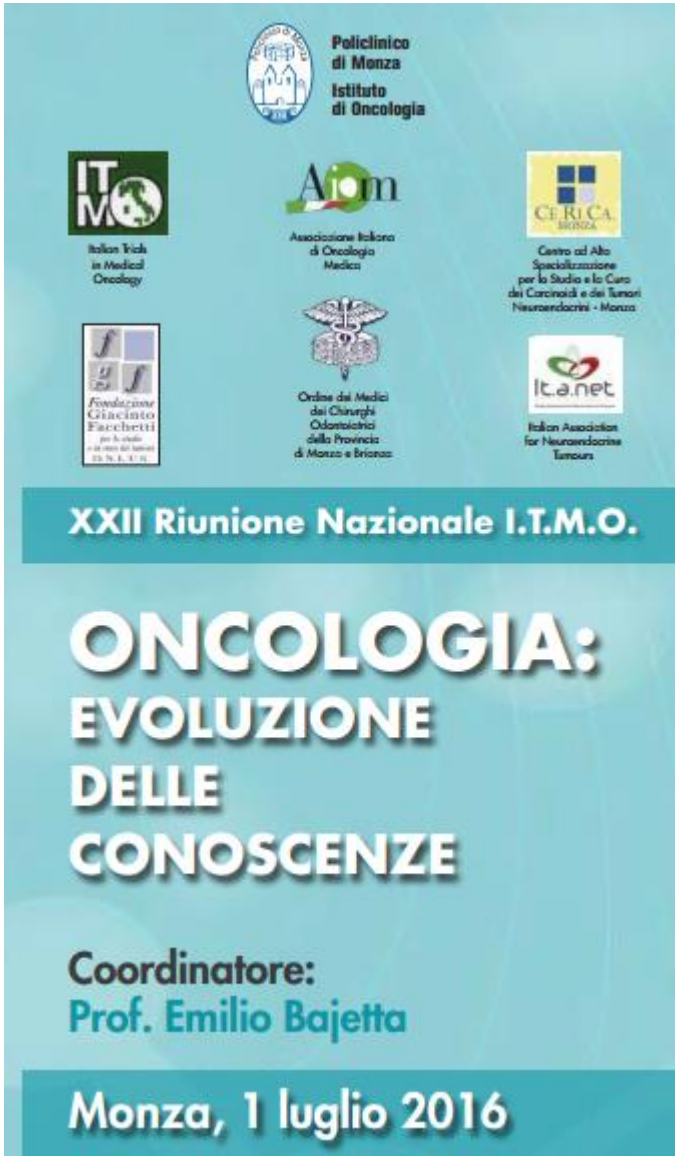


Le classificazioni di F. Bosman e W. Travis

ZONE GRIGIE

Stefano La Rosa

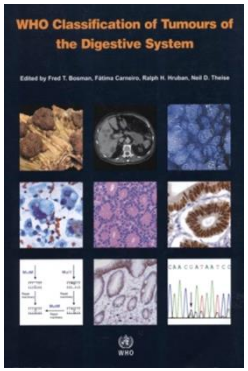
Anatomia Patologica, Ospedale di Circolo, Varese

WHO 2010 of digestive neoplasms

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	1. Well-differentiated endocrine tumour (WDET)[a]	1. NET G1 (carcinoid)[b]
	2. Well-differentiated endocrine carcinoma (WDEC)[a]	2. NET G2[b]
	3. Poorly differentiated endocrine carcinoma/small cell carcinoma (PDEC)	3. NEC (large cell or small cell type)[c]
II Mucocarcinoid III Mixed forms carcinoid-adenocarcinoma	4. Mixed exocrine-endocrine carcinoma (MEEC)	4. Mixed adenoneuroendocrine carcinoma (MANEC)
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.



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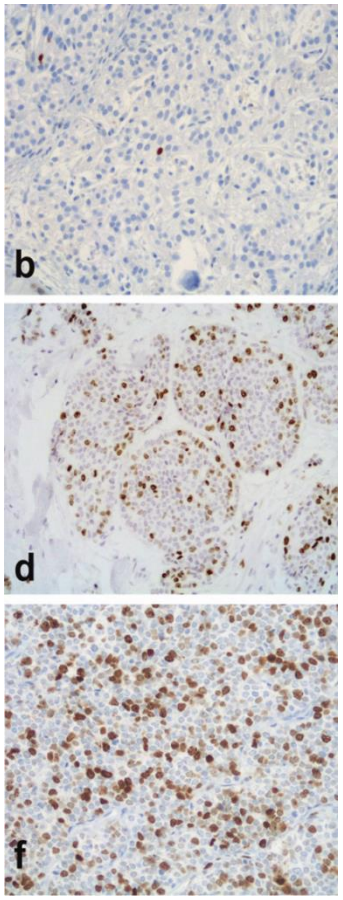
Tumore Neuroendocrino (NeuroEndocrine Tumor – NET)



