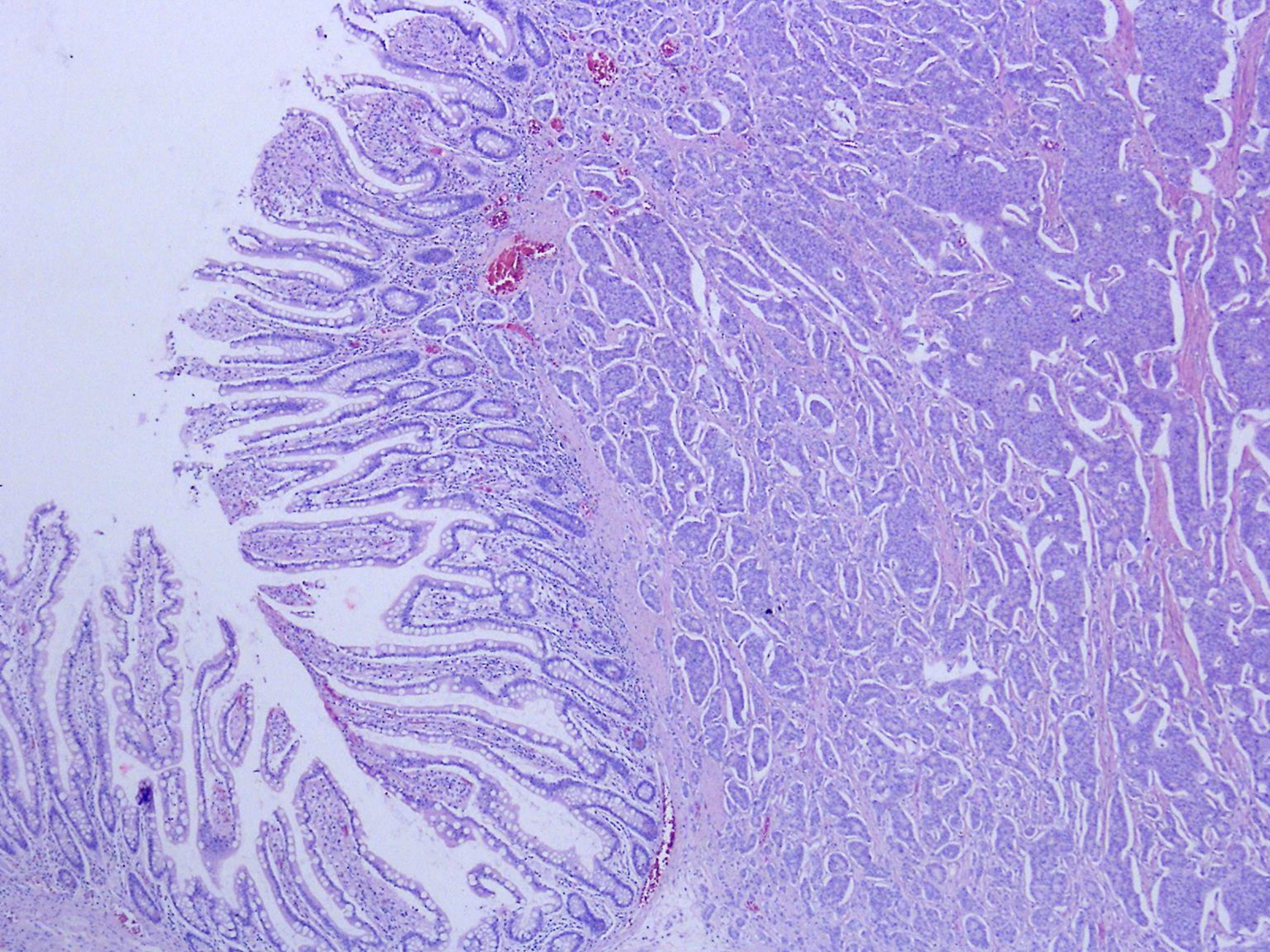

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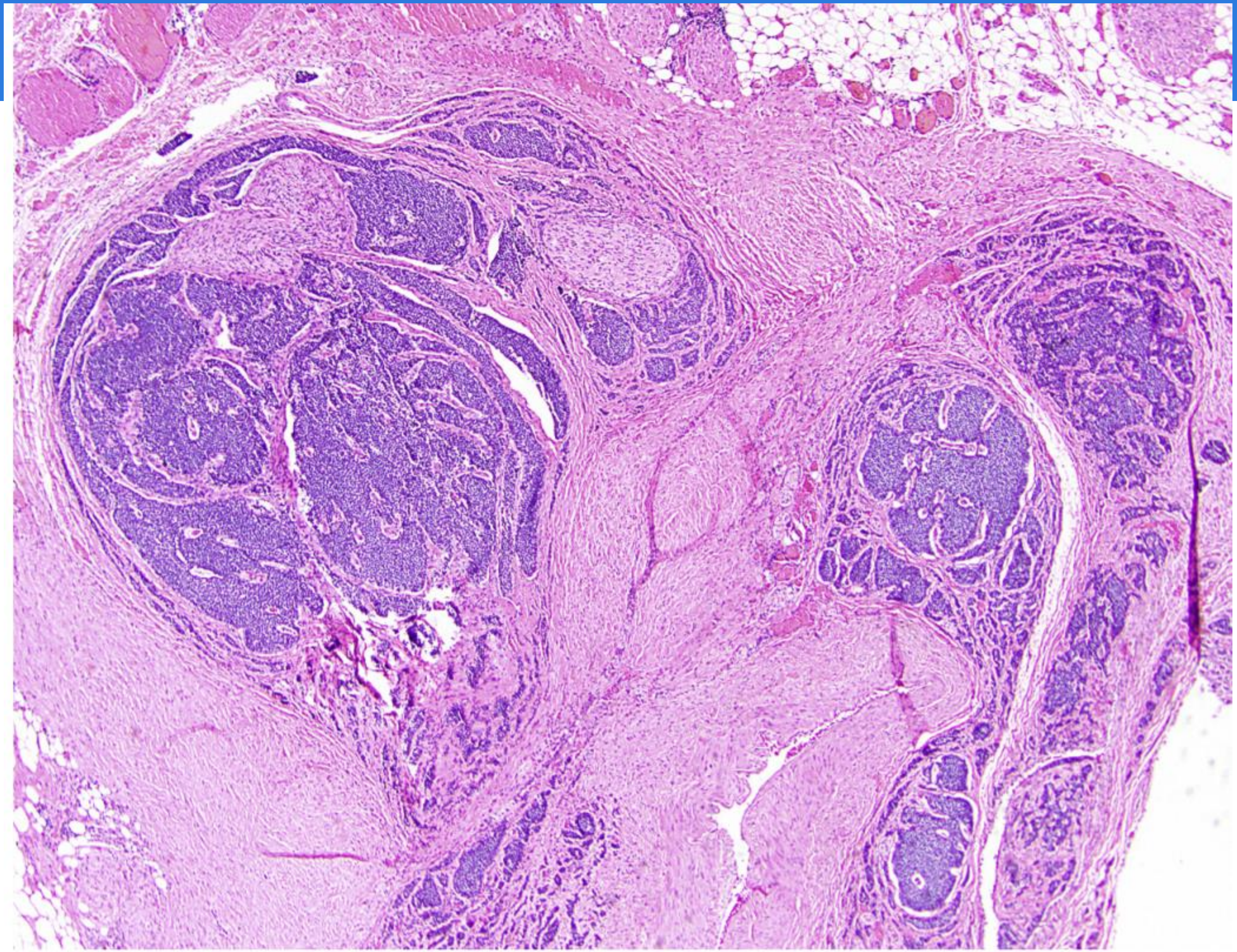
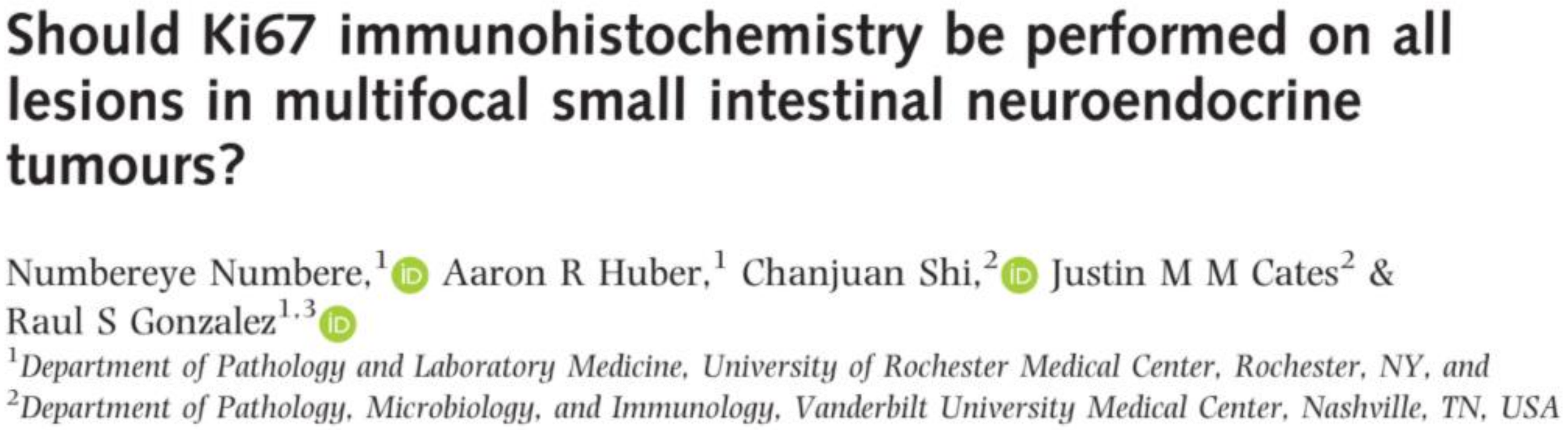


Tumores neuroendocrinos del íleon

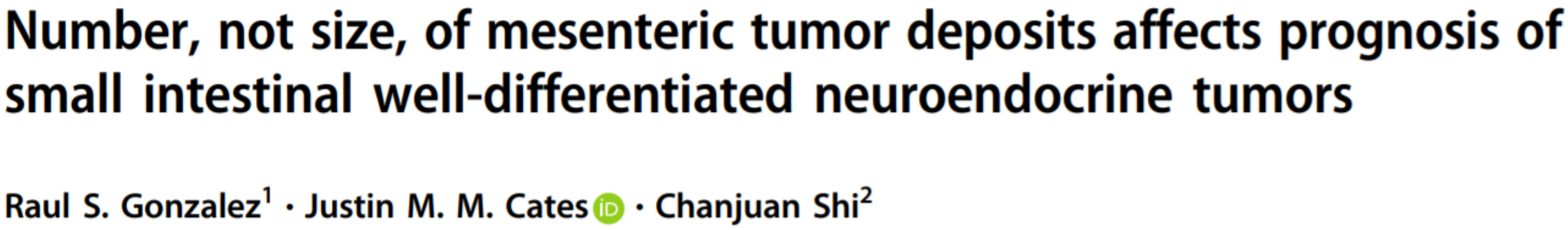


Should Ki67 immunohistochemistry be performed on all lesions in multifocal small intestinal neuroendocrine tumours?

Numbereye Numbere,[1] Aaron R Huber,[1] Chanjuan Shi,[2] Justin M M Cates[2] &
Raul S Gonzalez[1,3]
[1] *Department of Pathology and Laboratory Medicine, University of Rochester Medical Center, Rochester, NY, and*
[2] *Department of Pathology, Microbiology, and Immunology, Vanderbilt University Medical Center, Nashville, TN, USA*

Histopathology 2019, 74, 424–429.

