

NEN PRECEPTORSHIP

LA PRATICA CLINICA NELLE NEOPLASIE NEUROENDOCRINE

5/6 Aprile 2018 | IEO, Istituto Europeo di Oncologia - Milano

NEN  **Preceptorship**

 **IEO**
Istituto Europeo di Oncologia





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Terminologia, classificazione,
requisiti essenziali del referto patologico

Massimo Milione

MD, PhD

Anatomia Patologica 1

Dipartimento di Patologia e Diagnostica di Laboratorio

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Milano

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Outline

✓ **Materiali**

✓ **Terminologia e Classificazione**



Outline

✓ **Materiali**

✓ Terminologia e Classificazione



Milione M, Milano-IEO, 5 Aprile 2018

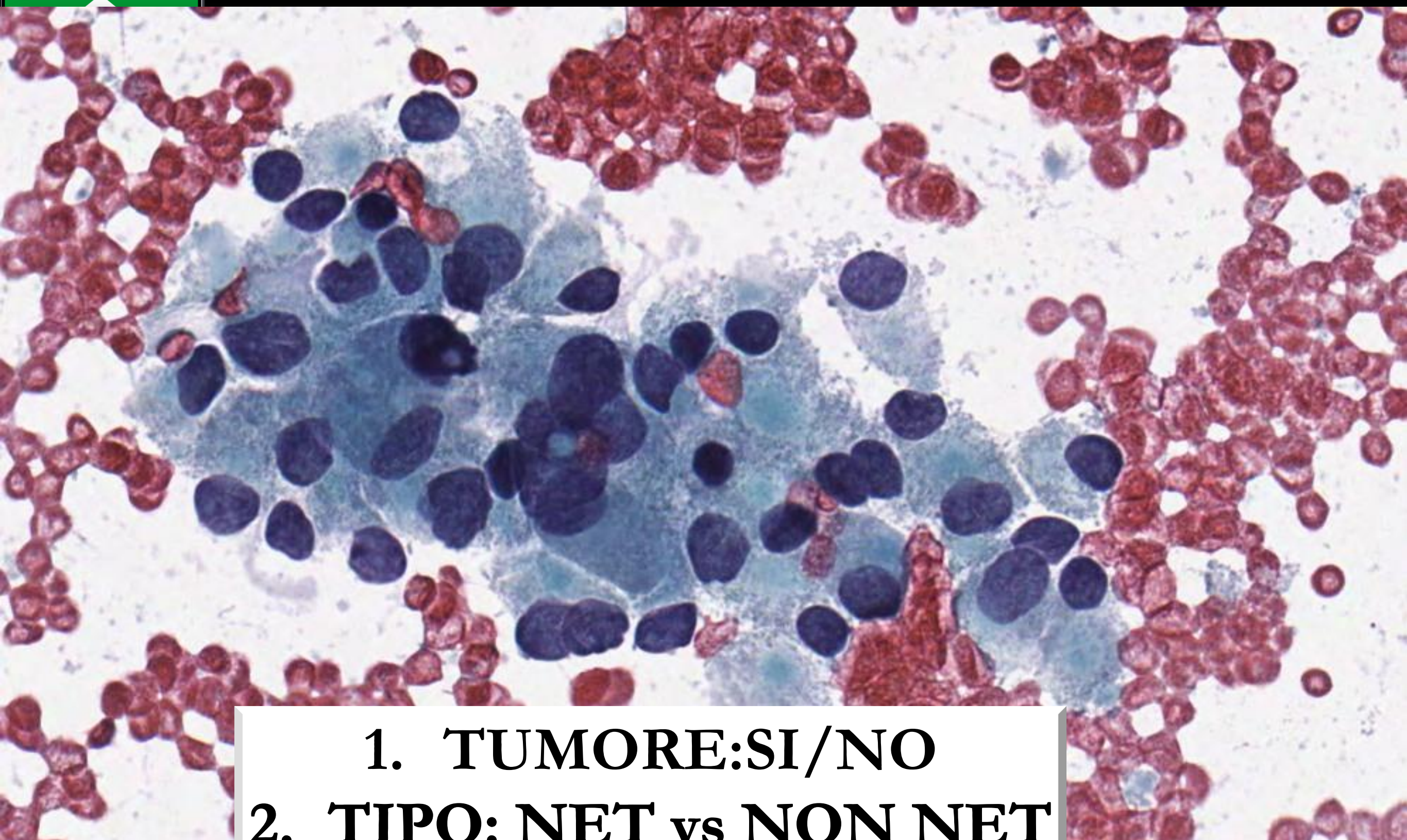
A conceptual image showing a person in a blue suit walking away from the viewer on a paved road that splits into two paths. The paths lead into a vast green field under a blue sky with large white clouds. The word 'citologia' is written in red above the left path, and 'istologia' is written in black above the right path.