G1

G2

G3

Grading

	Mitoses	Ki67 index
G1	m<2	Ki67<3%
G2	2< m <20	3%≤ Ki67≤20%
G3	m >20	Ki67 >20%

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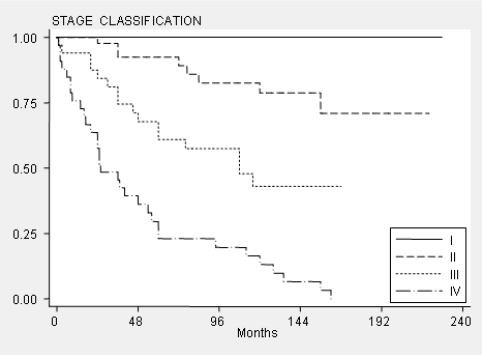
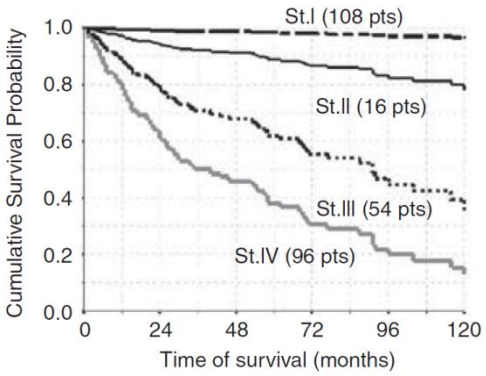
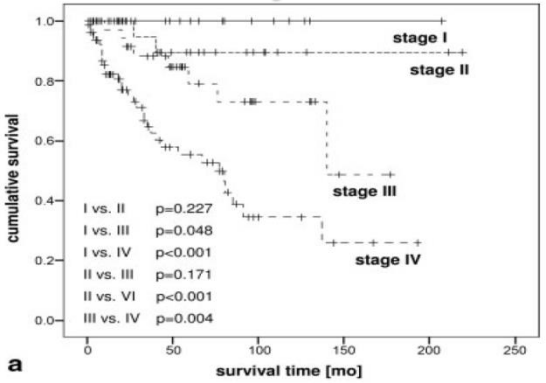
ENETS TNM staging and survival

Pancreas

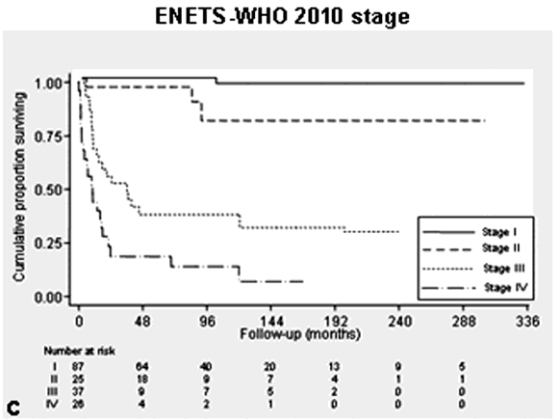




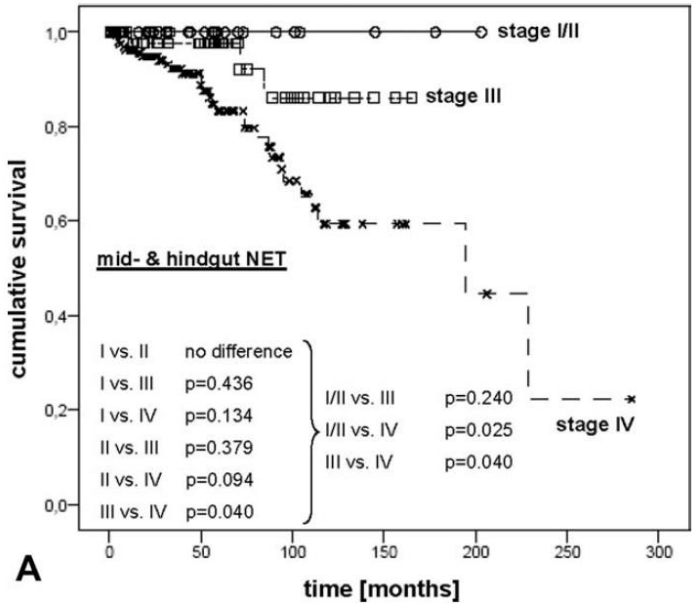
GEP system



Stomach



Midgut-hindgut



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Virchows Arch (2006) 449:395–401
DOI 10.1007/s00428-006-0250-1

ORIGINAL ARTICLE

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

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

Received: 11 April 2006 / Accepted: 6 June 2006 / Published online: 12 September 2006
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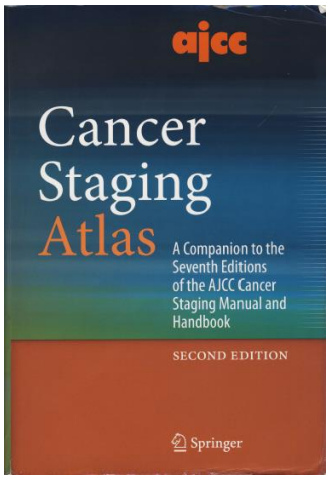
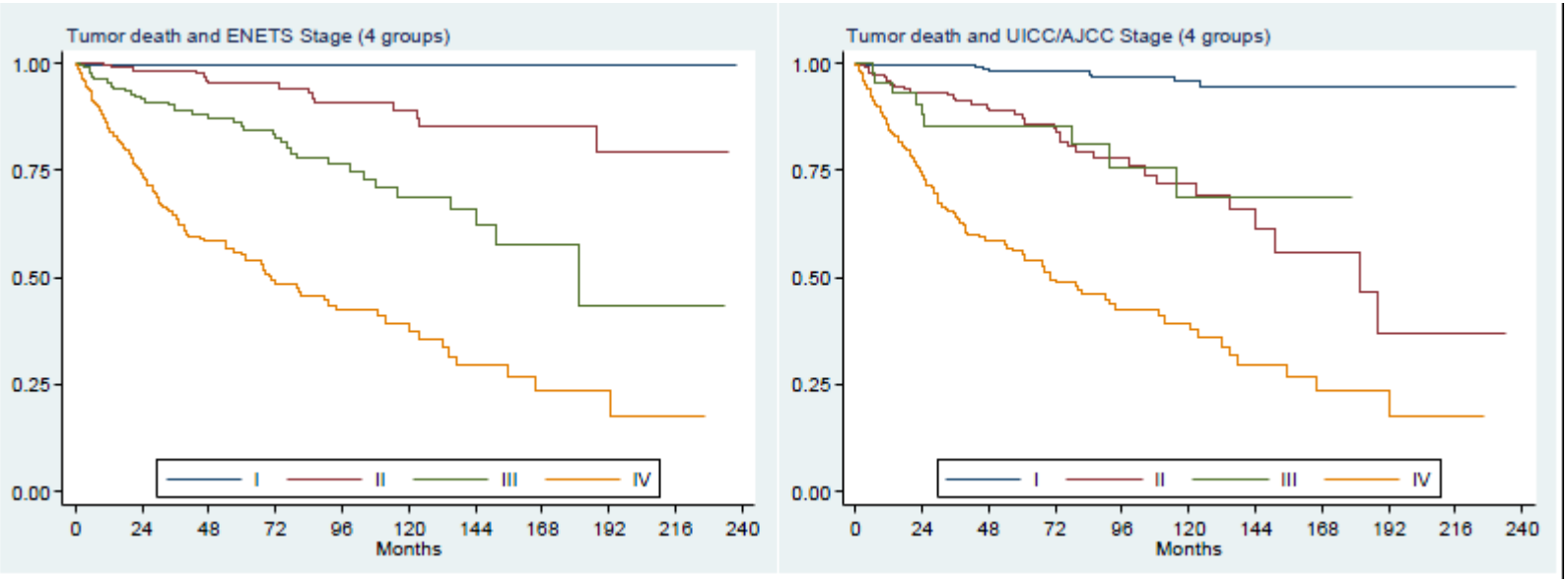


