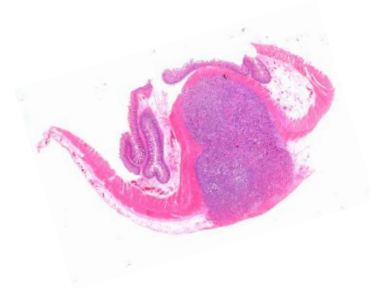


Doença de Órgão vs Entidade Nosológica



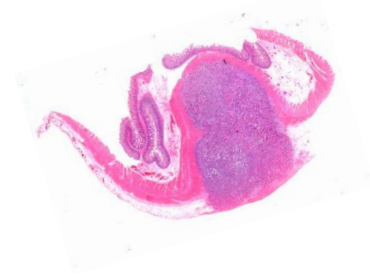
NET como case study

Paula Chaves



IPOLFG

NET como case study

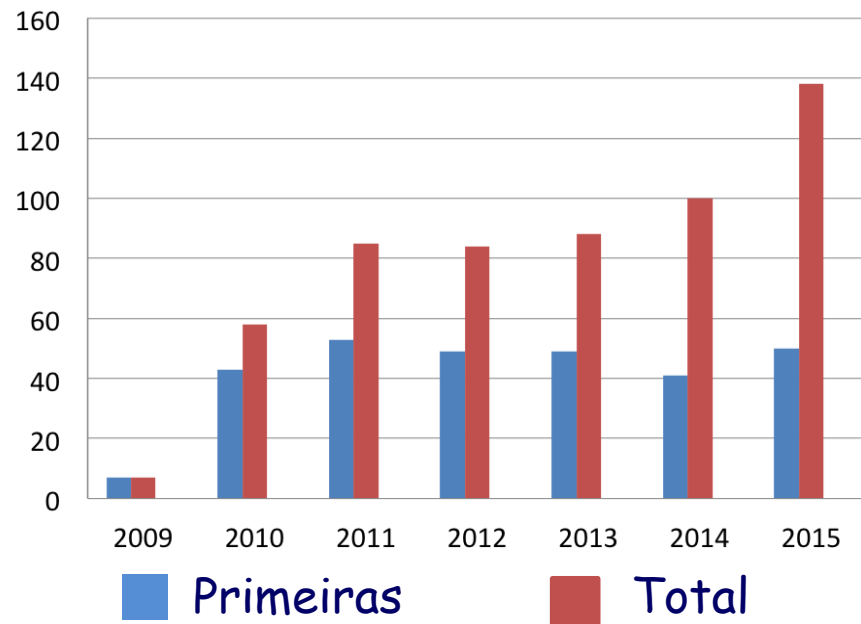


Porquê eu?

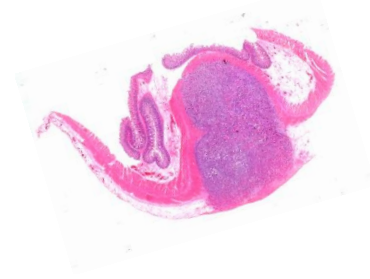
CONSULTA MULTIDISCIPLINAR DE TNE DO IPOLFG EPE (2009)

Gastrenterologia
Oncologia
Endocrinologia
Pneumologia
Radiologia
Medicina Nuclear
Cirurgia
Patologia

Nº doentes avaliados



NET como case study



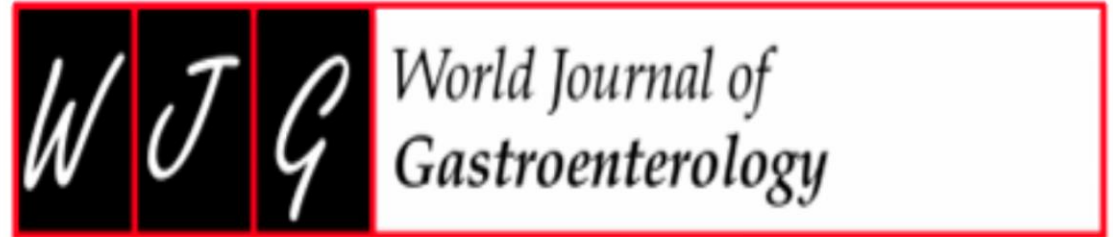
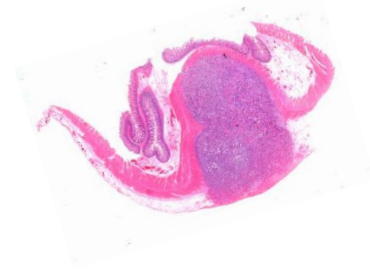
Porquê é que os TNE estão na Gastro?

- ☐ As céls. neuroendócrinas estão por todo o organismo?
- ☐ Os TNEs se podem originar em qualquer órgão?
- ☐ Sendo tumores raros...
- ☐ TNE Gastropancreáticos: 75% dos TNE
- ☐ Esófago: 0.4-0.5%
- ☐ Estômago: 11- 41%
- ☐ Delgado: duodeno 22%, jejuno 1%, íleon 23-28%
- ☐ Apêndice ileocecal: 19%
- ☐ Cólon e recto: 10-20%
- ☐ Pâncreas: 5-8%

Am J Clin Pathol, 2001



NET como case study



Online Submissions: <http://www.wjgnet.com/esps/>
bpgoffice@wjgnet.com
doi:10.3748/wjg.v19.i47.9012

World J Gastroenterol 2013 December 21; 19(47): 9012-9019
ISSN 1007-9327 (print) ISSN 2219-2840 (online)
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ORIGINAL ARTICLE

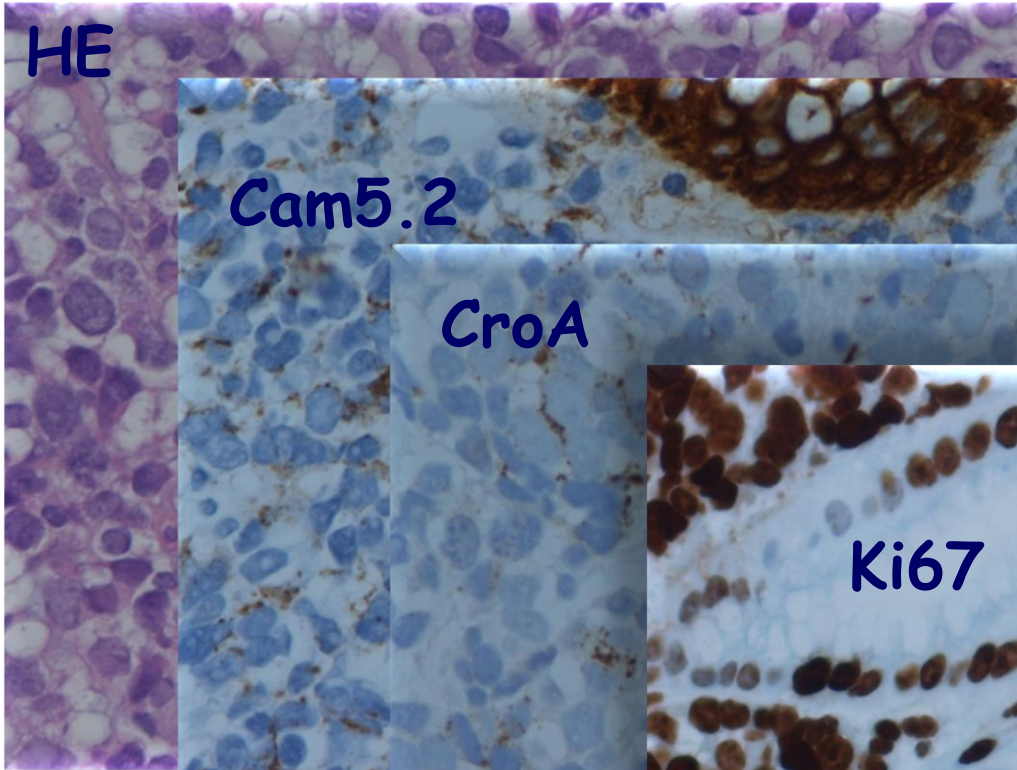
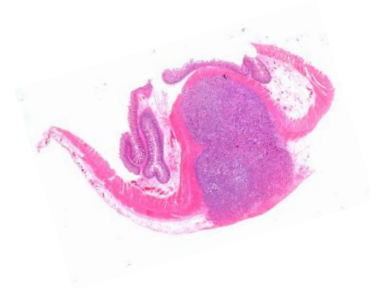
Clinically detected gastroenteropancreatic neuroendocrine tumors are on the rise: Epidemiological changes in Germany

Hans Scherübl, Brigitte Streller, Roland Stabenow, Hermann Herbst, Michael Höpfner, Christoph Schwertner, Joachim Steinberg, Jan Eick, Wanda Ring, Krishna Tiwari, Sören M Zappe

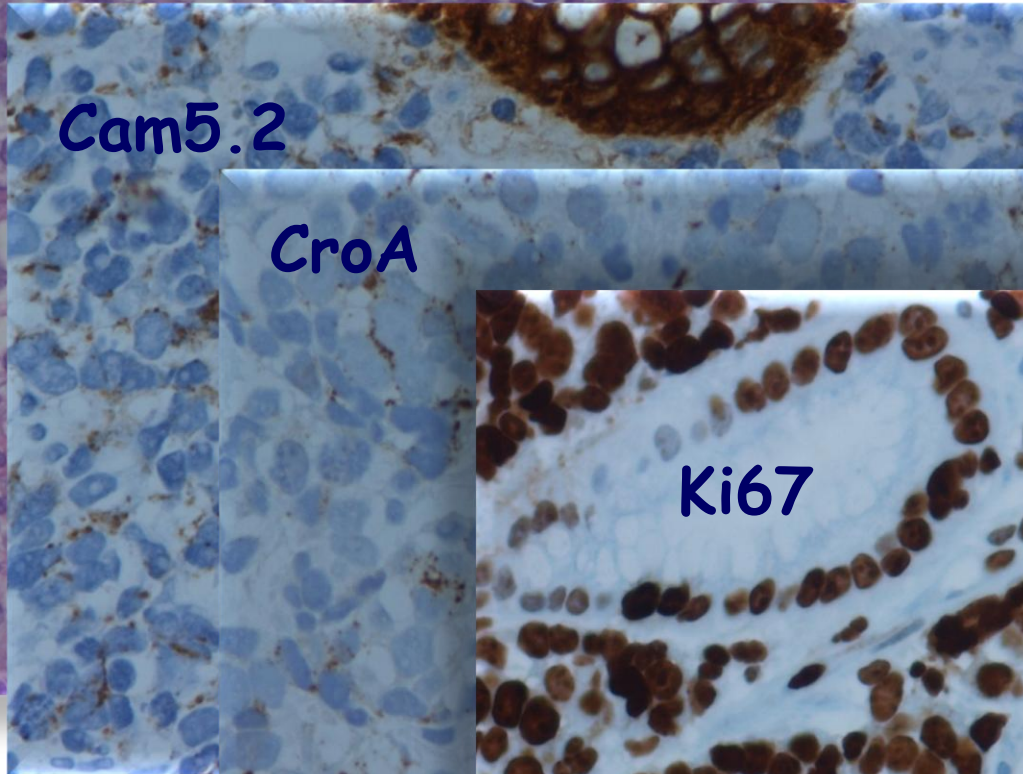
The increase in incidence of NETs is attributed to the improved diagnostic procedures and increased pathologic diagnosis of less differentiated tumours.