citologia

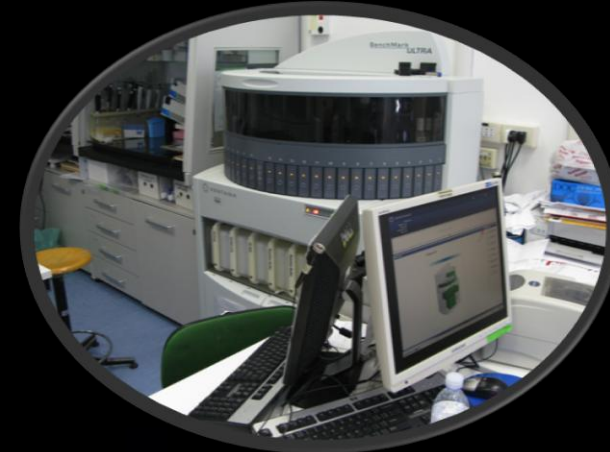
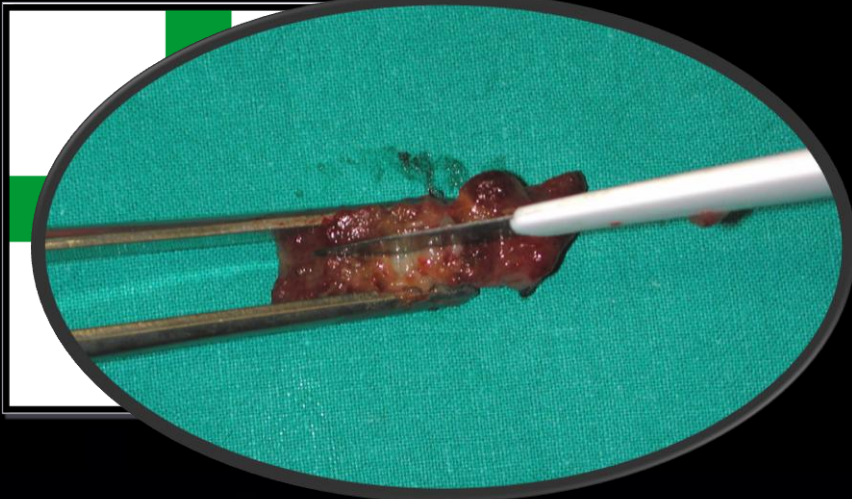
istologia