J Natl Cancer Inst 2012

ARTICLE

TNM Staging of Neoplasms of the Endocrine Pancreas: Results From a Large International Cohort Study

G. Rindi, M. Falconi, C. Klersy, L. Albarello, L. Boninsegna, M. W. Buchler, C. Capella, M. Caplin, A. Couvelard, C. Doglioni, G. Delle Fave, L. Fischer, G. Fusai, W. W. de Herder, H. Jann, P. Komminoth, R. R. de Krijger, S. La Rosa, T. V. Luong, U. Pape, A. Perren, P. Ruszniewski, A. Scarpa, A. Schmitt, E. Solcia, B. Wiedenmann



Dept. of Pathology, Ospedale di Circolo, Varese, Italy

Virchows Arch (2006) 449:395–401
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ORIGINAL ARTICLE

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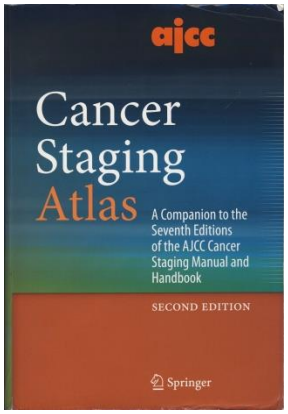


Table 1 Proposal for a TNM classification and disease staging for gastric endocrine tumors

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

TNM Clinical Classification-Stomach

T – Primary Tumour

TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoid in situ/dysplasia (tumour less than 0.5 mm, confined to mucosa)
T1	Tumour confined to mucosa and 0.5 mm or more but no greater than 1 cm in size; or invades submucosa and is no greater than 1 cm in greatest dimension
T2	Tumour invades muscularis propria or is more than 1 cm in greatest dimension
T3	Tumour invades subserosa
T4	Tumour perforates visceral peritoneum (serosa) or other organs or adjacent structures

Note: For any T, add (m) for multiple tumours.

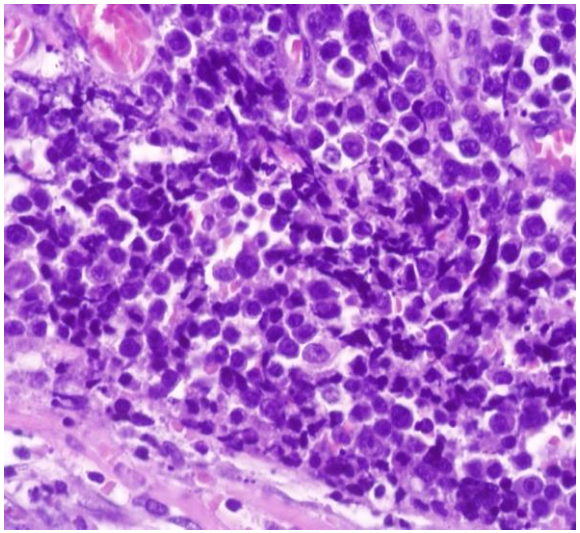
N – Regional Lymph Nodes

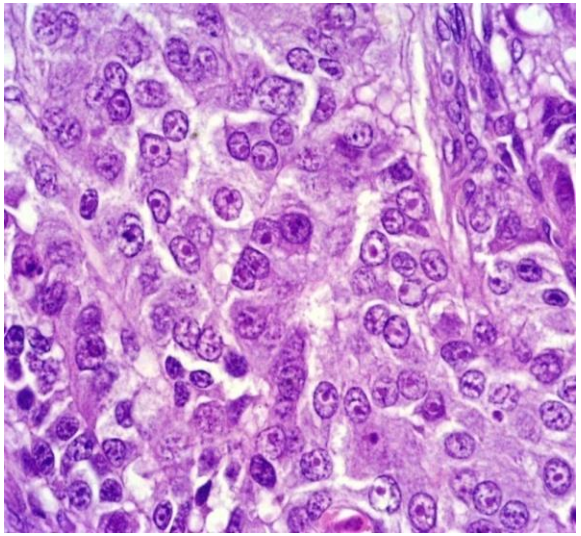
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

M – Distant Metastasis

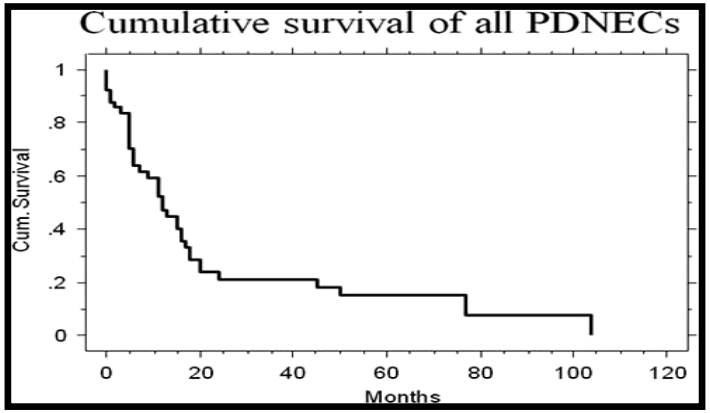
M0	No distant metastasis
M1	Distant metastasis

Carcinoma neuroendocrino (NeuroEndocrine Carcinoma – NEC)





	Mitoses	Ki67 index
G1	m<2	Ki67<3%
G2	2< m <20	3%≤ Ki67≤20%
G3	m >20	Ki67 >20%



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Proliferation and differentiation

J Gastroenterol
DOI 10.1007/s00535-014-0987-2

ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

The Japanese Society of Gastroenterology

Does the WHO 2010 classification of pancreatic neuroendocrine neoplasms accurately characterize pancreatic neuroendocrine carcinomas?