Tumores neuroendocrinos del íleon

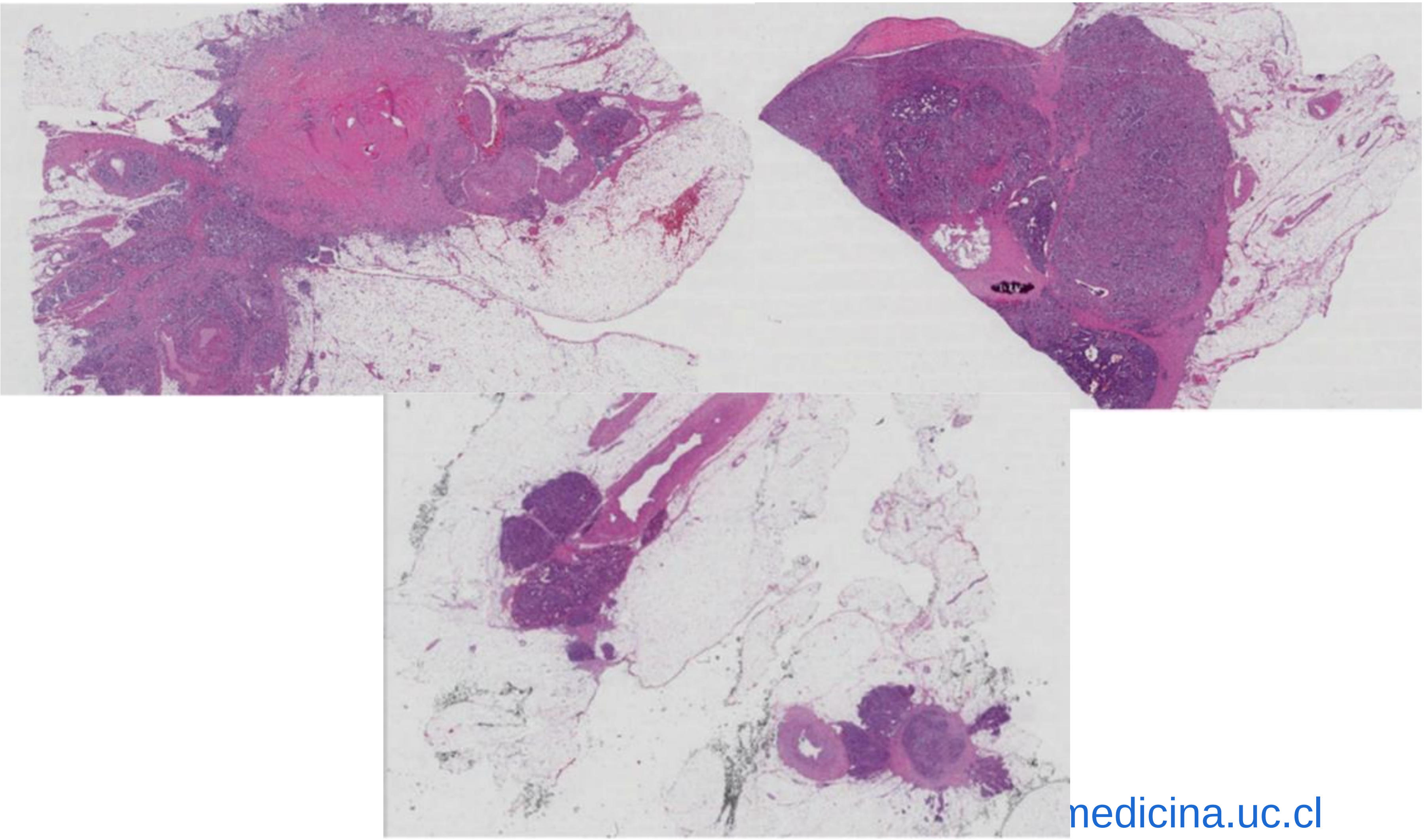


Number, not size, of mesenteric tumor deposits affects prognosis of small intestinal well-differentiated neuroendocrine tumors

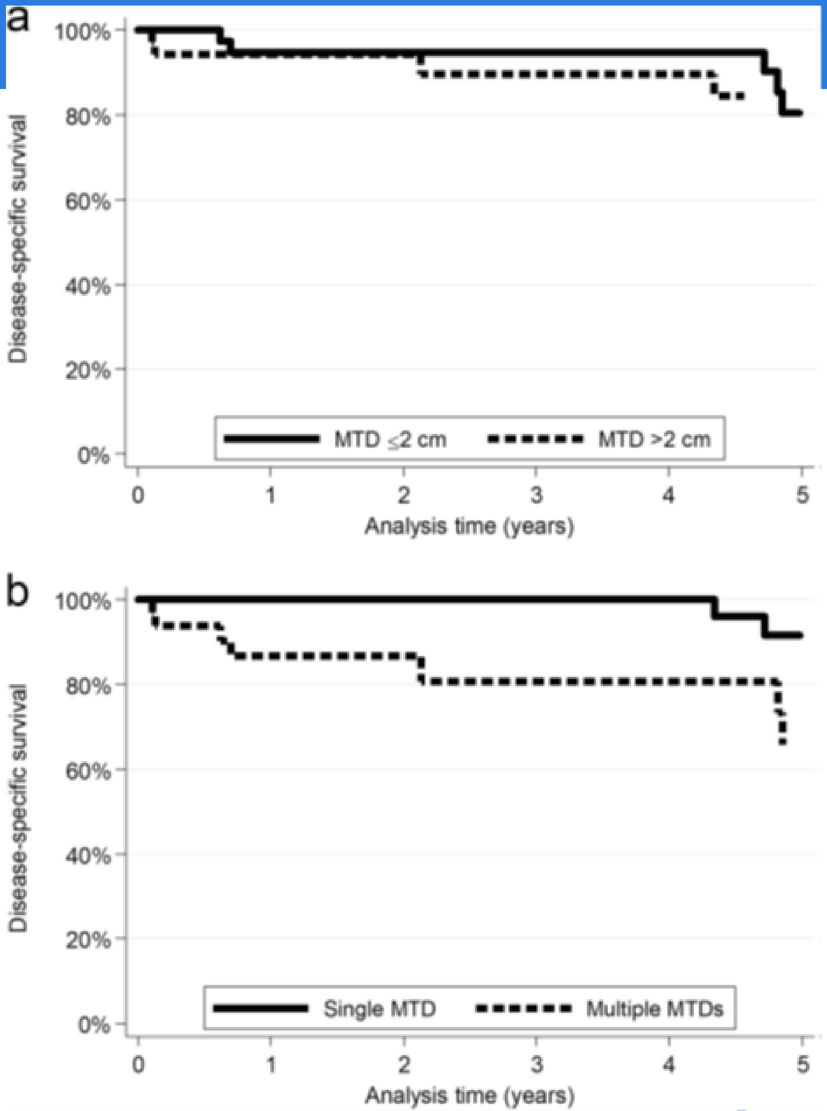
Raul S. Gonzalez[1] · Justin M. M. Cates · Chanjuan Shi[2]

Modern Pathology (2018) 31:1560–1566.