Citologico PURO



1. TUMORE:SI/NO
2. TIPO: NET vs NON NET



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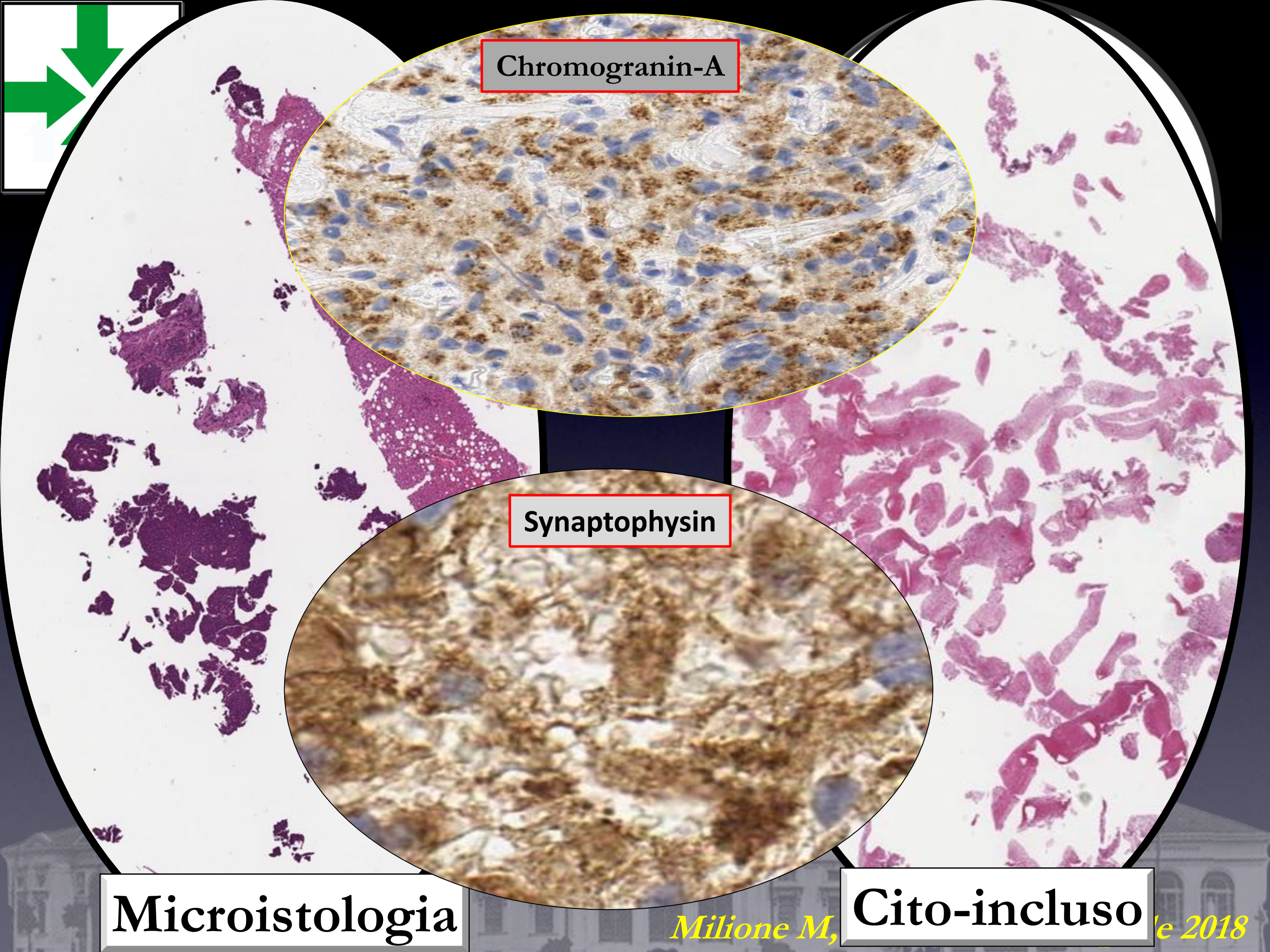
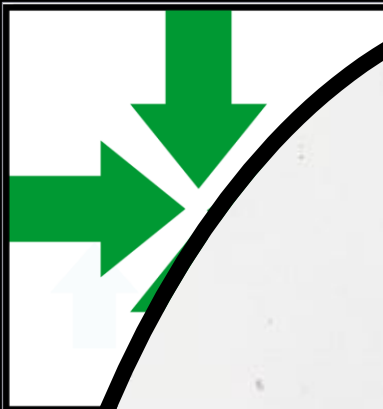
Istologico PURO



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Milione M, Milano-IEO, 5 Aprile 2018





Mucosa

Tumore



Outline

✓ Materials

✓ Terminologia e Classificazione



1980

**WDNET:WELL
DIFFERENTIATED
NEUROENDOCRINE
TUMORS**



2000

**PDNEC:POORLY
DIFFERENTIATED
NEUROENDOCRINE
CARCINOMAS**



2010



2017



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

WHO 2010
1. NET G1 (carcinoid) ^b
2. NET G2 ^b
3. NEC (large cell or small cell type) ^{b,c}