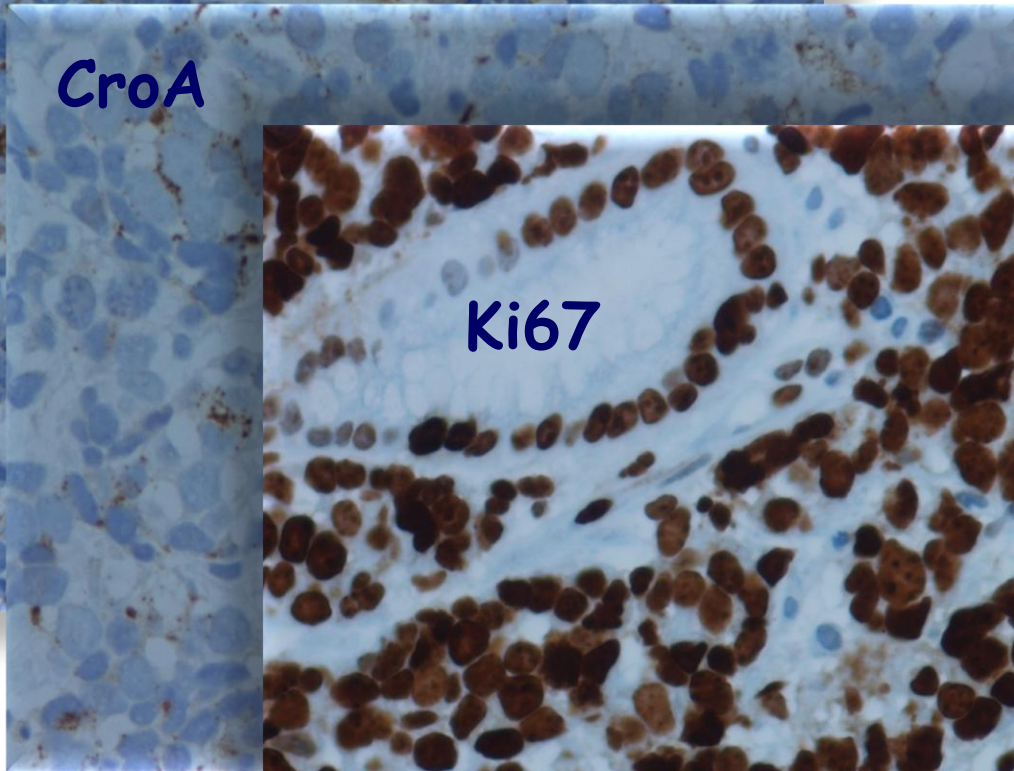
NET como case study



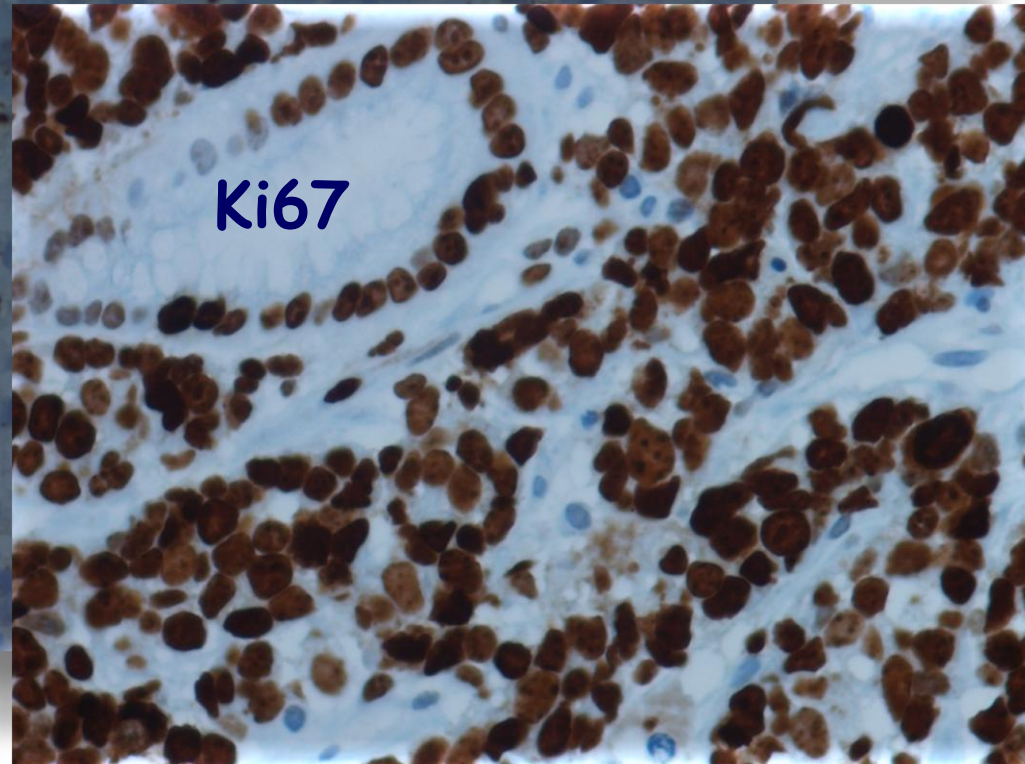
HE



Cam5.2



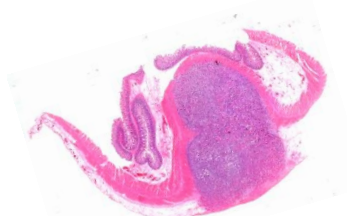
CroA



Ki67

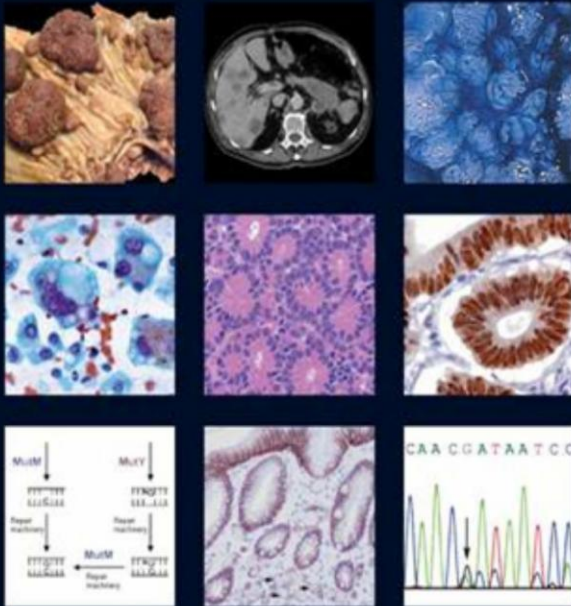
Carcinoma Neuroendócrino

NET como case study

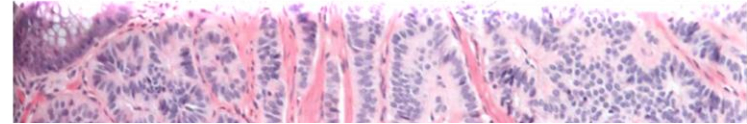


WHO Classification of Tumours of the Digestive System

Edited by Fred T. Bosman, Fátima Carneiro, Ralph H. Hruban, Neil D. Theise



2010

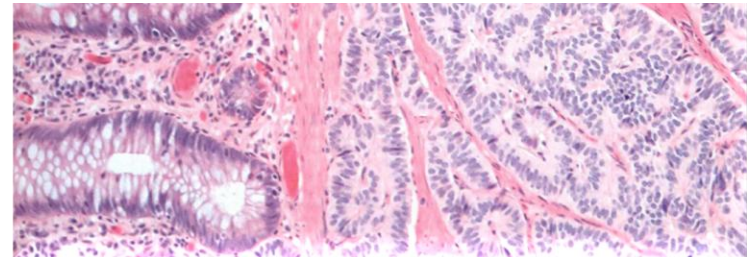


CHAPTER 1

Diagnostic terms revisited

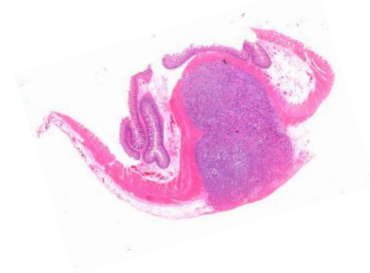
Premalignant lesions of the digestive system

Nomenclature and classification
of neuroendocrine neoplasms
of the digestive system



Paula Chaves

NET como case study



Porquê?