Tumores neuroendocrinos del íleon



Tumores neuroendocrinos del íleon

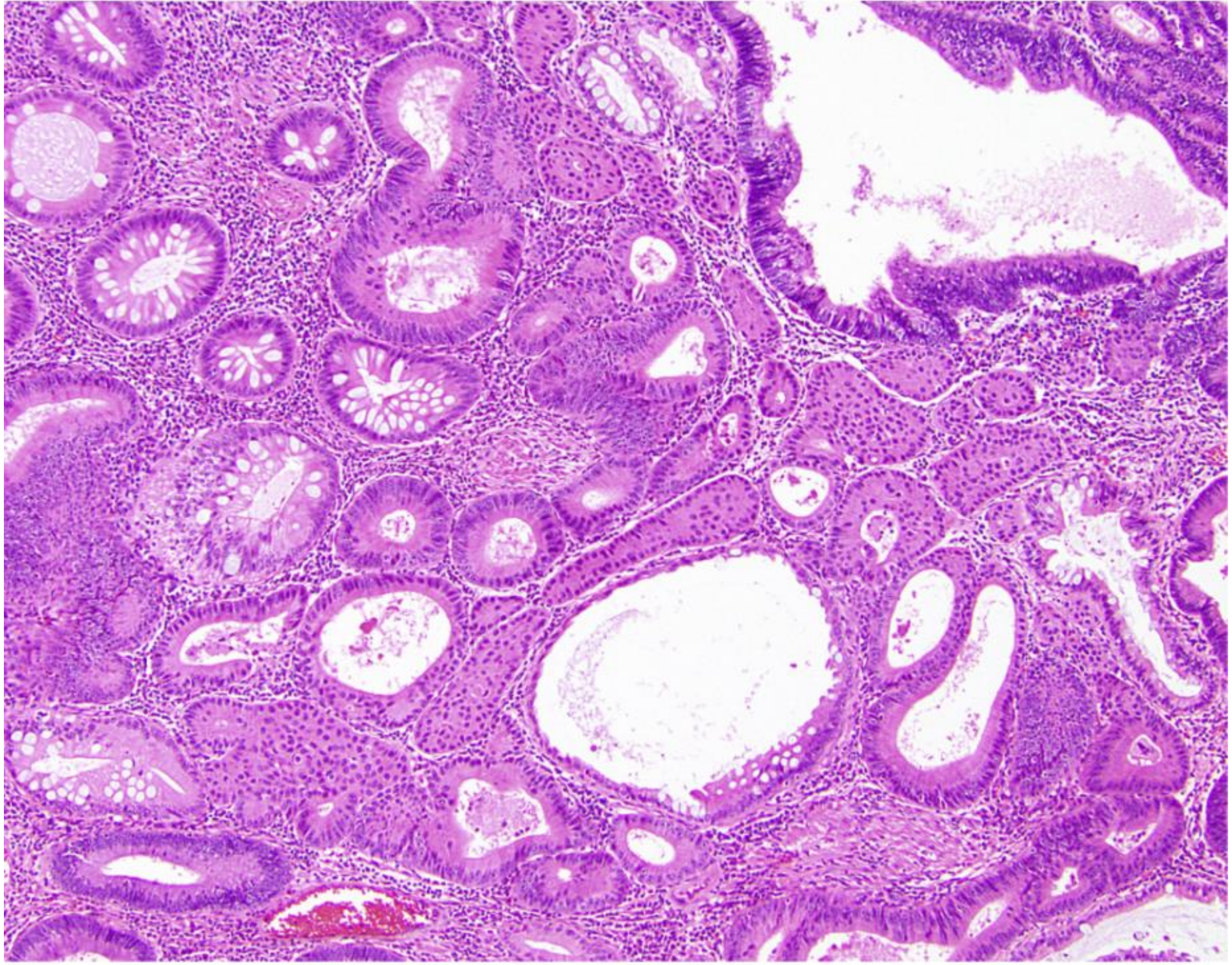


Modern Pathology (2018) 31:1560–1566.

Tumores neuroendocrinos del colon y recto.

- Tumores neuroendocrinos del recto son relativamente frecuentes.
- La mayoría pólipos incidentales.
- Pueden presentar reacción positiva con anticuerpos para PSAP (NKX3.1).
- Los tumores neuroendocrinos del colon son raros.
- Algunos se presentan en el contexto de Enfermedad Inflamatoria Intestinal. Se plantea posiblemente forma de hiperplasia más que NET.
- En ocasiones pueden presentarse pequeños nidos de células neuroendocrinas en adenomas tubulovellosos (microcarcinoides).

Tumores neuroendocrinos del colon y recto.

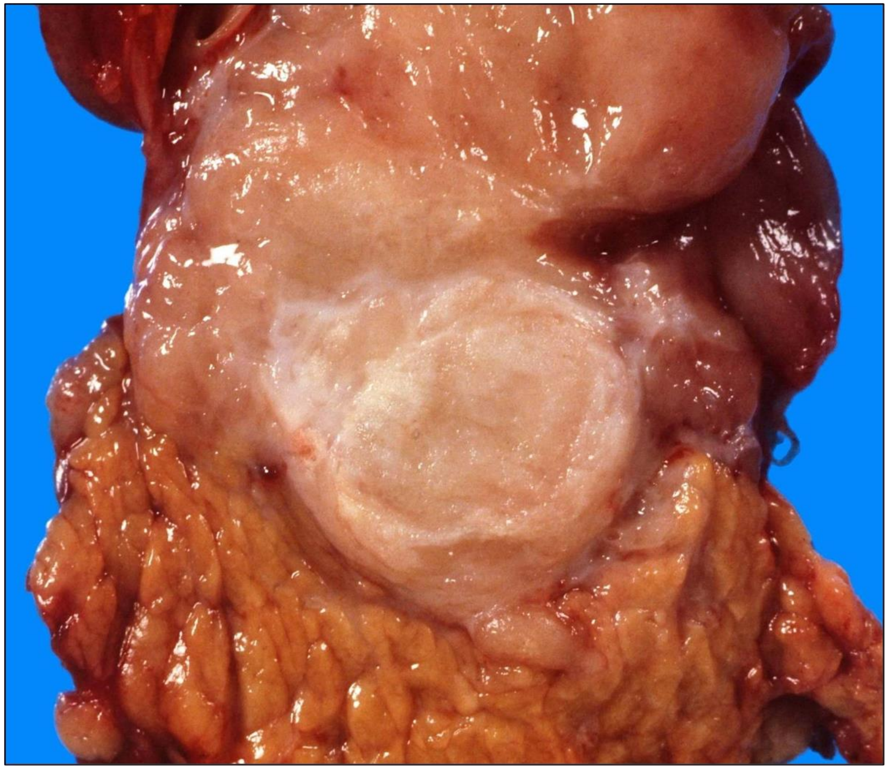


Tumores neuroendocrinos del páncreas

- Segunda neoplasia más frecuente en el páncreas.
- La incidencia ha ido en aumento.
- Al igual que en otros órganos del tracto digestivo se clasifican en:
  - Tumores neuroendocrinos bien diferenciados.
  - Carcinomas neuroendocrinos (células pequeñas o de células grandes)