Buona Prognosi

Cattiva Prognosi

NET G1
NET G2

NEC

...a piccole
cellule
....a grandi
cellule



Tumore Neuroendocrino Ben Differenziato

NET G1

FIN

ISH

NET G1

$\frac{\text{N}^\circ \text{ di nuclei positivi}}{2000 \text{ nuclei Totali}} \% = \text{Valore di Ki67}$

$\text{Ki67} = 0,3\% \longrightarrow \text{NET G1}$

Mib-1/Ki-67

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Tumore Neuroendocrino Ben Differenziato



$\frac{\text{N}^\circ \text{ di nuclei positivi}}{2000 \text{ nuclei Totali}} \% = \text{Valore di Ki67}$

2/3%

5%

8%

10%

15%

20%

Ki67 = 18% → NET G2

Ca m Neuroendocrino Scarsamente Differenziato



NEC

N° di nuclei positivi % = Valore di Ki67

Oncologo?



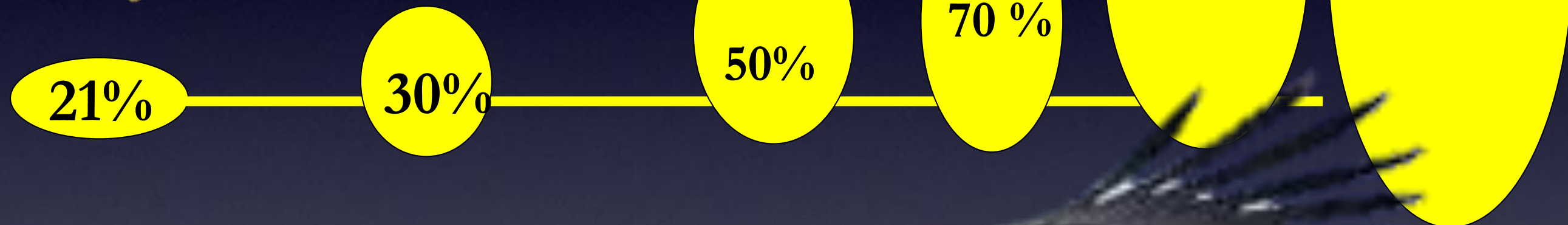
Ki67 = 80% → NEC

Mib-1/Ki-i67

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NEC



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Table 6.01 2017 WHO classification and grading of pancreatic neuroendocrine neoplasms (PanNENs)

	Ki-67 proliferation index ^a	
Well-differentiated pancreatic neuroendocrine tumours		
PanNET G1	< 1%	NET G1
PanNET G2	1–20%	
PanNET G3	> 20%	

NET G3

NET G2

NET G1

Poorly differentiated PanNENs: pancreatic neuroendocrine carcinomas (PanNECs)

PanNEC (G3)

> 20%

Small cell type

Large cell type

Mixed neuroendocrine and non-neuroendocrine neoplasm

^a The Ki-67 proliferation index is determined on the evaluation of ≥ 500 cells in areas of higher tumour cellularity (so-called hotspots). The Ki-67 index is based on the evaluation of mitoses in 50 high-power fields (HPF; 0.2 mm^2 each) in areas of higher tumour cellularity and is expressed as mitoses per 10 high-power fields (HPF). The final grade is determined by the highest index (Ki-67 or mitotic) places the tumour in the highest grade category. For assessing Ki-67, casual visual estimation (eyeballing) is not recommended; manual counting using printed images is advocated (2267).