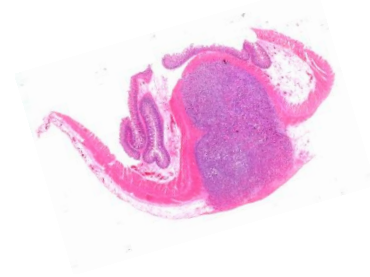
- ☐ Falta de consenso na nomenclatura e estadiamento...
- ☐ WHO 2000:
 - ...abordagem racional da nomenclatura e classificação...
 - ...EU... sim
 - ... USA ... não
- ☐ Confusão entre estadiamento e grau...
- ☐ Complicada classificação clinico-patológica...
- ☐ Categoria ... "*comportamento incerto*"...
- ☐ Utilização do termo... "*carcinóide*"...
- ☐ ENETS

Grau/Estadiamento específico de órgão

- ... os NETs diferem conforme o órgão de origem...
- ... os NETs diferem conforme a diferenciação...
- ... todos os NETs são malignos...



NET como case study



WHO 2010:

Grau/Estadiamento

NET e NEC ... amplamente aceites nos USA e EU

Table 1.03 Transition scheme for the new classification (WHO 2010) including previous definitions for neuroendocrine neoplasms of the digestive system (WHO 1980 and 2000).

WHO 1980	WHO 2000	WHO 2010
I Carcinoid	<div style="display: flex; align-items: center;"> <div style="margin-right: 10px;">↕</div> <div> 1. Well-differentiated endocrine tumour (WDET)^a 2. Well-differentiated endocrine carcinoma (WDEC)^a 3. Poorly differentiated endocrine carcinoma/small cell carcinoma (PDEC) </div> </div>	1. NET G1 (carcinoid) ^b 2. NET G2 ^b 3. NEC (large cell or small cell type) ^{b,c}
II Mucocarcinoid	4. Mixed exocrine-endocrine carcinoma (MEEC)	4. Mixed adenoneuroendocrine carcinoma (MANEC)
III Mixed forms carcinoid-adenocarcinoma		
IV Pseudotumour lesions	5. Tumour-like lesions (TLL)	5. Hyperplastic and preneoplastic lesions

{1106, 3013, 3516}

G, grade (for definition, see text); NEC, neuroendocrine carcinoma; NET, neuroendocrine tumour.

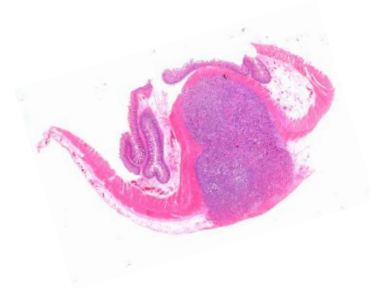
^a The difference between WDET and WDEC was defined according to staging features in the WHO 2000 classification. G2 NET does not necessarily translate into WDEC of the WHO 2000 classification.

^b Definition in parentheses for the International Classification of Diseases for Oncology (ICD-O) coding.

^c "NET G3" has been used for this category but is not advised, since NETs are by definition well-differentiated.



NET como case study

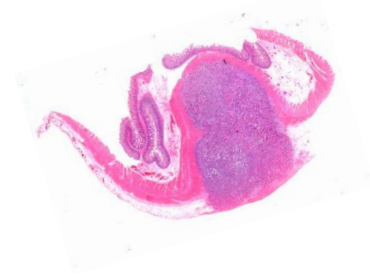


WHO 2010 ↔ ENETS 2006 e 2009

- ... grau histológico aplicável a todos os NETs...
(independentemente do estadio)
- ... idêntico aos restantes tumores epiteliais...
- ... estadia os NETs usando o TNM (ajcc)



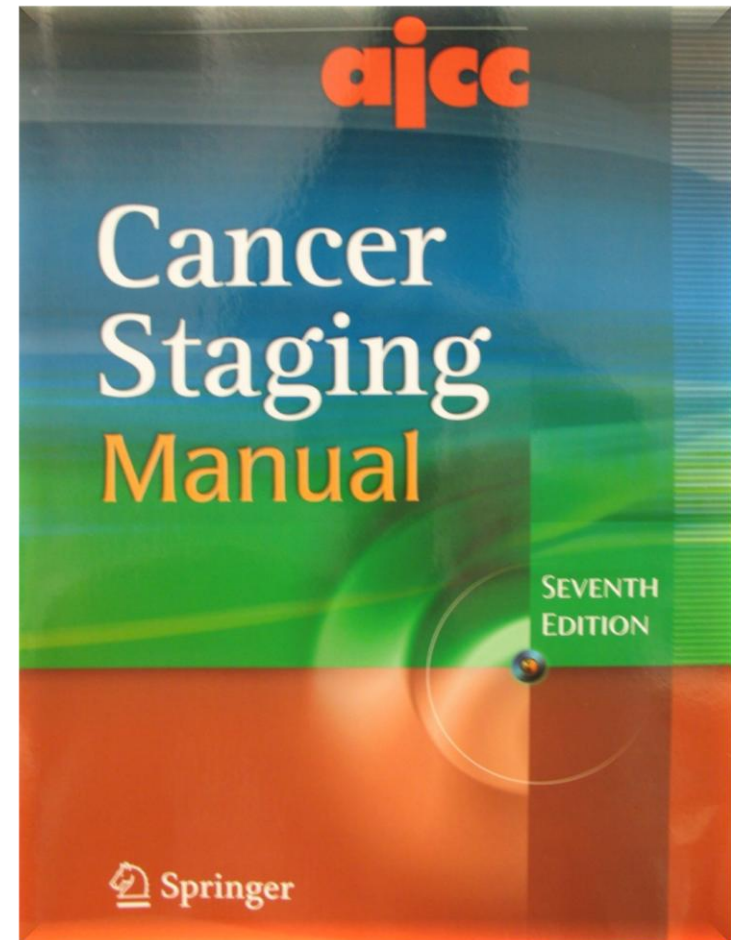
NET como case study



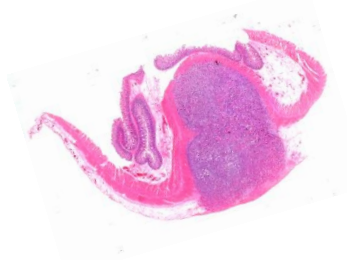
ÚLTIMA EDIÇÃO (7ª)

Tumores Neuroendócrinos

Estômago.....	Cap. 17
Intestino delgado.....	Cap. 17
Cólon e Recto.....	Cap. 17
Ampola de Vater.....	Cap. 17
Apêndice Ileo-Cecal.....	Cap. 13
Pâncreas.....	Cap. 24



NET como case study



O que é um NET?

- ❑ É um tumor com origem no sistema neurendócrino difuso, que compreende células neuroendócrinas dispersas no trato Gastrointestinal, Broncopulmonar e Urogenital.
- ❑ 1907 Oberndorfer*carcinóide* ...
- ❑baseada na presumida origem embrionária comum ...

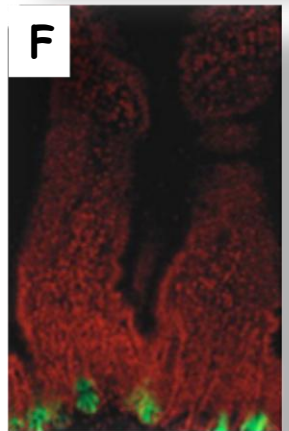
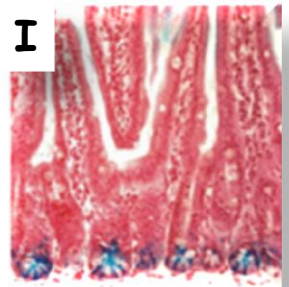
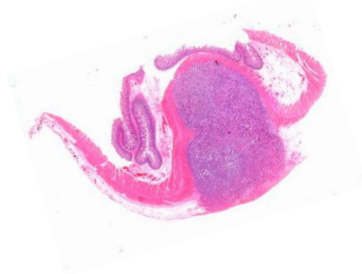
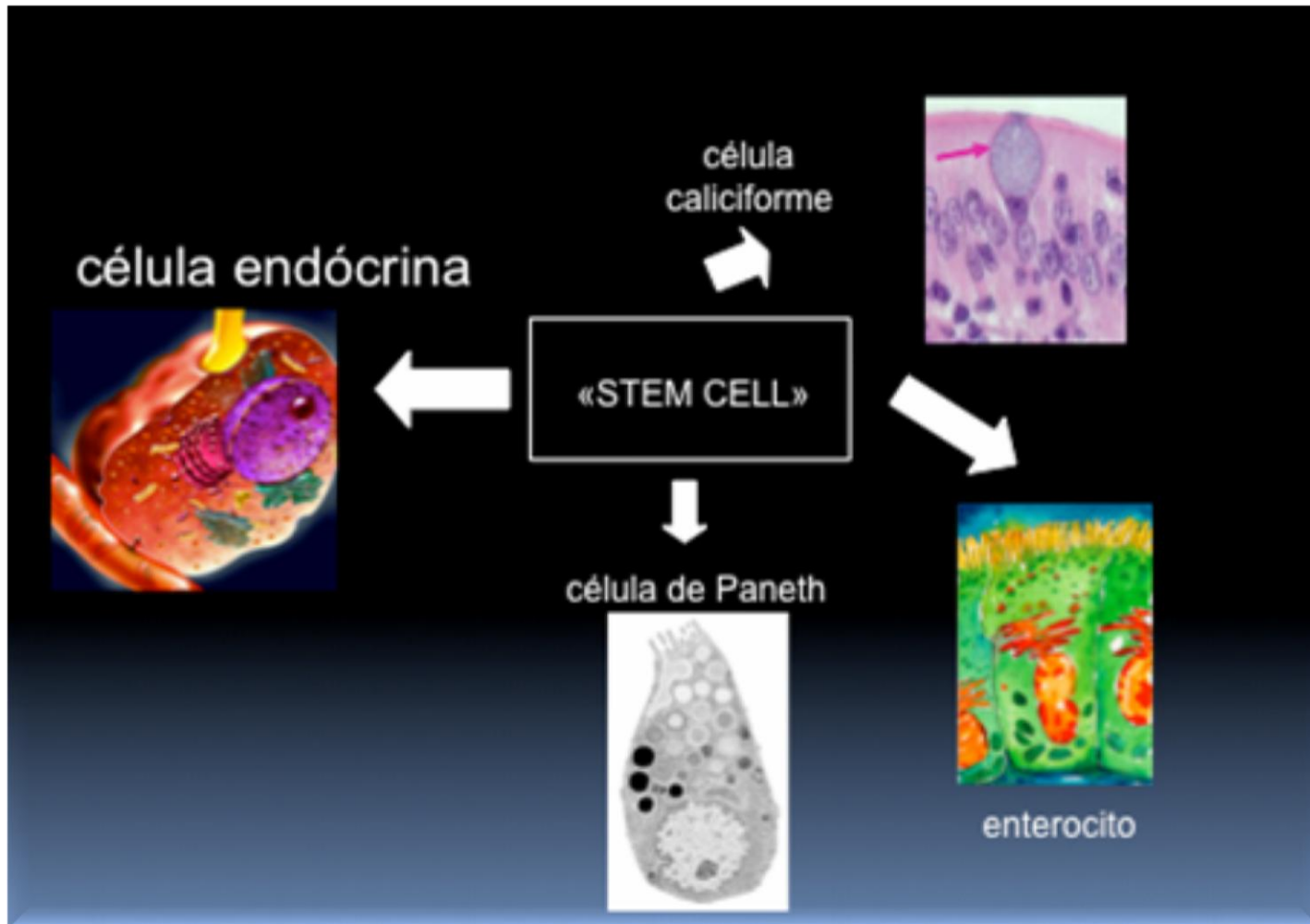
Que conceitos mudaram?