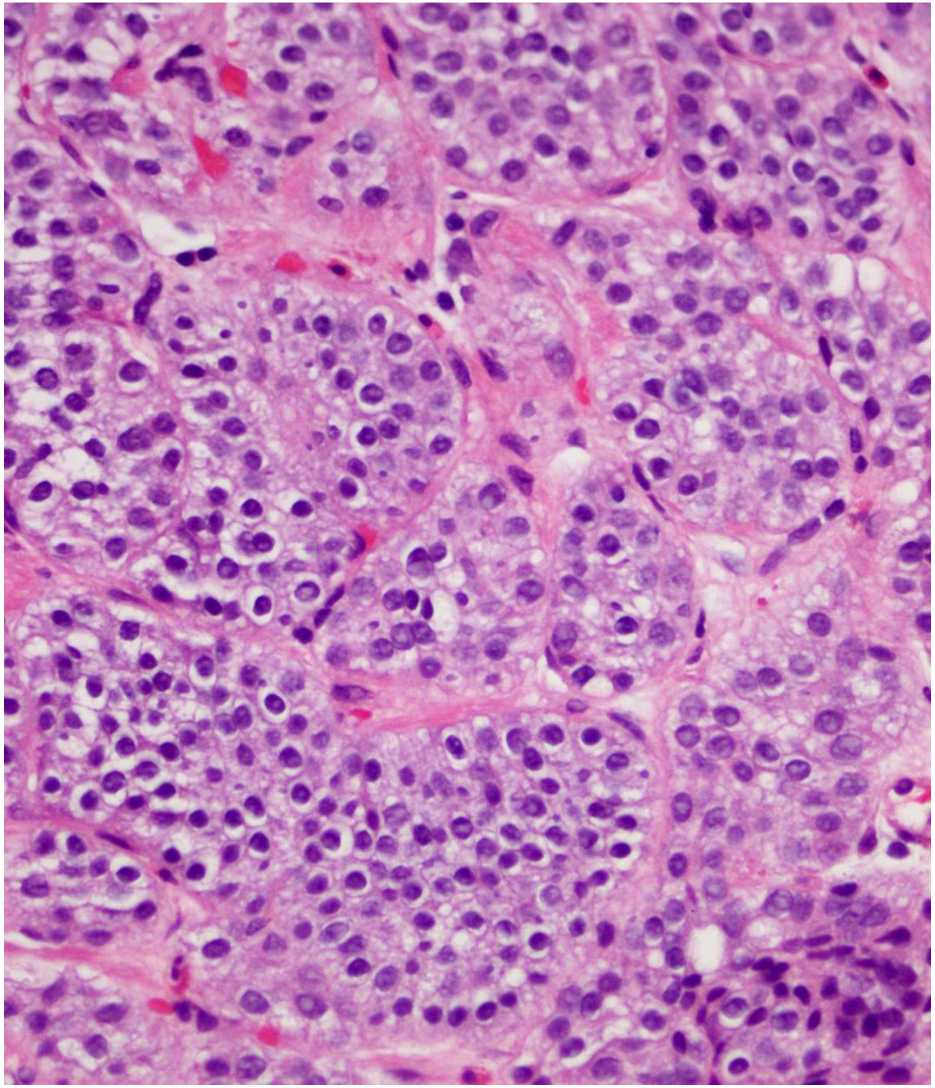
Tumores neuroendocrinos del páncreas bien diferenciado.

- En general son tumores únicos.
- Adultos: 5-6 década de la vida.
- Sintomáticos o no: secreción hormonal con manifestación clínica de síntomas: insulinomas, glucagonomas, vipomas.
- Elevación en sangre de marcadores neuroendocrinos: Cromogranina A.
- Estudio funcional de imágenes: Altamente captantes a la cintigrafía con octeótrido.
- Tratamiento: Cirugía con intensión curativa. En casos metastásicos: análogos de somatostatina, inhibidores de mTOR.



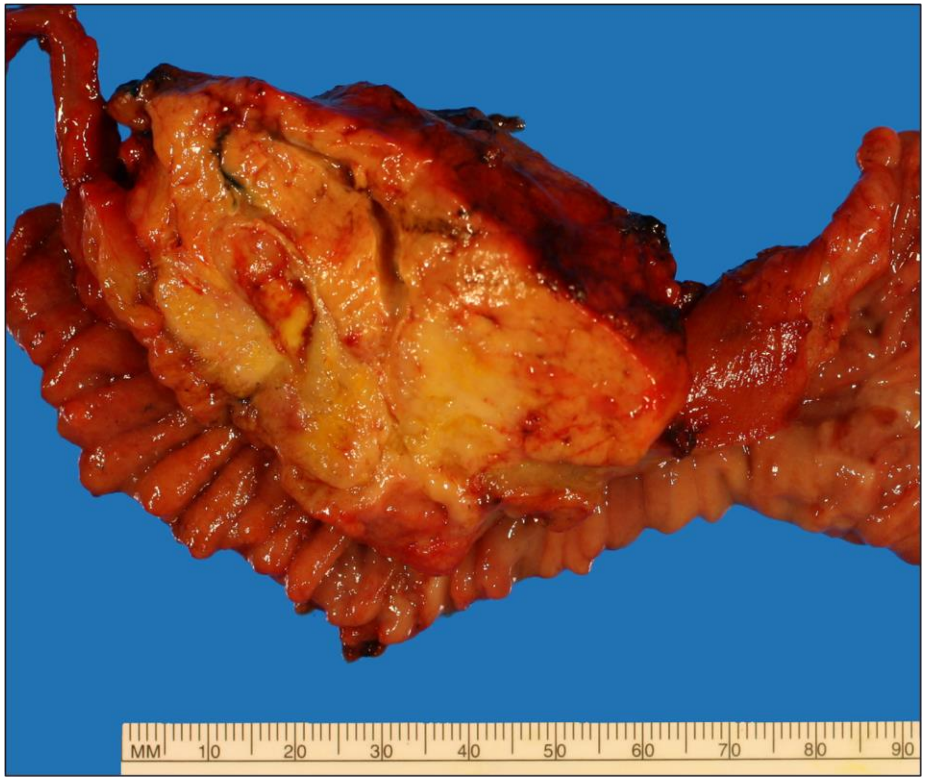
Tumores neuroendocrinos del páncreas bien diferenciado.

- Asociados con síndrome MEN1 i vHL.
- La mayor parte están incluidos en los NET G1 y NET G2.
- Sin embargo, incluye un grupos que por morfología es bien diferenciado pero con NETG3.