NEC

NEC

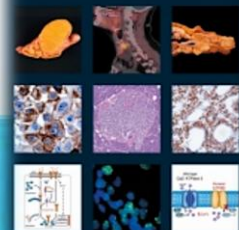


Table 6.01 2017 WHO classification and grading of pancreatic neuroendocrine neoplasms (PanNENs)

Classification/grade	Ki-67 proliferation index ^a	Mitotic index ^a
Well-differentiated PanNENs: pancreatic neuroendocrine tumours (PanNETs)		
PanNET G1	< 3%	< 2
PanNET G2	3–20%	2–20
PanNET G3	> 20%	> 20
Poorly differentiated PanNENs: pancreatic neuroendocrine carcinomas (PanNECs)		
PanNEC (G3)	> 20%	> 20
Small cell type		
Large cell type		
Mixed neuroendocrine–non-neuroendocrine neoplasm		

^a The Ki-67 proliferation index is based on the evaluation of ≥ 500 cells in areas of higher nuclear labelling (so-called hotspots). The mitotic index is based on the evaluation of mitoses in 50 high-power fields (HPF; 0.2 mm^2 each) in areas of higher density, and is expressed as mitoses per 10 high-power fields (2.0 mm^2). The final grade is determined based on whichever index (Ki-67 or mitotic) places the tumour in the highest grade category. For assessing Ki-67, casual visual estimation (eyeballing) is not recommended; manual counting using printed images is advocated (2267).



30% ADENO



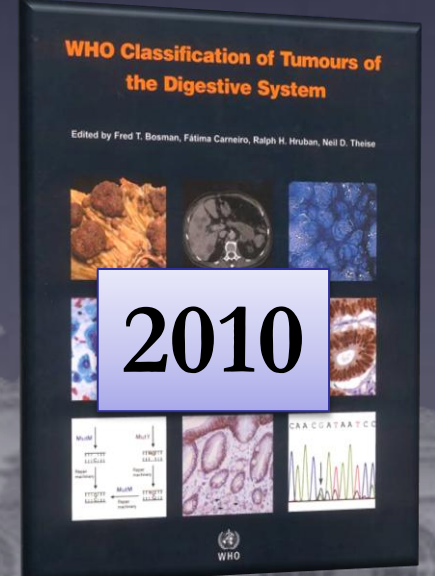
30% NEUROENDOCRINE
(CARCINOMA)



MANEC

ADENOCARCINOMA
ADENOMA

NEC G3





ADENOCARCINOMA

MANEC

Endocrine Carcinoma)

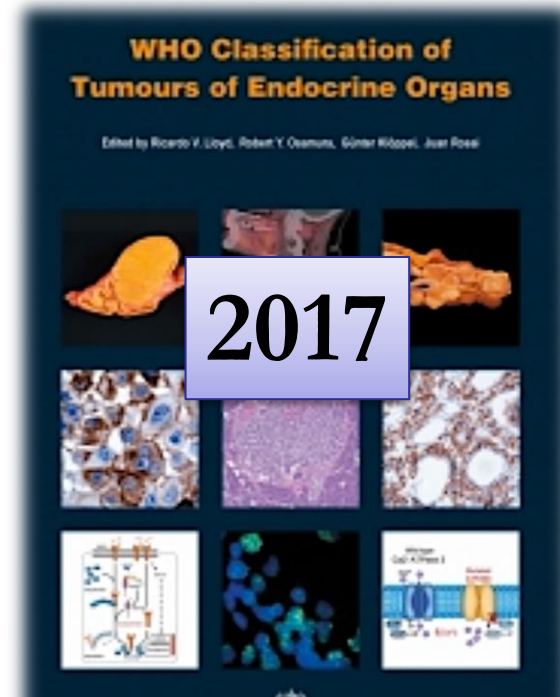


MiNEN

Endoc
DOI 10.

Mixed Neur
(MiNENs): Un
Group of Neoplas

Stefano La Rosa¹ • Fausto Sessa² • Silvia Uccella³



2017



TU
NON NE

NEUR



MANEC

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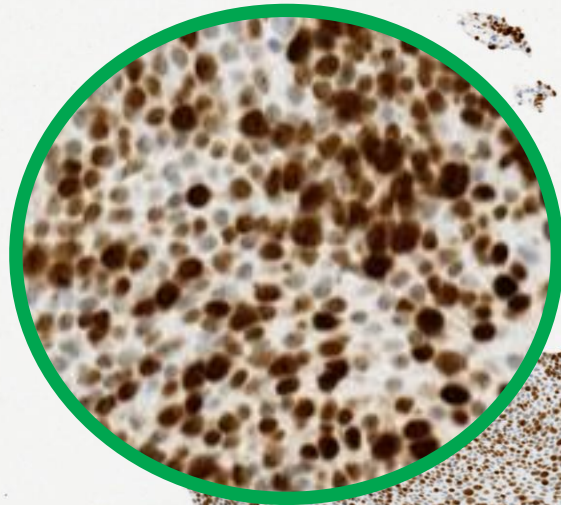