Susumu Hijioka · Waki Hosoda · Nobumasa Mizuno · Kazuo Hara · Hiroshi Imaoka · Vikram Bhatia · Mohamed A. Mekky · Masahiro Tajika · Tsutomu Tanaka · Makoto Ishihara · Tatsuji Yogi · Hideharu Tsutumi · Toshihisa Fujiyoshi · Takamitsu Sato · Nobuhiro Hieda · Tsukasa Yoshida · Nozomi Okuno · Yasuhiro Shimizu · Yasushi Yatabe · Yasumasa Niwa · Kenji Yamao

The High-grade (WHO G3) Pancreatic Neuroendocrine Tumor Category Is Morphologically and Biologically Heterogenous and Includes Both Well Differentiated and Poorly Differentiated Neoplasms

Olca Basturk, MD,* Zhaohai Yang, MD, PhD,† Laura H. Tang, MD, PhD,* Ralph H. Hruban, MD,‡ Volkan Adsay, MD,§ Chad M. McCall, MD,‡ Alyssa M. Krasinskas, MD,§ Kee-Taek Jang, MD,‖ Wendy L. Frankel, MD,¶ Serdar Balci, MD,§ Carlie Sigel, MD,* and David S. Klimstra, MD*

(Am J Surg Pathol 2015;39:683–690)

Research

M Heetfeld et al. | Characteristics and treatment of gastroenteropancreatic G3 NEN

Characteristics and treatment of patients with G3 gastroenteropancreatic neuroendocrine neoplasms

M Heetfeld, C N Chougnet[1], I ... M Pavel, D O'Toole[7], T Walte... G Crespo[5], J Barriuso[6], ... Network members'

F-L Vélayoudom-Céphise et al. | Features of grade 3 ENETS neuroendocrine tumors

Are G3 ENETS neuroendocrine neoplasms heterogeneous?

Fritz-Line Vélayoudom-Céphise[1], Pierre Duvillard[2], Lydia Foucan[3], Julien Hadoux[1], Cecile N Chougnet[1], Sophie Leboulleux[1], David Malka[4], Joël Guigay[5,6], Diane Goere[6], Thierry Debaere[7], Caroline Caramella[7], Martin Schlumberger[1], David Planchard[5,6], Dominique Elias[6], Michel Ducreux[1,6], Jean-Yves Scoazec[3], ... c Baudin[1]