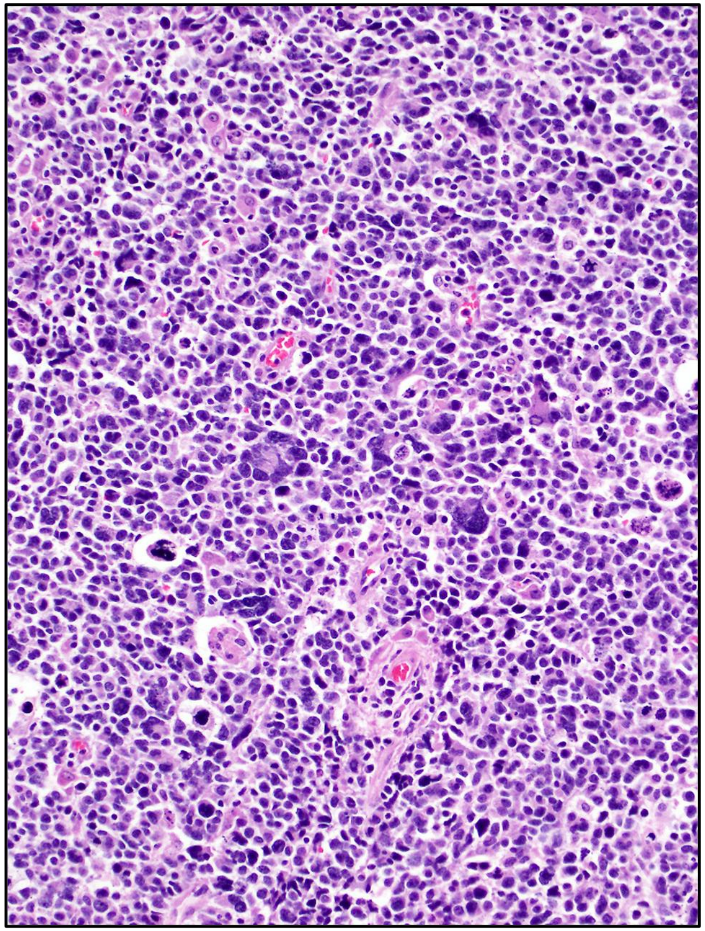


Carcinomas neuroendocrinos del páncreas

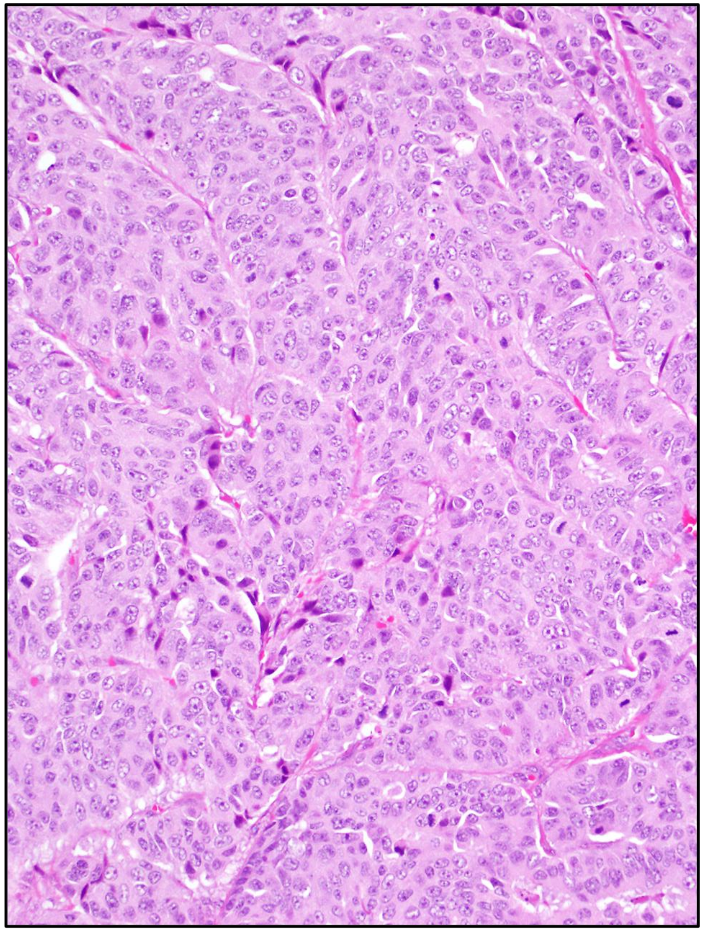
- Adultos: gente mayor.
- No presentan síndromes clínicos.
- No tienen elevación en sangre de marcadores neuroendocrinos: cromogranina A normal.
- Elevación en sangre de otros marcadores usualmente elevados en adenocarcinomas: Ca19.9, CEA.
- Estudio de imágenes con octeótrido es negativa.
- Casi el 100% se presenta con enfermedad metastásica.
- Tratamiento sistémico con quimioterapia basada en cisplatino.



Carcinomas neuroendocrinos del páncreas



Carcinoma de células pequeñas



Carcinoma de células grandes

Tumores neuroendocrinos del páncreas

Desde el punto de vista molecular

Tumores neuroendocrinos bien diferenciados:

Sin alteración de KRAS, p16, CDK2A ni SMAD4.

Presentan alteración de genes involucrados en la remodelación de la cromatina:

- MEN1 (44%).
- DAXX o ATRX (43%): Pérdida de la expresión de la proteína.
- No hay mutación de *RB1*.

Carcinoma neuroendocrino:

Comparte alteraciones con el adenocarcinoma ductal: KRAS, p16, p53, CDKN2A y SMAD4.