- ❑ As céls. neuroendócrinas NÃO têm origem na crista neural...
- ❑ Mas em "stem cells" locais.
- ❑ A diferenciação neuroendócrina é promovida péptidos ...
- ❑ Modulada por factores de transcrição...
- ❑ O conceito APUD (outdated)
... permitiu a compreensão de uma linhagem comum ...
- ❑ Classificar de acordo com a diferenciação...

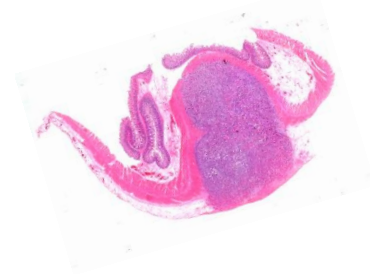


NET como case study

Neoplasia..GI...



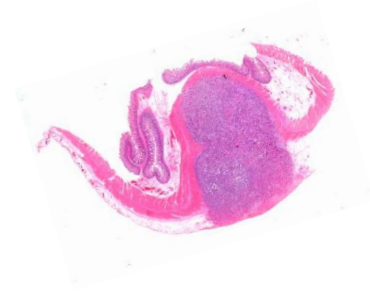
NET como case study



Actualmente...

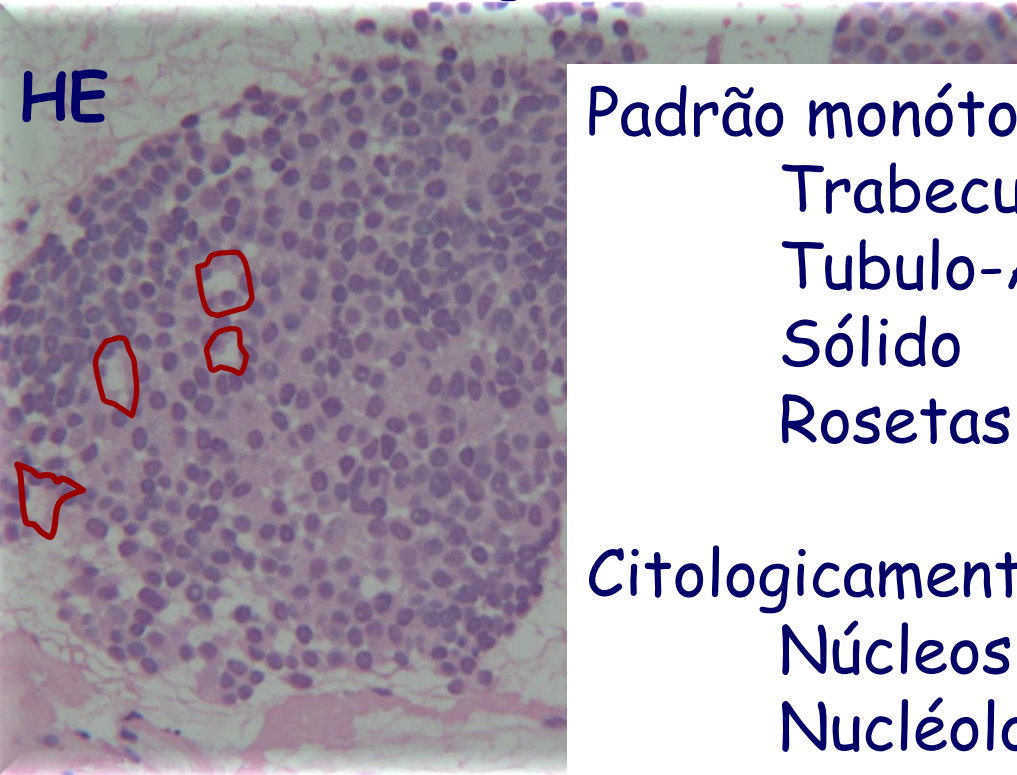
- ❑ Reconhecer (*identificar diferenciação neuroendócrina*)
 - Padrão histológico
 - Imunocitoquímica (≤ 2 marcadores)
 - Ultraestrutura (*grãos neuroendócrinos*)
- ❑ Classificar (*categorizar*)
 - Classificação Histológica
 - Estadiamento Patológico
- ❑ Relatório Anatomo-Patológico

NET como case study



Reconhecer um NET...

□ Padrão histológico



Padrão monótono

Trabecular

Tubulo-Acinar

Sólido

Rosetas

Citologicamente

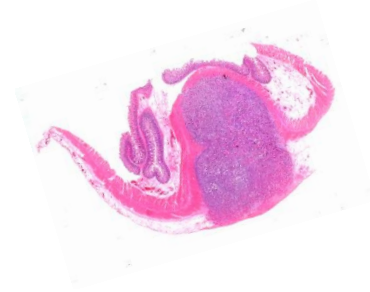
Núcleos ovais ou redondos

Nucléolo indistinto

Cromatina finamente granular



NET como case study

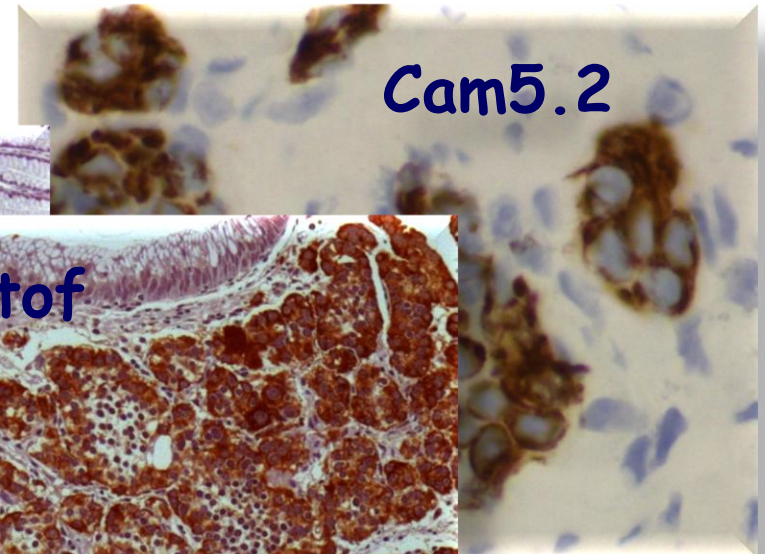
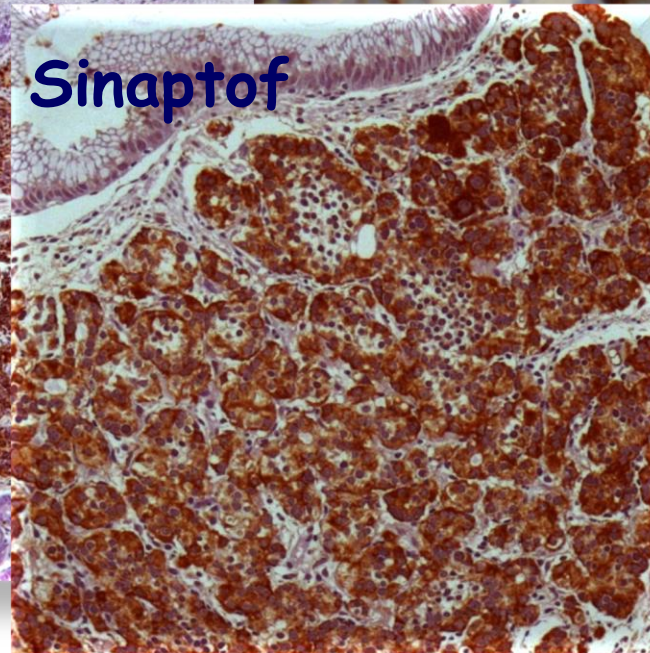
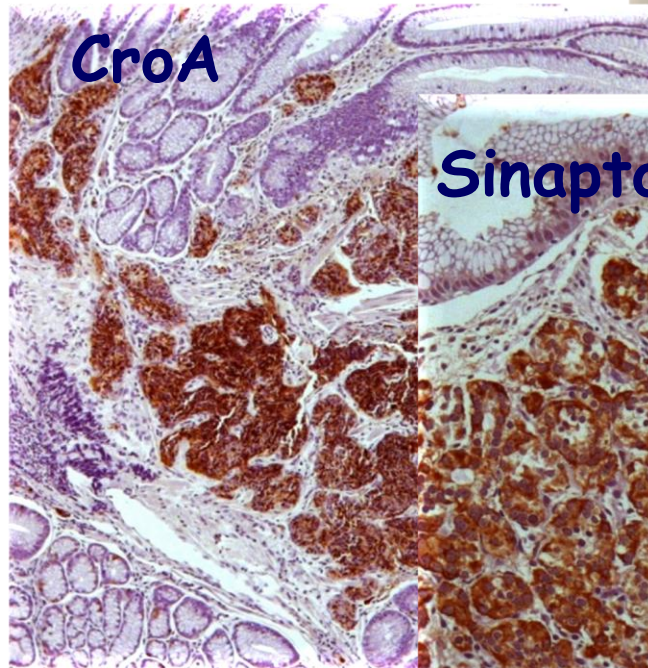


NET

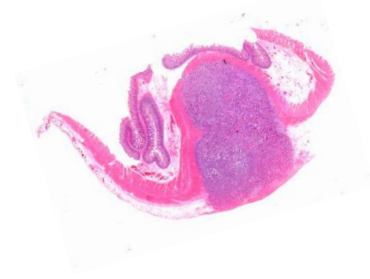
□Imunocitoquímica

Citoqueratina e ≤ 2 marcadores NE

CroA
Sinaptofisina
NSE
CD56
CD57



NET como case study



Classificar um NET...