Endocrine-Related Cancer (2013) 20, 649–657

Neuro-endocrinology

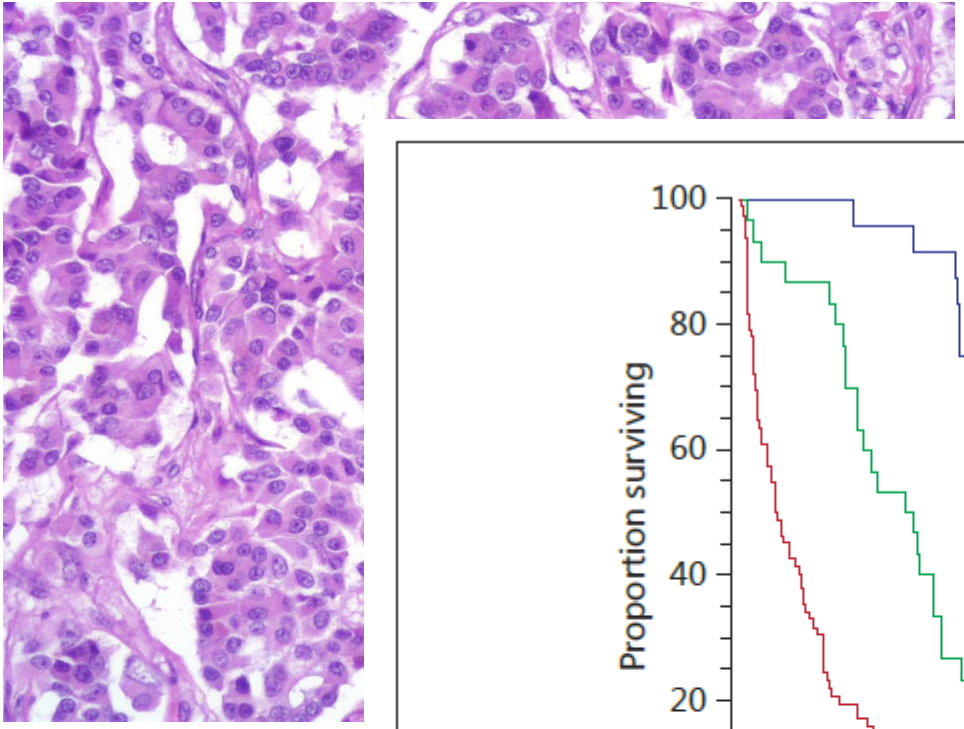
Original Paper

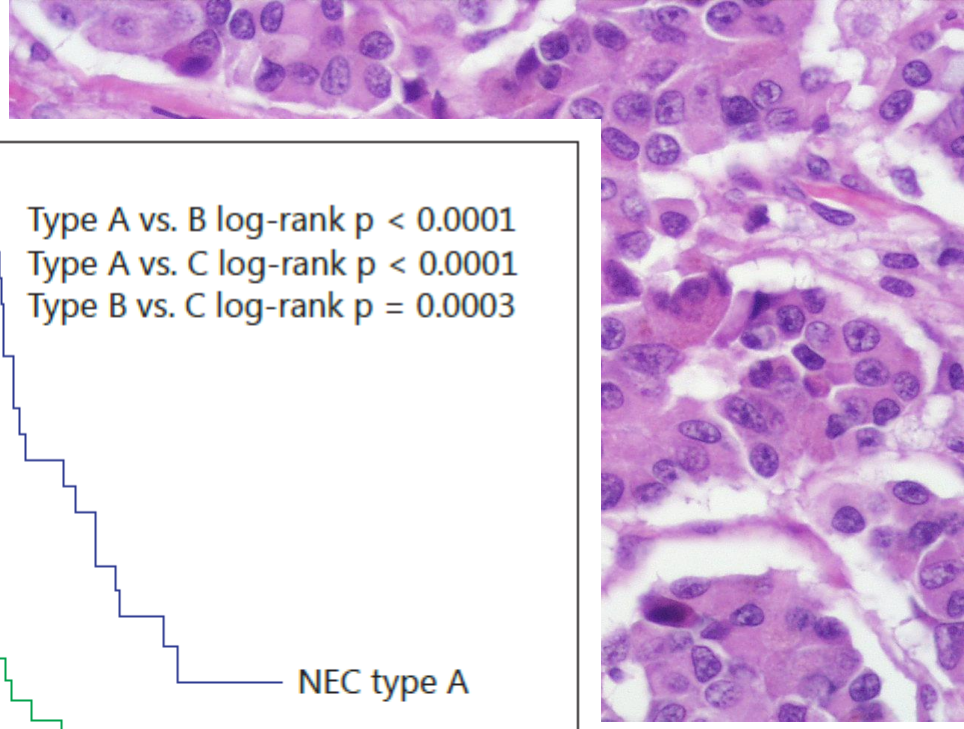
Neuroendocrinology
DOI: 10.1159/000445165

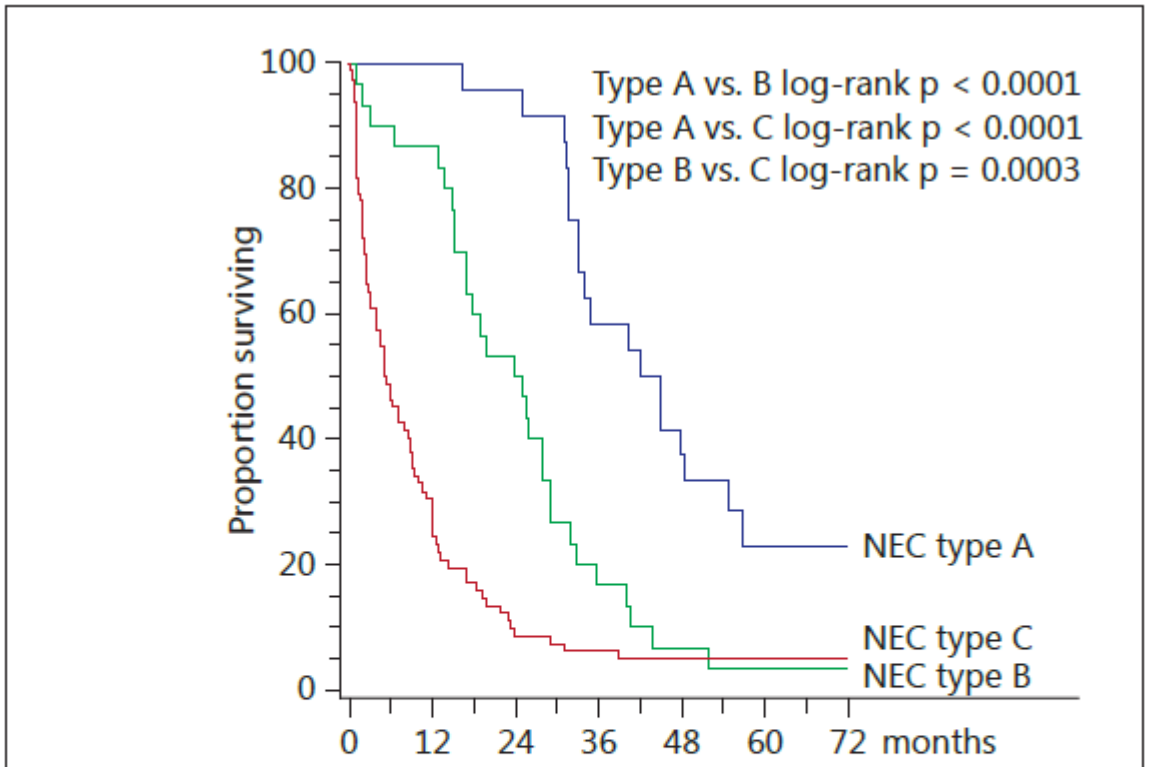
Received: November 11, 2015
Accepted after revision: March 2, 2016
Published online: March 5, 2016

The Clinicopathologic Heterogeneity of Grade 3 Gastroenteropancreatic Neuroendocrine Neoplasms: Morphological Differentiation and Proliferation Identify Different Prognostic Categories

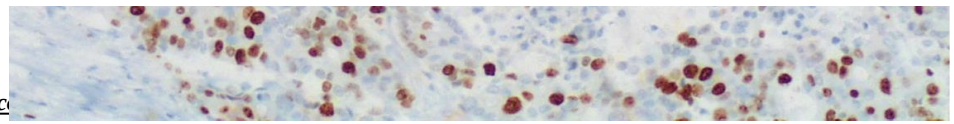
Massimo Milione[a] Patrick Maisonneuve[c] Francesca Spada[d] Alessio Pellegrinelli[a] Paola Spaggiari[f] Luca Albarello[g] Eleonora Pisa[e] Massimo Barberis[e] Alessandro Vanoli[h] Roberto Buzzoni[b] Sara Pusceddu[b] Laura Concas[b] Fausto Sessa[i] Enrico Solcia[h] Carlo Capella[i] Nicola Fazio[d] Stefano La Rosa[j]