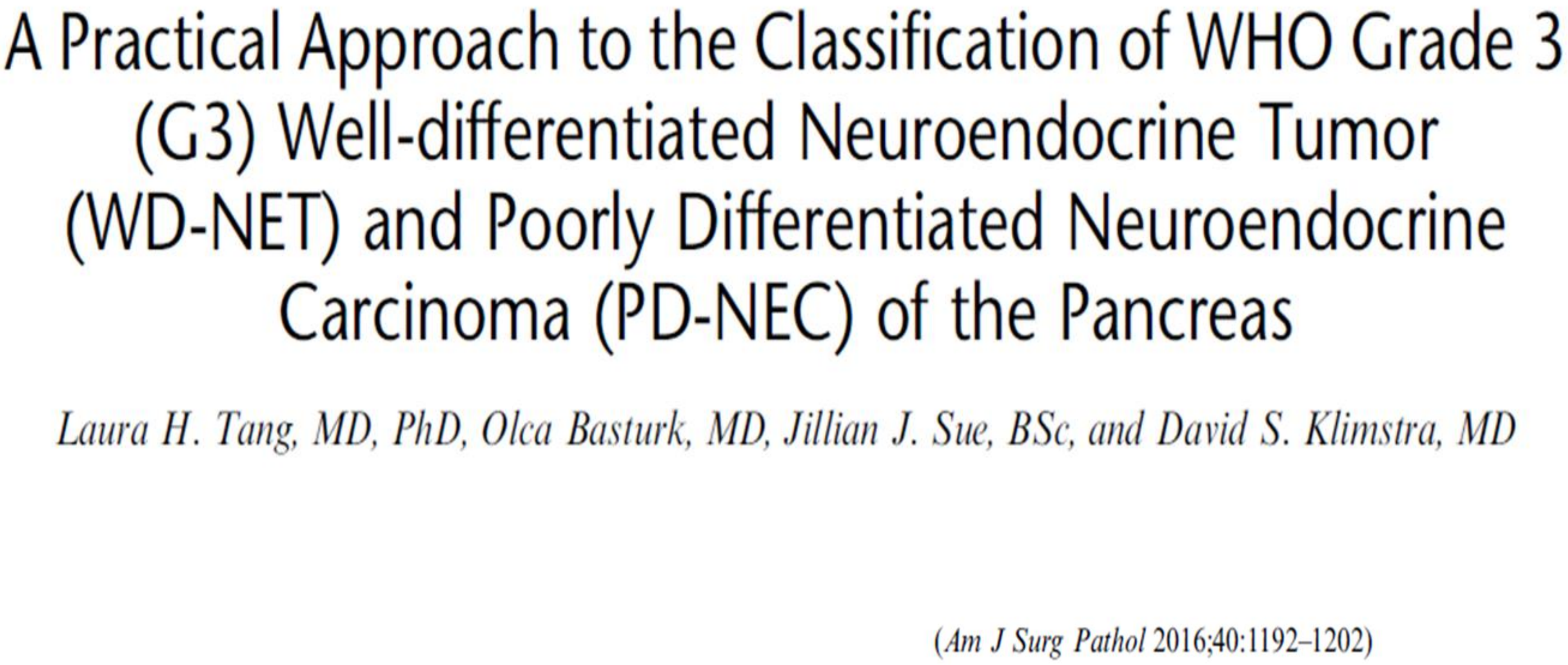
No tiene alteración de MEN1, DAXX o ATRX.

Mutación del gen *RB1* que se asocia con la pérdida de la expresión de la proteína Rb (89% en los carcinomas de células pequeñas y 60% en los de células grandes)

Tumores neuroendocrinos del páncreas

NET	NEC
No KRAS, p16, CDK2, SMAD4	KRAS, p16, CDK2, SMAD4, p53
Si MEN1, DAXX o ATRX	No MEN1, DAXX o ATRX
No RB1	Si RB1

Tumores neuroendocrinos del páncreas



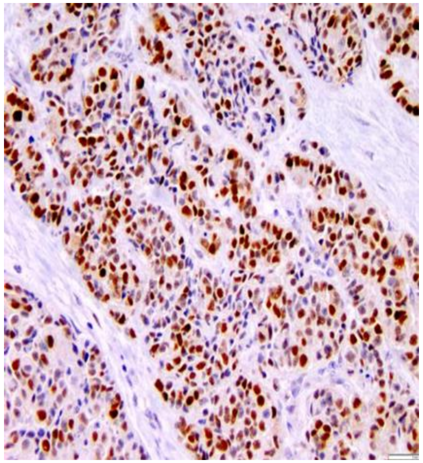
A Practical Approach to the Classification of WHO Grade 3 (G3) Well-differentiated Neuroendocrine Tumor (WD-NET) and Poorly Differentiated Neuroendocrine Carcinoma (PD-NEC) of the Pancreas

Laura H. Tang, MD, PhD, Olca Basturk, MD, Jillian J. Sue, BSc, and David S. Klimstra, MD

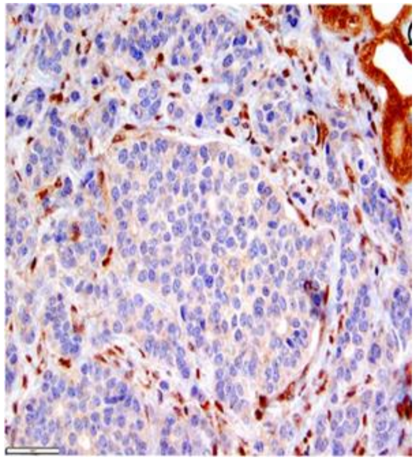
(*Am J Surg Pathol* 2016;40:1192–1202)