□ Graduar (*Grau Histológico*)

Nº de Mitoses (50 HPF)

Ki 67 index (%)

G1	<2/10 HPF
G2	2-20/10 HPF
G3	>20/10 HPF

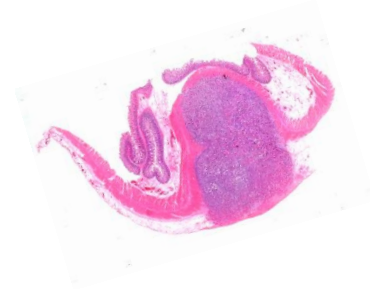
G1	≤ 2
G2	3-20
G3	>20

"hot spots"

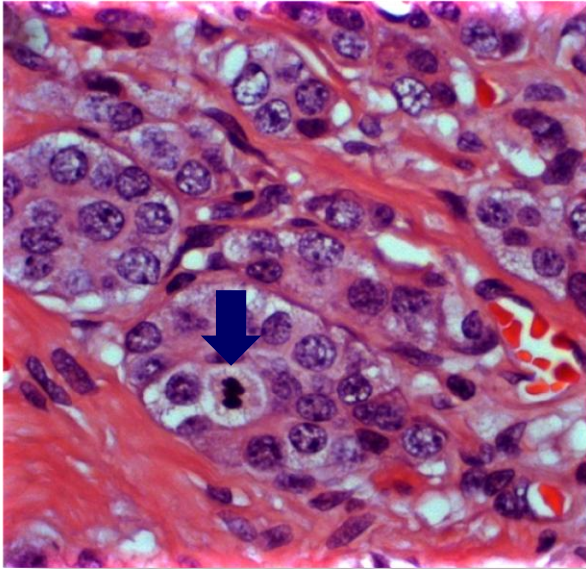
...se não coincidem assume-se o mais alto grau...



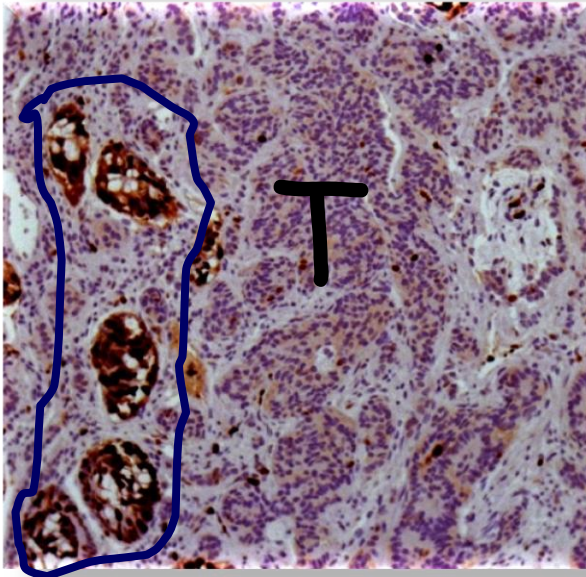
NET como case study



Nº de Mitoses



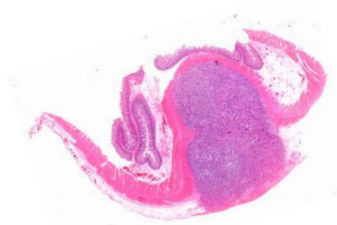
Nº de mitoses/10 HPF (50 campos)
Nº de mitoses/2 mm².



Ki67%

Ki 67: <2%.

NET como case study



Ki67? Problemas?

☐ Técnicos

Fixação

Processamento

Imunocitoquímica

☐ Análise Manual

Intra-observador

Inter-observador

☐ Análise Digital

"Aceitáveis"

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*

Abstract: Pathologic grading for prognostic stratification of neuroendocrine tumors (NETs) is critical but presents a challenging interpretive dilemma. Tumor cell proliferative rate is an important factor in the determination of prognosis, and immunohistochemical analysis with Ki67 is becoming more widely used to quantify the proliferative rate. However, Ki67 assessment has limitations due to lack of uniformity and consistency in quantification. These limitations are accentuated in well-differentiated NETs, as differences in the range of 1% to 5% can alter tumor grade, with potential implications for treatment. We therefore performed a concordance study to assess different Ki67 quantification techniques including: (a) digital image analysis (DIA); (b) manual counting (MC) of > 2000 cells; and (c) "eyeballed" estimate (EE) of labeling percentage by pathologists ($n = 18$), including individuals experienced in evaluating Ki67 labeling as well as others who had little prior experience assessing Ki67 percentages. Forty-five Ki67 images were selected and analyzed using the 3 methods. On the basis of the recommendations of the World Health Organization (WHO) for grading NETs, MC of 2000 cells was used as the "gold standard" reference against which the other techniques were compared. Three images were presented twice, the second being

(ICC = 0.13). The ICC for intraobserver consistency was 0.39 ± 0.26 . With Ki67 in the ranges of $< 1\%$, 2% to 3% , and $> 20\%$, the mean of Ki67 by EE was, respectively, $93\% \pm 2\%$, $55\% \pm 7\%$, and $55\% \pm 15\%$ correct against the gold standard. The κ statistics for EE exhibited low agreement ($\kappa = 0.24$; 95% confidence interval, 0.23-0.25) for all WHO NET grades. Incorrect assessment by EE resulted in upgrading of all WHO G1 group tumors ($n = 14$); in the WHO G2 group, downgrading of 41% cases occurred ($n = 11$) when Ki67 was $< 5\%$ (by DIA or MC), and upgrading of 59% cases occurred ($n = 16$) when Ki67 was $> 5\%$. We conclude that DIA and MC are the acceptable standards for NET assessment. Given the inherent discordance in determining the grade, the use of an approximate EE of the Ki67-labeling index requires critical reevaluation, especially for NETs with a labeling index straddling the cut-points between grades. Consequently, determination of therapeutic strategies should be guided by an amalgamation of clinicopathologic characteristics, including but not limited to the Ki67 index.

Key Words: neuroendocrine tumor, NET, Ki67, MIB-1, NET grade, NET classification

(*Am J Surg Pathol* 2012;00:000-000)



NET como case study

Journal of Surgical Oncology 2012;106:724–727

Ki-67 Labeling: A More Sensitive Indicator of Malignant Phenotype Than Mitotic Count or Tumor Size?

KEVIN LOWE, MD, PhD,¹ AMIT KHITHANI, MBBS,² ELIZABETH LIU, BS,² TANYSS WINSTON, RN, BSN, OCN,²
DERRICK CHRISTIAN, MD,¹ JOE SAAD, MD,³ AND DHIRESH ROHAN JEYARAJAH, MD^{1*}

¹Department of HPB Surgery, Methodist Dallas Medical Center, Dallas, Texas

²Cancer Center, Methodist Dallas Medical Center, Dallas, Texas

³Department of Pathology, Methodist Dallas Medical Center, Dallas, Texas

G1 e G2

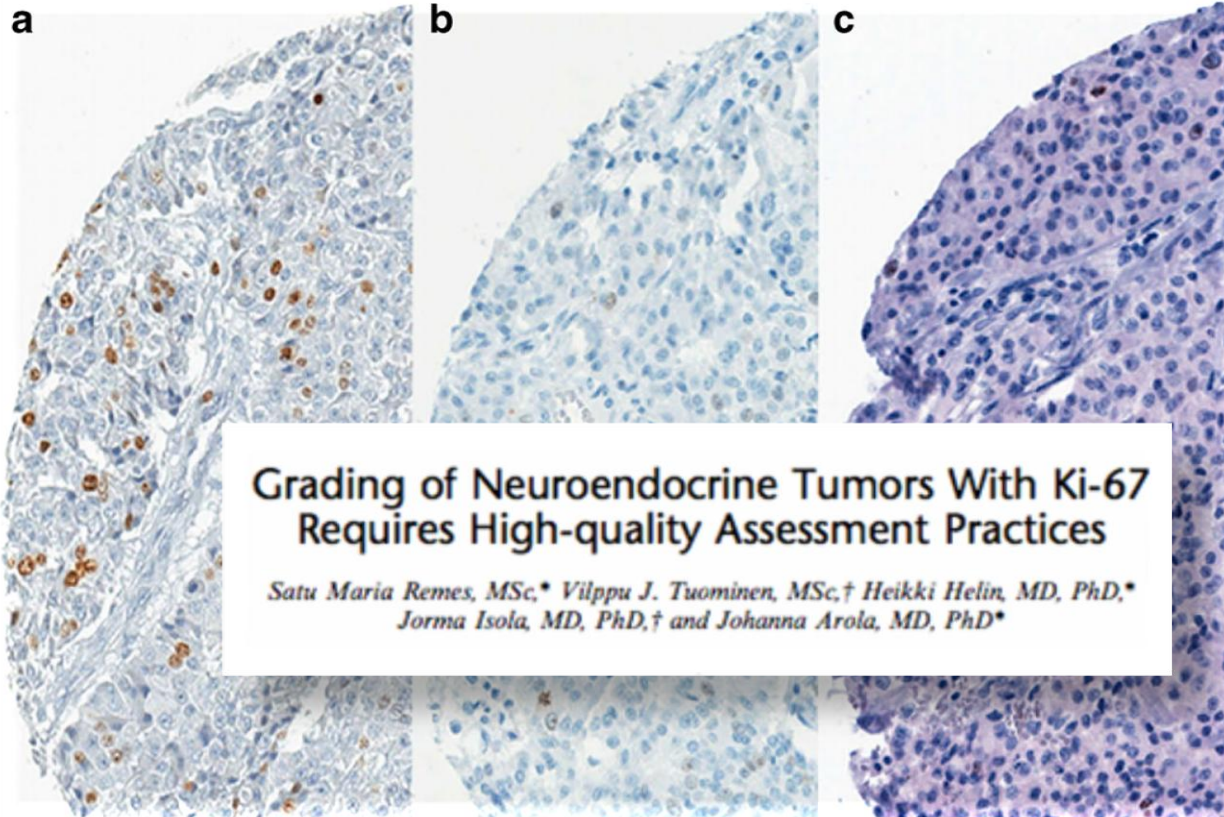
Background and Objectives: The Ki-67 index is a sensitive indicator of proliferative activity in neuroendocrine tumors. However, pathologists have not standardized the assessment of Ki-67 labeling. The intent of the current study was to evaluate the relationship between Ki-67 labeling and lymph node metastasis and survival.