Patients at risk (n)							
Type A	24	24	23	14	9	4	3
Type B	30	26	16	5	2	1	1
Type C	82	25	7	5	4	4	4
OS (%)							
Type A	100	100	96	58	38	23	23
Type B	100	87	53	17	7	3	3
Type C	100	31	9	6	5	5	5



Novità

World Health Organization Classification 2017 for Pancreatic Neuroendocrine Neoplasms

Well differentiated NENs	**Ki67index*|**		**Mitotic index**	
Neuroendocrine tumour (NET) G1	<3	%	<2/10	HPF
Neuroendocrine tumour (NET) G2	3-20	%	2-20/10	HPF
Neuroendocrine tumour (NET) G3	>20	%	>20/10	HPF
Poorly differentiated NENs				
Neuroendocrine carcinoma (NEC) G3	>20	%	>20/10	HPF
Small cell type				
Large cell type				

Mixed neuroendocrine-nonneuroendocrine neoplasm (MiNEN)

Novità

PanNEN

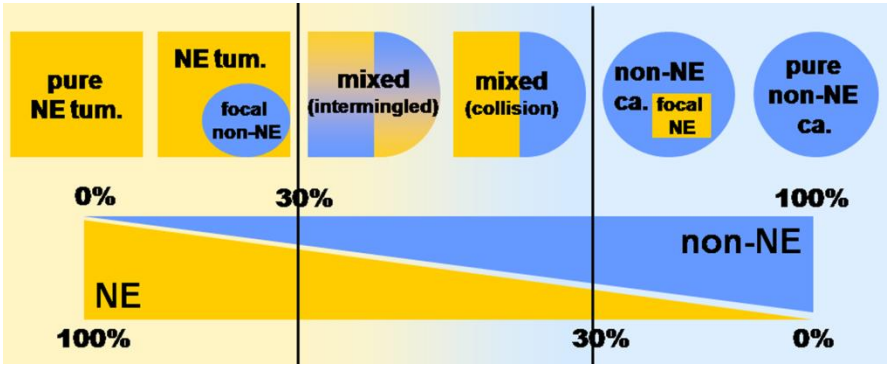
WHO 1980	WHO 2000/2004	WHO 2010
Islet cell tumour	Well-differentiated endocrine tumour/carcinoma (WDET; WDEC)	Neuroendocrine tumour NET G1/G2
Poorly differentiated endocrine carcinoma	Poorly differentiated endocrine carcinoma/small cell carcinoma (PDEC)	Neuroendocrine carcinoma NEC G3 large or small cell type
	Mixed exocrine-endocrine carcinoma (MEEC)	Mixed adenoneuroendocrine carcinoma (MANEC)
Pseudotumour lesions	Tumour-like lesions (TLL)	Hyperplastic and preneoplastic lesions

Novità

PanNEN

WHO 1980	WHO 2000/2004	WHO 2010	WHO 2017
Islet cell tumour	Well-differentiated endocrine tumour/carcinoma (WDET; WDEC)	Neuroendocrine tumour NET G1/G2	Neuroendocrine tumour **NET G1/G2/G3** (Well differentiated neuroendocrine neoplasm)
Poorly differentiated endocrine carcinoma	Poorly differentiated endocrine carcinoma/small cell carcinoma (PDEC)	Neuroendocrine carcinoma NEC G3 large or small cell type	Neuroendocrine carcinoma **NEC G3** (Poorly differentiated neuroendocrine neoplasm), large or small cell type
	Mixed exocrine-endocrine carcinoma (MEEC)	Mixed adenoneuroendocrine carcinoma (MANEC)	Mixed neuroendocrine-nonneuroendocrine neoplasm (**MiNEN**)
Pseudotumour lesions	Tumour-like lesions (TLL)	Hyperplastic and preneoplastic lesions	

Mixed adenoneuroendocrine carcinoma (MANEC)



MANECs are a heterogeneous group of neoplasms

Exocrine component	Neuroendocrine component
1. Adenoma	1. NET G1
2. Adenocarcinoma	2. NET G2
3. Signet ring cell carcinoma	3. NET G3
4. Squamous cell carcinoma	4. NEC
5. Acinar cell carcinoma	

Dept. of Pathology, Ospedale di Circolo, Varese, Italy

Endocr Pathol
DOI 10.1007/s12022-016-9432-9

Mixed Neuroendocrine-Nonneuroendocrine Neoplasms (MiNENs): Unifying the Concept of a Heterogeneous Group of Neoplasms

Stefano La Rosa[1] · Fausto Sessa[2] · Silvia Uccella[2]

Mixed neuroendocrine-nonneuroendocrine neoplasms (MiNENs) of the digestive system
High-grade malignant
Tubular gut
Mixed adenoma/adenocarcinoma-NEC
Mixed squamous cell carcinoma-NEC
Pancreas
Mixed ductal adenocarcinoma-NEC[a]
Mixed acinar cell carcinoma-NEC[a]
Mixed acinar-ductal carcinoma-NEC[a]
Biliary system
Mixed adenocarcinoma-NEC[a]
Liver
Mixed hepatocellular carcinoma-NEC[a]
Mixed cholangiocarcinoma-NEC
Intermediate-grade malignant
Tubular gut
Mixed adenocarcinoma-G1/G2 NET[b]
Mixed signet ring cell carcinoma-G1/G2 NET[b]
Pancreas
Mixed intraductal papillary mucinous neoplasm-G1/G2 NET
Low-grade malignant
Tubular gut
Mixed adenoma-NET (MANET)

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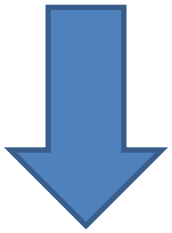
Mixed adenoneuroendocrine carcinoma (MANEC)