Tumores neuroendocrinos del páncreas

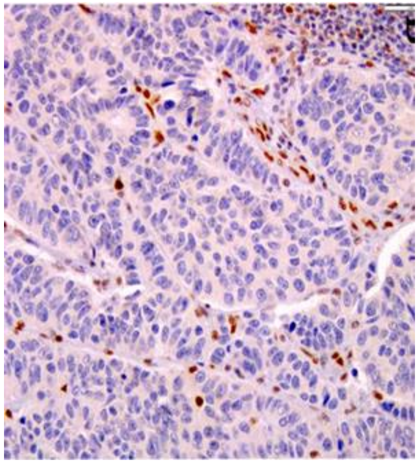
p53



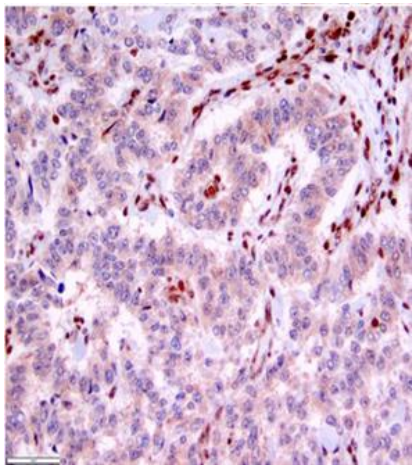
RB



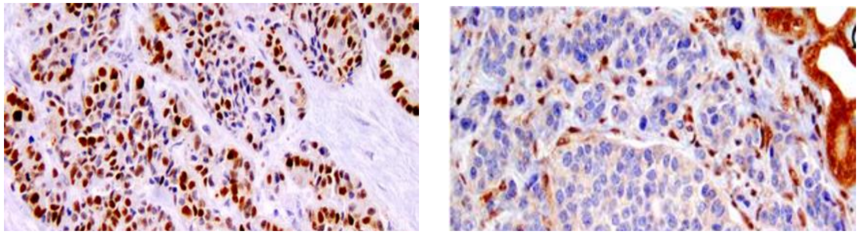
SMAD4



DAXX

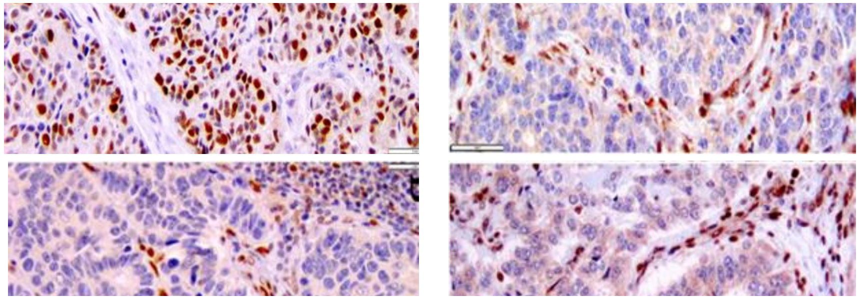


Tumores neuroendocrinos del páncreas



p53

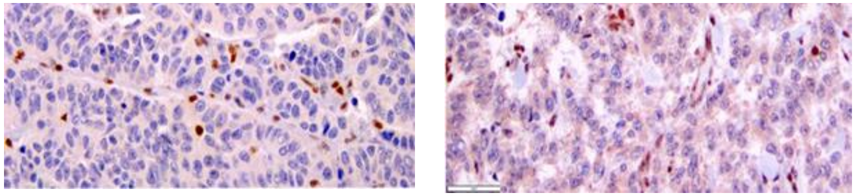
Pérdida de ATRX/DAXX: NET

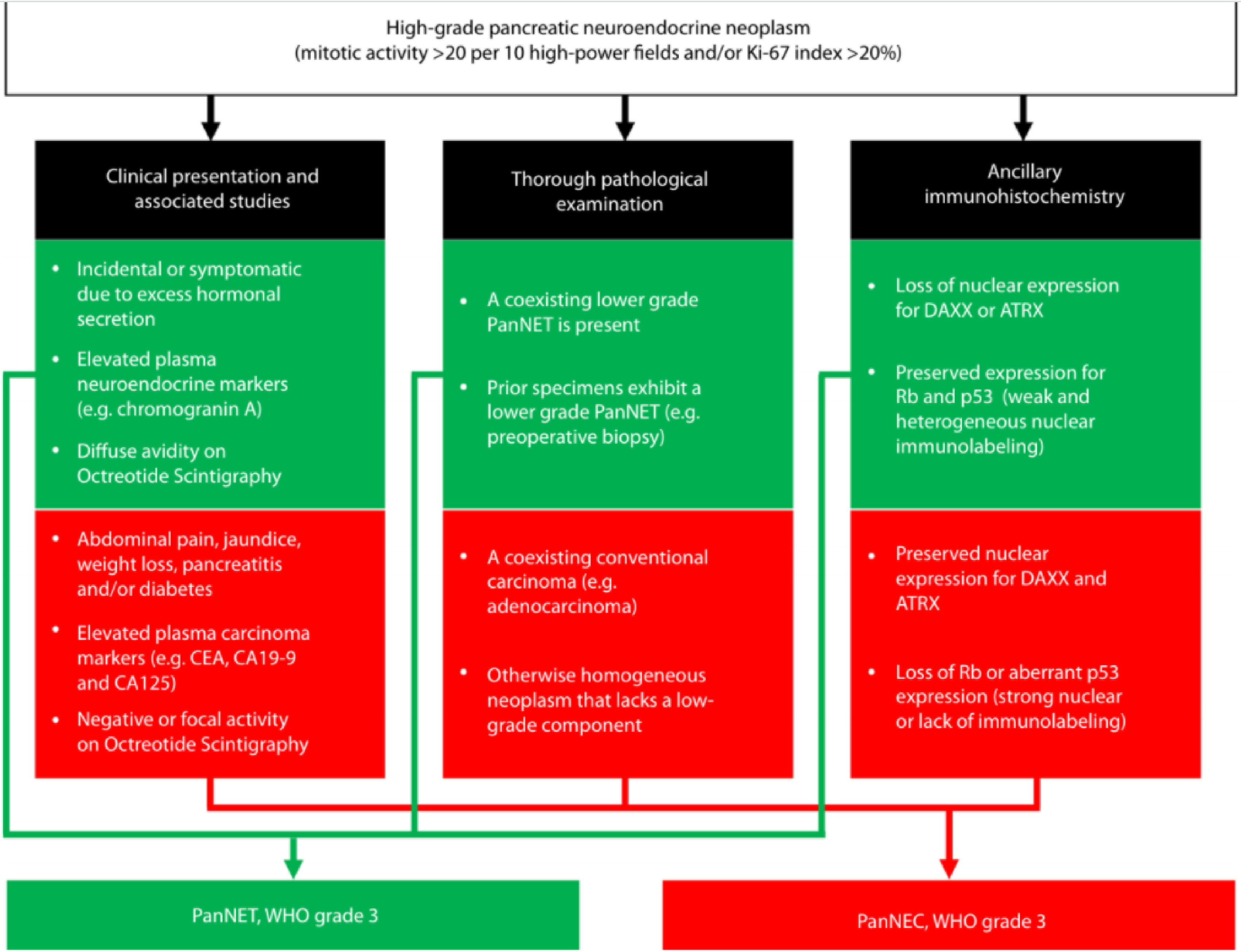


Sobreexpresión de p53/pérdida de SMAD4, RB/ preservación de DAXX: NEC

DAXX

SMAD4





High-grade pancreatic neuroendocrine neoplasm
(mitotic activity >20 per 10 high-power fields and/or Ki-67 index >20%)

Clinical presentation and associated studies

- Incidental or symptomatic due to excess hormonal secretion
- Elevated plasma neuroendocrine markers (e.g. chromogranin A)
- Diffuse avidity on Octreotide Scintigraphy

- Abdominal pain, jaundice, weight loss, pancreatitis and/or diabetes
- Elevated plasma carcinoma markers (e.g. CEA, CA19-9 and CA125)
- Negative or focal activity on Octreotide Scintigraphy

Thorough pathological examination

- A coexisting lower grade PanNET is present
- Prior specimens exhibit a lower grade PanNET (e.g. preoperative biopsy)

- A coexisting conventional carcinoma (e.g. adenocarcinoma)
- Otherwise homogeneous neoplasm that lacks a low-grade component

Ancillary immunohistochemistry

- Loss of nuclear expression for DAXX or ATRX
- Preserved expression for Rb and p53 (weak and heterogeneous nuclear immunolabeling)

- Preserved nuclear expression for DAXX and ATRX
- Loss of Rb or aberrant p53 expression (strong nuclear or lack of immunolabeling)

PanNET, WHO grade 3

PanNEC, WHO grade 3

Histopathology 2018, 72, 168–177.

En resumen…

- Los tumores neuroendocrinos incluyen en este momento una gama amplia y mezclada de enfermedades.
- Analizarlas de acuerdo al órgano afectado.
- Muestreo y examen correcto de la pieza.
- Integración con la presentación clínica.
- Estudio moleculares van a mejorar a diferenciarlas y dirigir la terapias.
- El intestino delgado es un área en exploración.
- Correcta clasificación (no al Ki-67 subjetivo).

¡Muchas gracias!

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