Methods: The current study is a review of 24 patients with neuroendocrine tumors.

Results: Regional LNM were present in 100% of patients with Ki-67 index of >10% (P = 0.003). No tumors <2 cm had >10% Ki-67 labeling.

Conclusion: Ki-67 index of >10% is a sensitive indicator of malignant phenotype. The current study will require development of staging guidelines as disease may contribute to such improvements.

J. Surg. Oncol. 2012;106:724–727. © 2012 Wiley Periodicals, Inc.

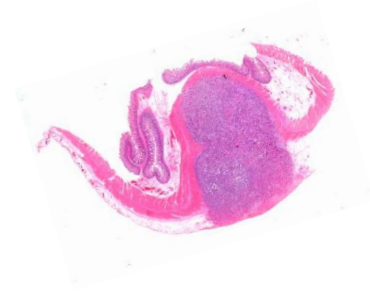


Grading of Neuroendocrine Tumors With Ki-67 Requires High-quality Assessment Practices

Satu Maria Remes, MSc,* Vilppu J. Tuominen, MSc,† Heikki Helin, MD, PhD,*
Jorma Isola, MD, PhD,† and Johanna Arola, MD, PhD*

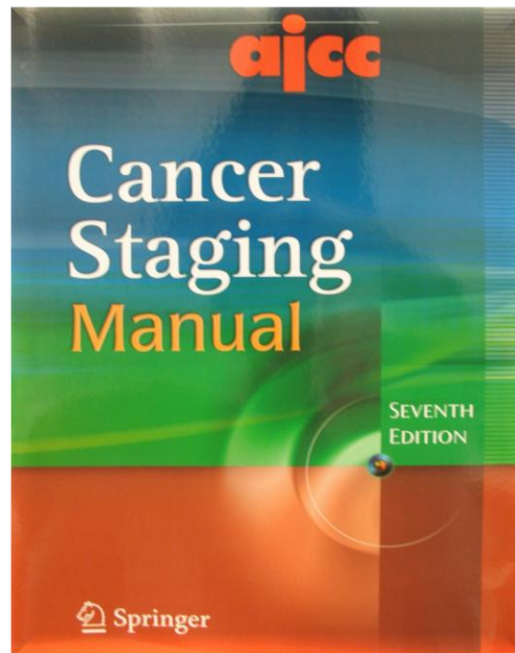


NET como case study



□Estadiamento TNM (*ajcc*)

“Site-specific staging system (*WHO 2010*)”



NET como case study

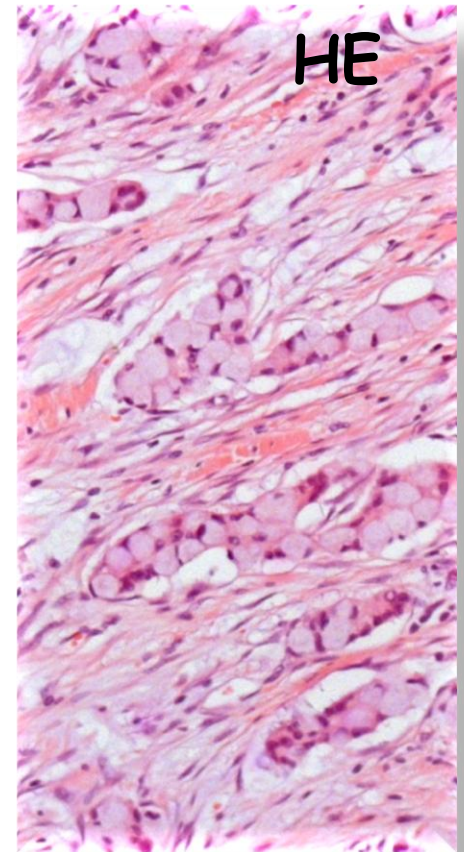
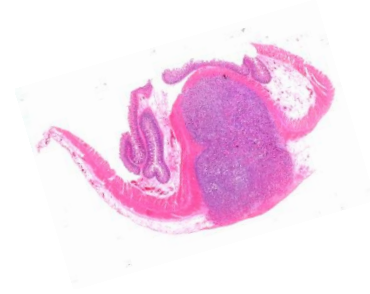
Porquê há pequenas diferenças...

- ☐ Apêndice
- ☐ Pâncreas

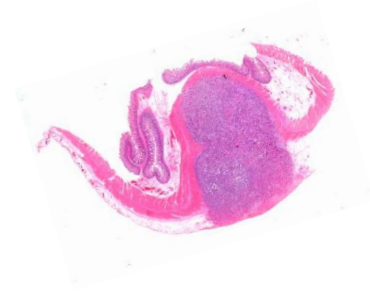
ENETS

- ☐ Extensão da invasão do mesoapêndice >3 mm
- ☐ Dimensão (> 2 cm)
- ☐ Variante "goblet cell"

Indicação Colectomia



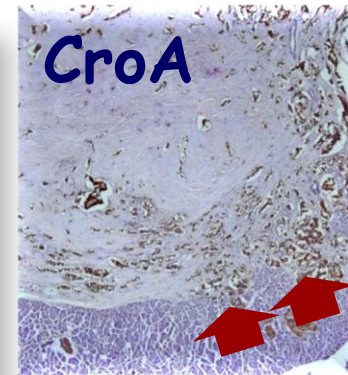
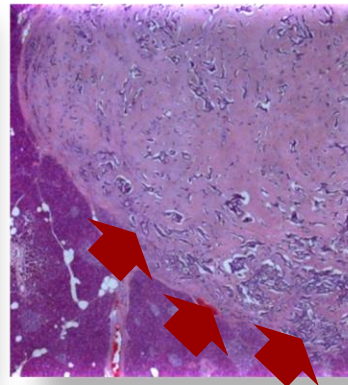
NET como case study



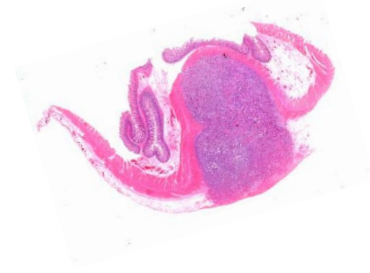
❑ Pâncreas

TNM (ajcc)

- ❑ Estadiados como as neoplasia exócrinas
- ❑ Invasão peripancreática ... T3



NET como case study



Relatório Anatomopatológico

Am J Surg Pathol • Volume 34. Number 3. March 2010

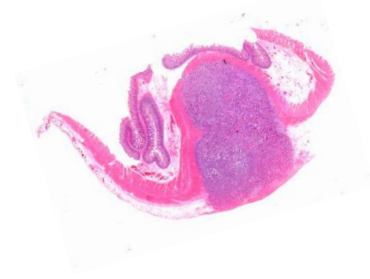
ORIGINAL ARTICLE

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

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



NET como case study



□ Relatório anatomopatológico (*dados mínimos*)

Biopsia

Localização

Diagnóstico

Achados menos usuais

Grau de diferenciação

Nº de mitoses

Ki 67

Necrose não isquémica

Componentes não NE

DIAGNÓSTICO

Peça

Dimensão

Multicentricidade

Extensão da invasão

Invasão linfovascular/perineural

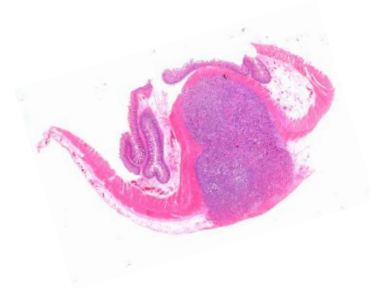
Metástases ganglionares

Margens de ressecção

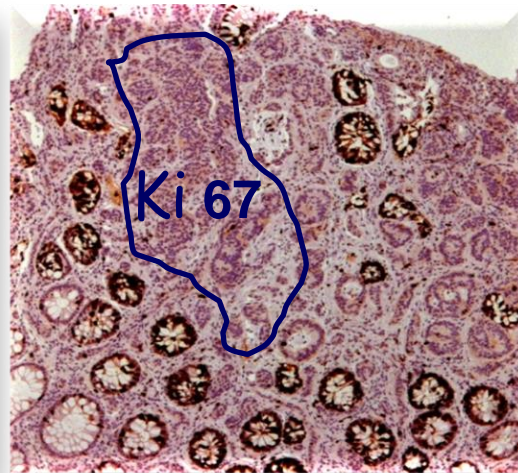
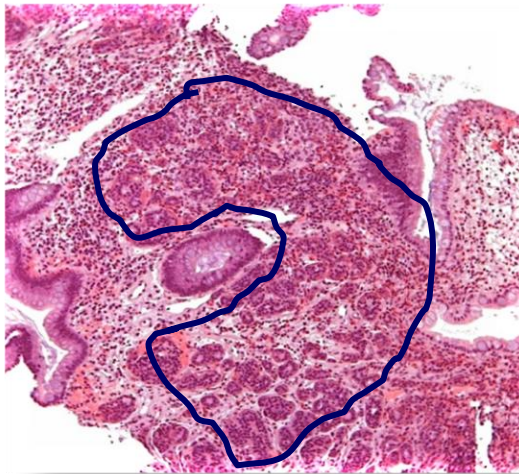
ESTADIAMENTO