Mixed neuroendocrine-nonneuroendocrine neoplasm (MiNEN)

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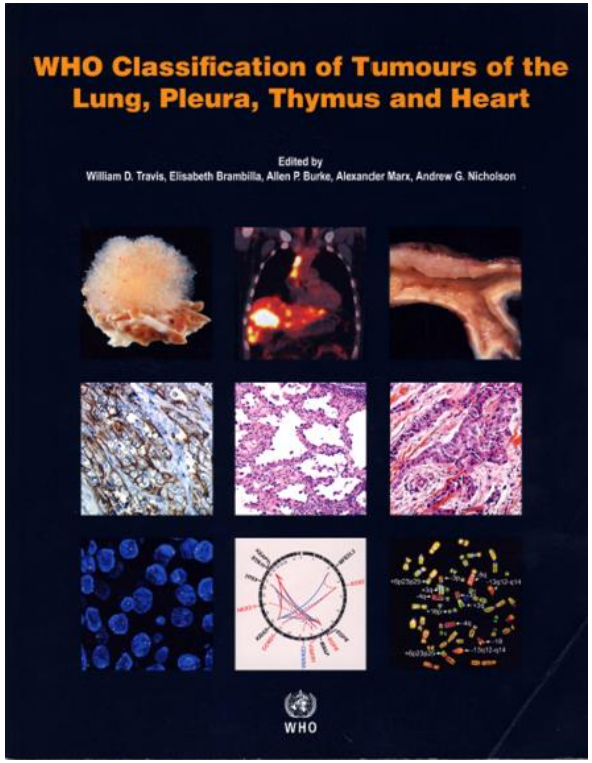


Table 1.16 Differential diagnosis of neuroendocrine tumours based on clinicopathological characteristics.

	Typical carcinoid	Atypical carcinoid	Large cell neuroendocrine carcinoma	Small cell lung carcinoma
Average age	Sixth decade	Sixth decade	Seventh decade	Seventh decade
Sex predominance	Female	Female	Male	Male
Smoking association	No	Variable*	Yes	Yes
Diagnostic criteria				
Mitoses per 2 mm^2	0–1	2–10	> 10 (median of 70)	> 10 (median of 80)
Necrosis	No	Focal, if any	Yes	Yes
Neuroendocrine morphology	Yes	Yes	Yes	Yes
Ki-67 proliferation index	Up to 5%	Up to 20%	40–80%	50–100%
TTF1 expression	Mostly negative	Mostly negative	Positive 50%	Positive 85%
Synaptophysin / chromogranin	Positive	Positive	Positive 80–90%	Positive 80–90%
CD56	Positive	Positive	Positive 80–90%	Positive 80–90%
Combined with a non-small cell lung carcinoma component	No	No	Sometimes	Sometimes

* The majority of carcinoid patients are never-smokers or light smokers, although atypical carcinoid is more associated with current or former smokers than typical carcinoid patients.

Table 1.17 Criteria for diagnosis of neuroendocrine tumours. Reprinted from Travis WD et al. (2678)

Typical carcinoid
A tumour with carcinoid morphology and < 2 mitoses per 2 mm^2, lacking necrosis, and ≥ 0.5 cm

Atypical carcinoid
A tumour with carcinoid morphology and 2–10 mitoses per 2 mm^2 and/or necrosis (often punctuate) or both

Large cell neuroendocrine carcinoma
1. A tumour with a neuroendocrine morphology (organoid nesting, palisading, rosettes, trabeculae)
2. High mitotic rate: > 10 mitoses per 2 mm^2, median of 70 mitoses per 2 mm^2
3. Necrosis (often in large zones)
4. Cytological features of a non-small cell carcinoma: large cell size, low nuclear-to-cytoplasmic ratio, vesicular, coarse or fine chromatin, and/or frequent nucleoli; some tumours have fine nuclear chromatin and lack nucleoli, but qualify as non-small cell lung carcinoma because of large cell size and abundant cytoplasm
5. Positive immunohistochemical staining for one or more neuroendocrine markers (other than neuron-specific enolase) and/or neuroendocrine granules by electron microscopy.

Small cell carcinoma
Small size (generally less than the diameter of 3 small resting lymphocytes)
1. Scant cytoplasm
2. Nuclei: finely granular nuclear chromatin, absent or faint nucleoli
3. High mitotic rate: > 10 mitoses per 2 mm^2, median of 80 mitoses per 2 mm^2
4. Frequent necrosis (often in large zones)

Ki-67 Antigen in Lung Neuroendocrine Tumors

Unraveling a Role in Clinical Practice

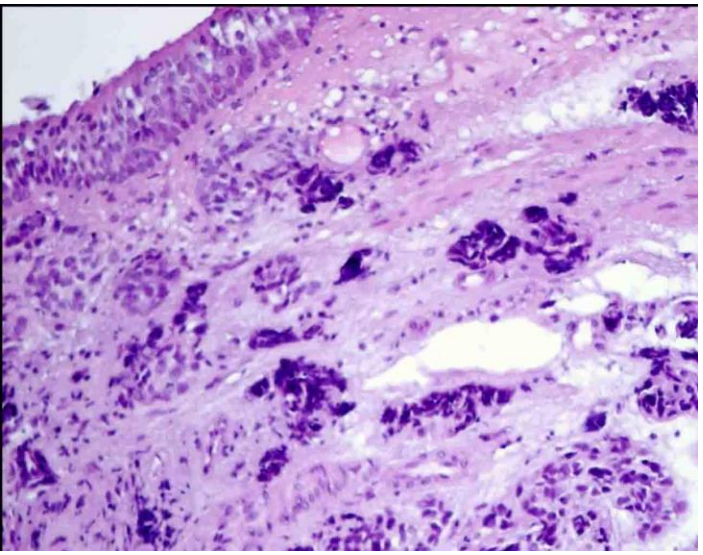
Giuseppe Pelosi, MD, MIAC,† Guido Rindi, MD, PhD,‡ William D. Travis, MD,§ and Mauro Papotti, MD‖*