grazie

Massimo Milione

NO! SQUAMOUS!

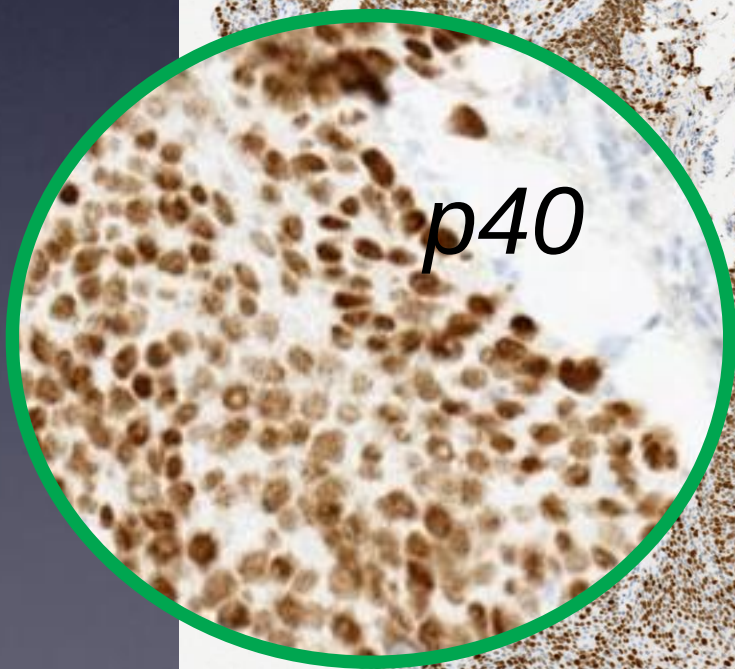
Mib-1