NET como case study



□ Biopsia gástrica



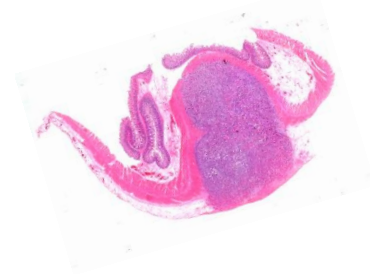
- ✓ Corpo gástrico
- ✓ NET
- ✓ G1

<2 mitoses/10 HPF

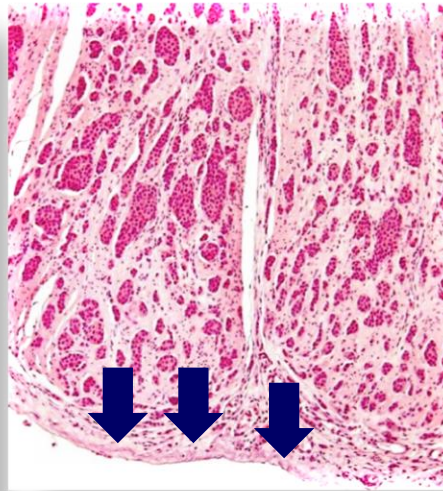
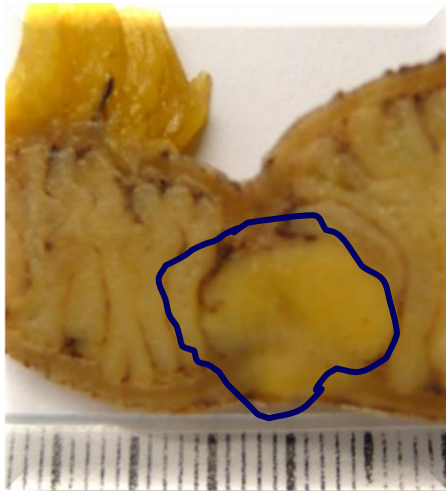
Ki 67 < 2%

- ✓ Gastrite atrófica

NET como case study



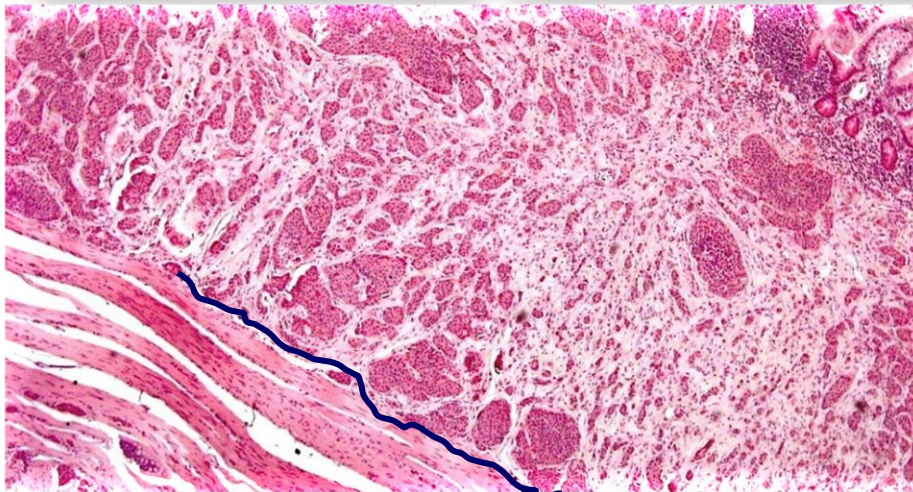
□ Peça de ressecção de íleon



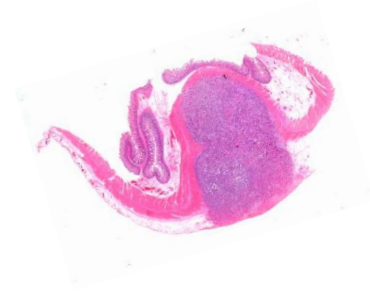
- ✓ Intestino delgado/íleon
- ✓ NET
- ✓ Dimensão 12 x 10 x 8 mm
- ✓ Única
- ✓ G1

1 mitoses/10 HPF
Ki 67 <2%

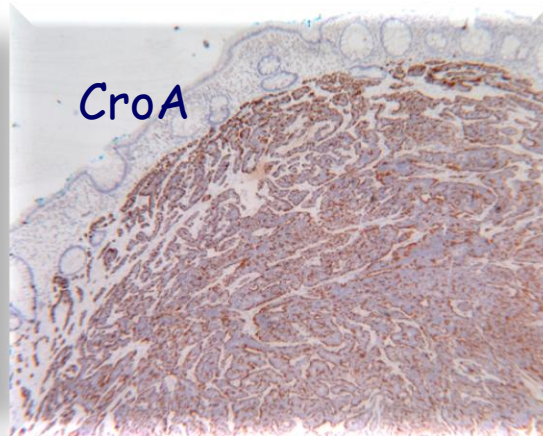
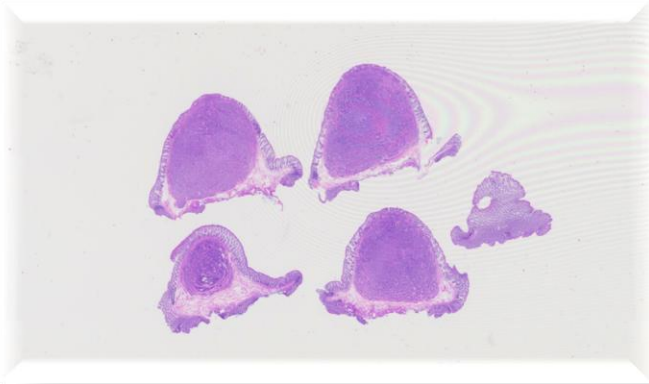
- ✓ Necrose ausente
- ✓ Invasão transmural
- ✓ ILV: não documentado
- ✓ Metástases em 2/10 ggs
- ✓ Margens sem neoplasia



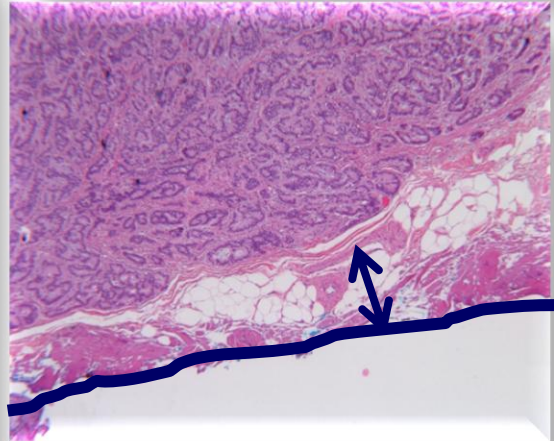
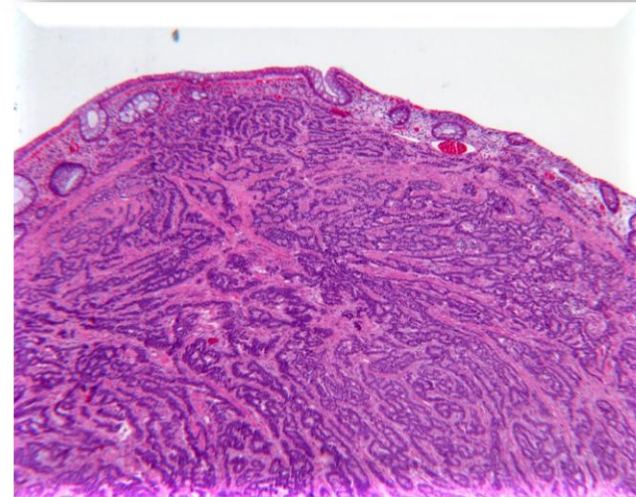
NET como case study



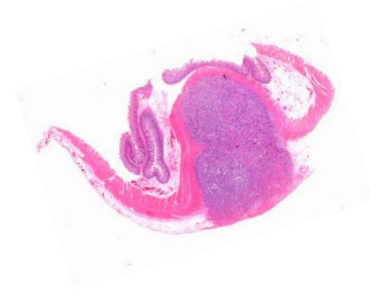
□ Mucosectomia



- ✓ Recto
- ✓ NET
- ✓ Dimensão: 6mm
- ✓ G1
 - <2 mitoses/10 HPF*
 - Ki 67 < 2%*
- ✓ Invasão: Submucosa
- ✓ ILV: (-)
- ✓ Margem: s/neoplasia
- ✓ Distância: 2mm



NET como case study



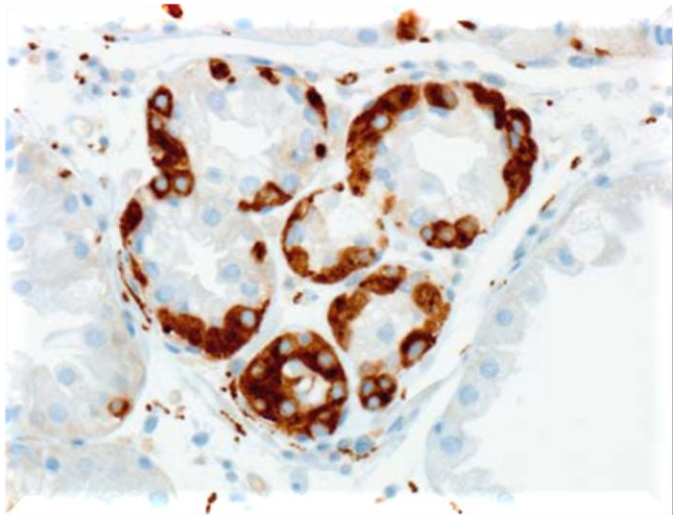
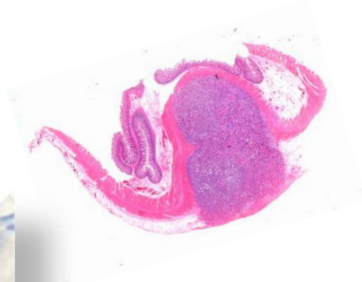
Lesões precursoras...