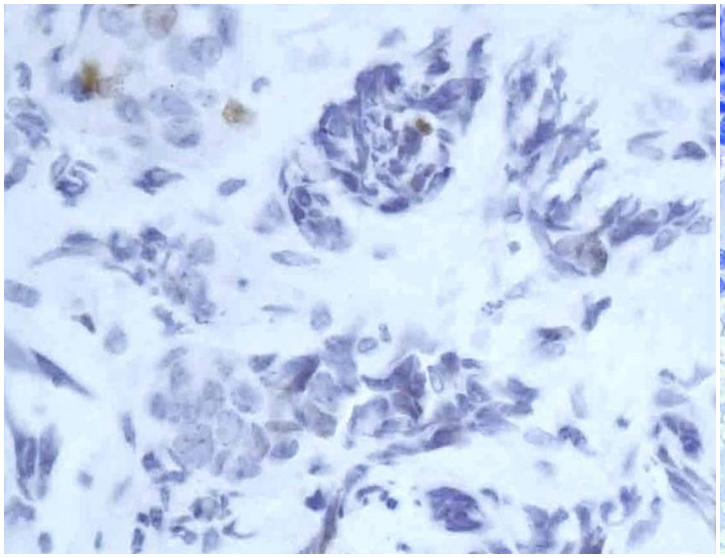
Dept. of Pathology, Ospedale di Circolo, Varese, Italy

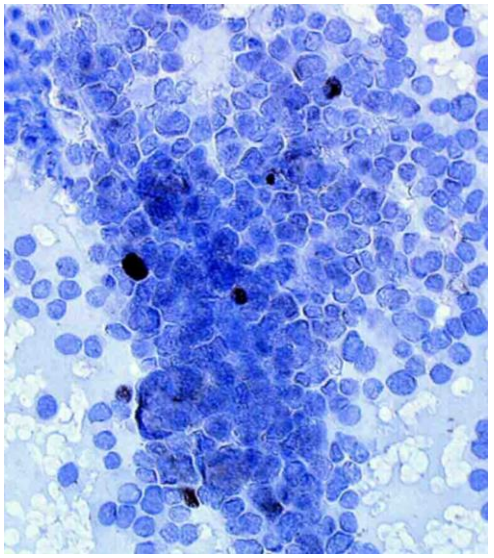
H&E

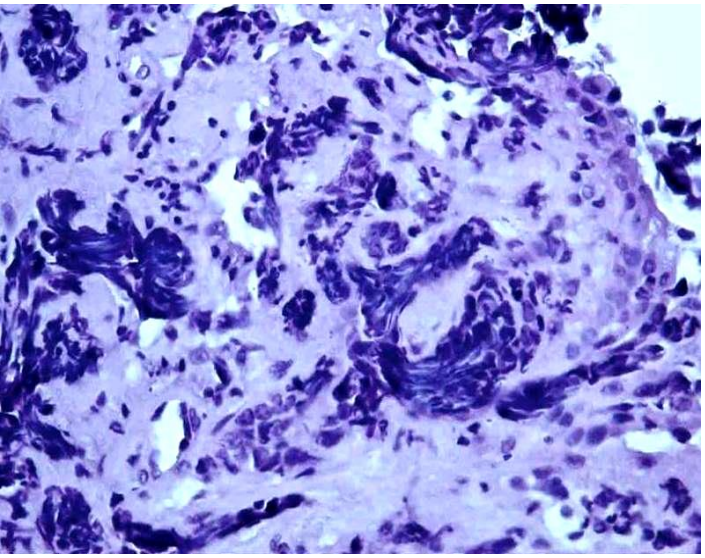
Ki67-histology

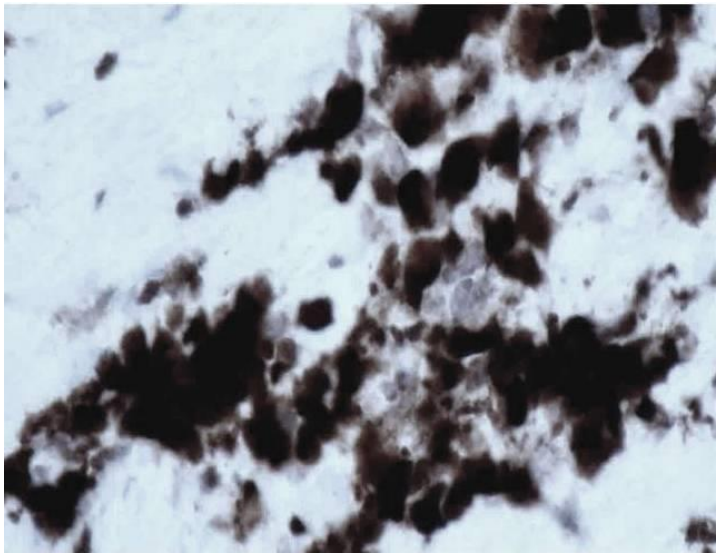
Ki67-cytology

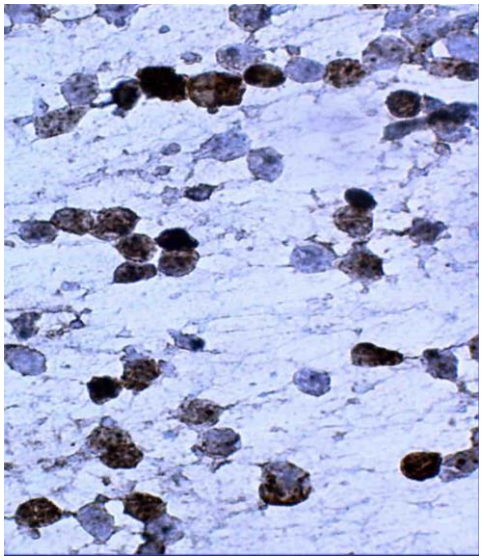












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