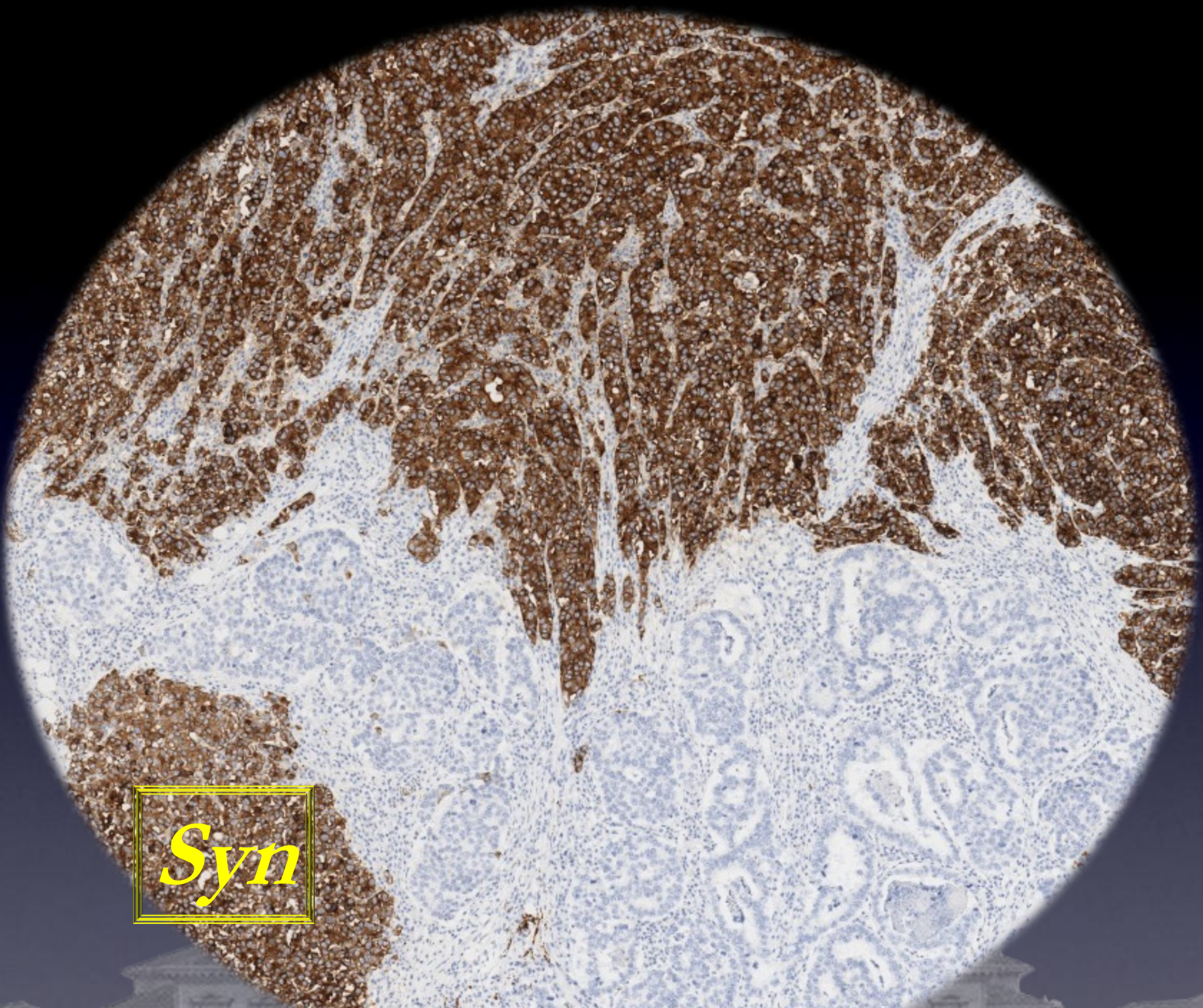


Syn



p40





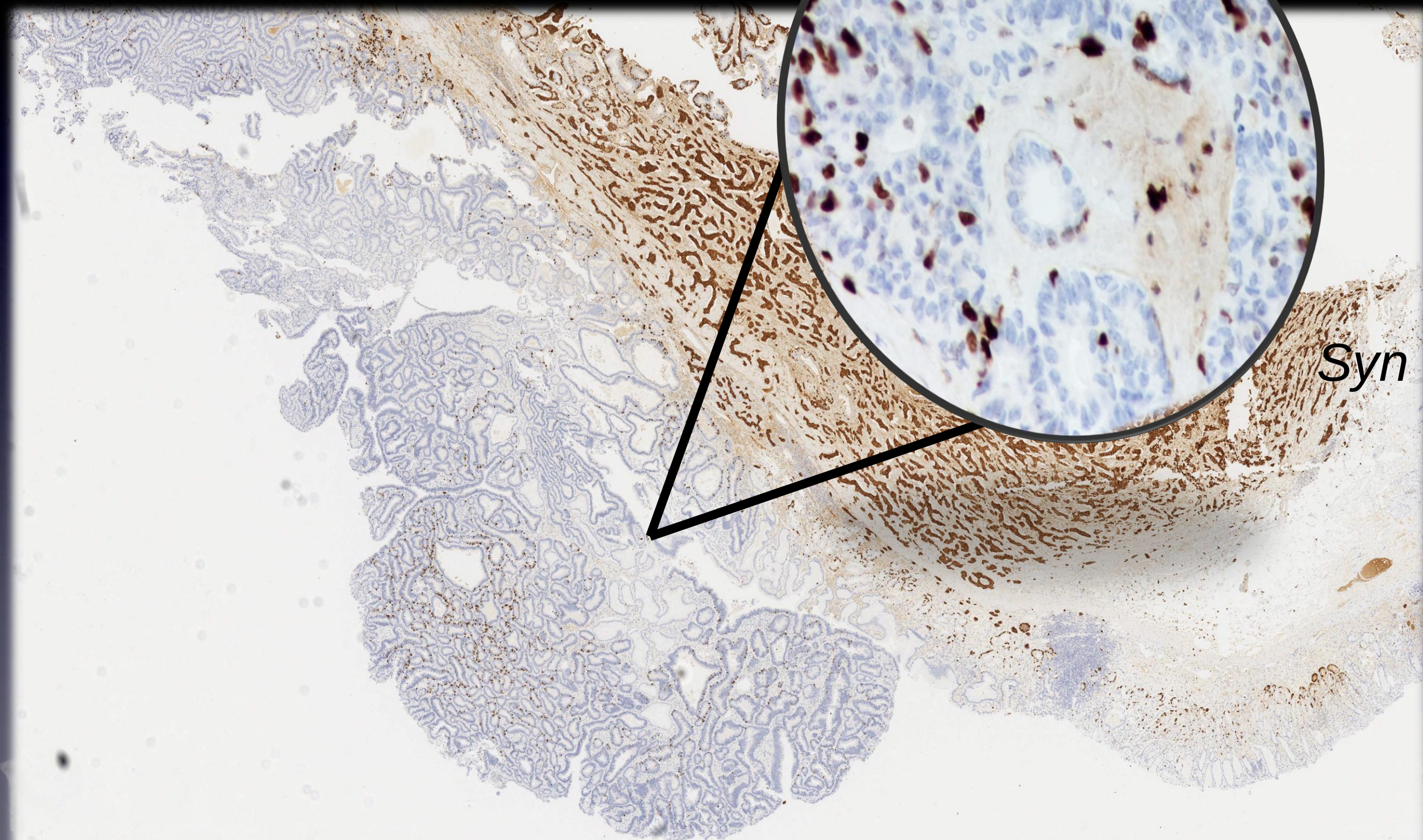
>
30%