- ☐ NET Gástrico
- ☐ Sequência hiperplasia - displasia - neoplasia..
- ☐ Lesões precursoras
 - ✓ Hiperplasia
 - ✓ Hiperplasia linear
 - ✓ Hiperplasia nodular
 - ✓ Hiperplasia adenomatóide
 - ✓ Displasia

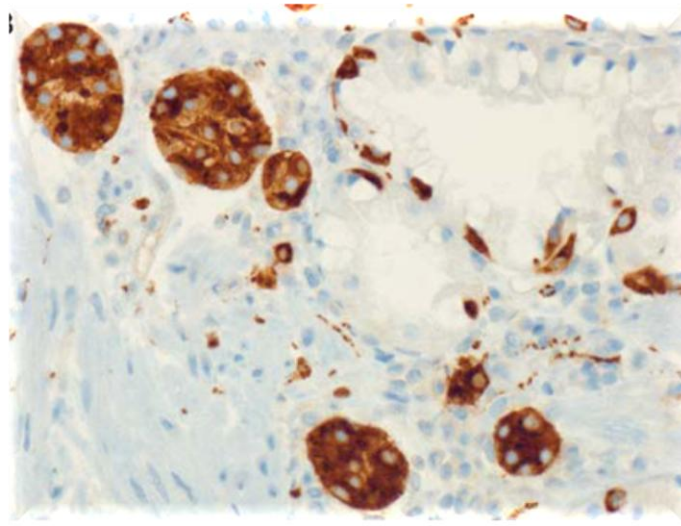
Reconhecer
Reportar



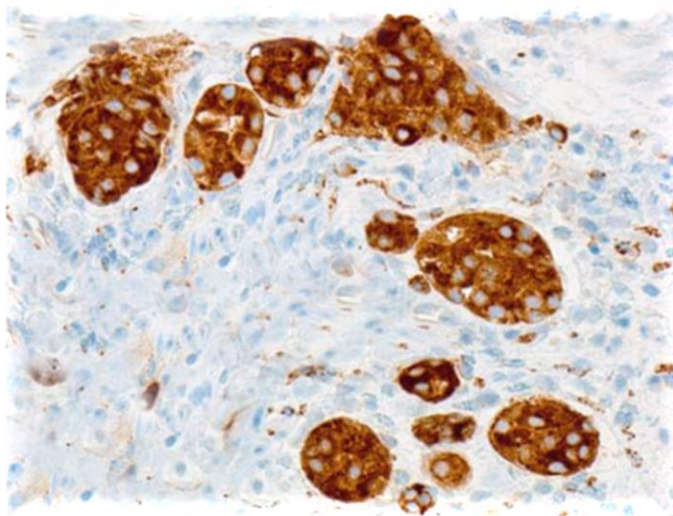
NET como case study



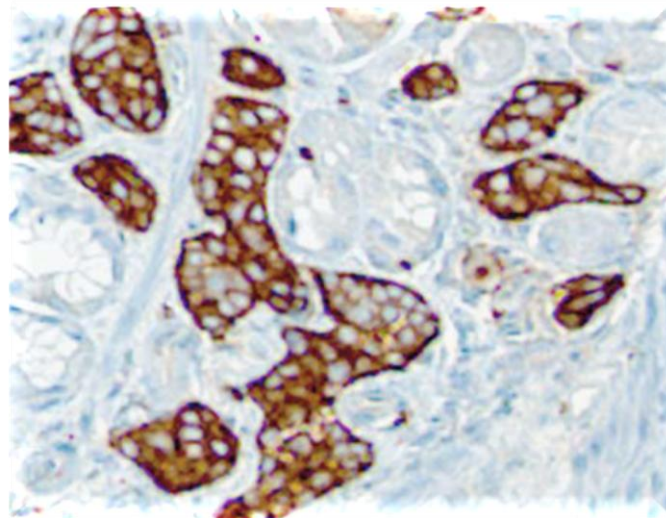
Hiperplasia linear



Hiperplasia nodular

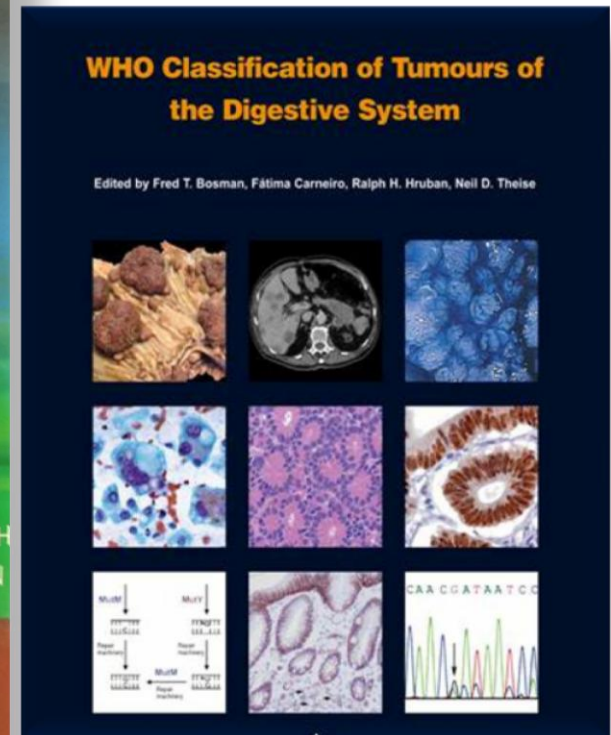
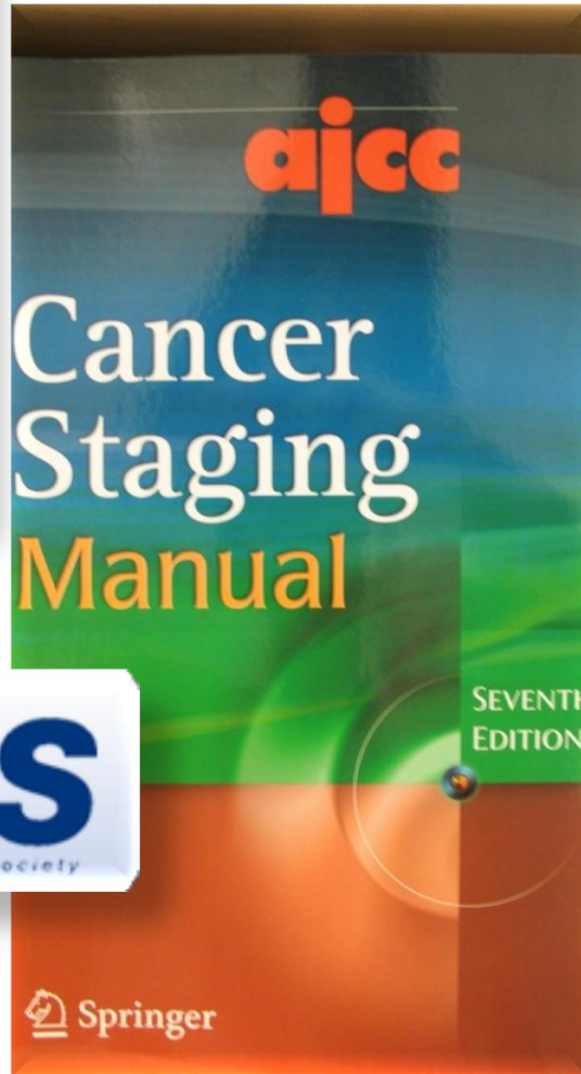
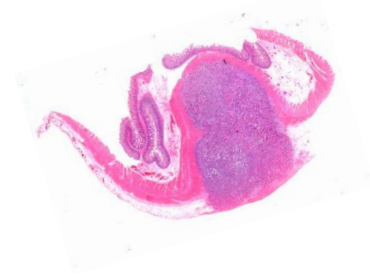


Hiperplasia adenomatóide

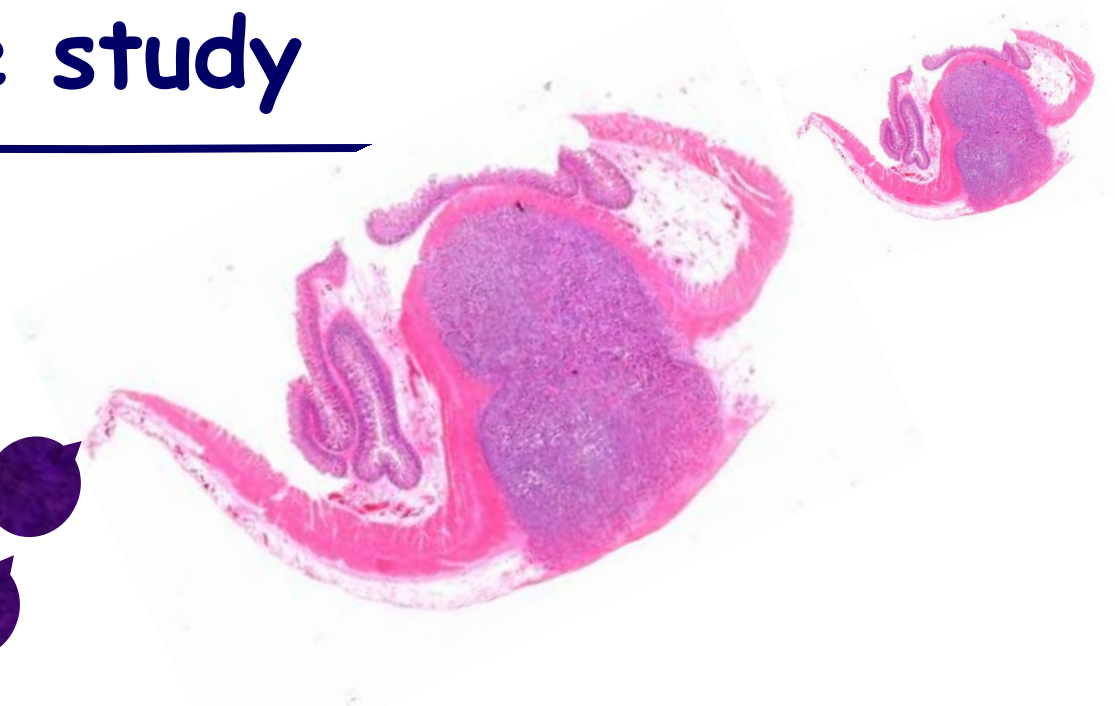


Displasia

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São uma doença de órgão...
Doença de Órgão...
vs
Do sistema neuroendócrino
difuso...
Do sistema neuroendócrino
difuso...

NET como case study