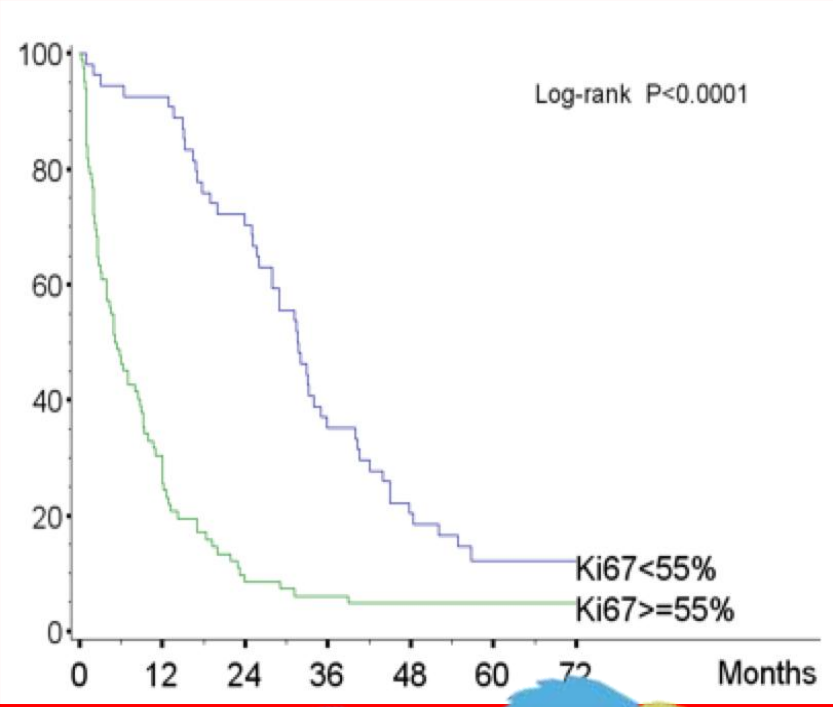
Syn

Adenocarcinoma + **NEC G3**

MILIONE M, MILANO-LEO, 3 Aprile 2018

MANET????





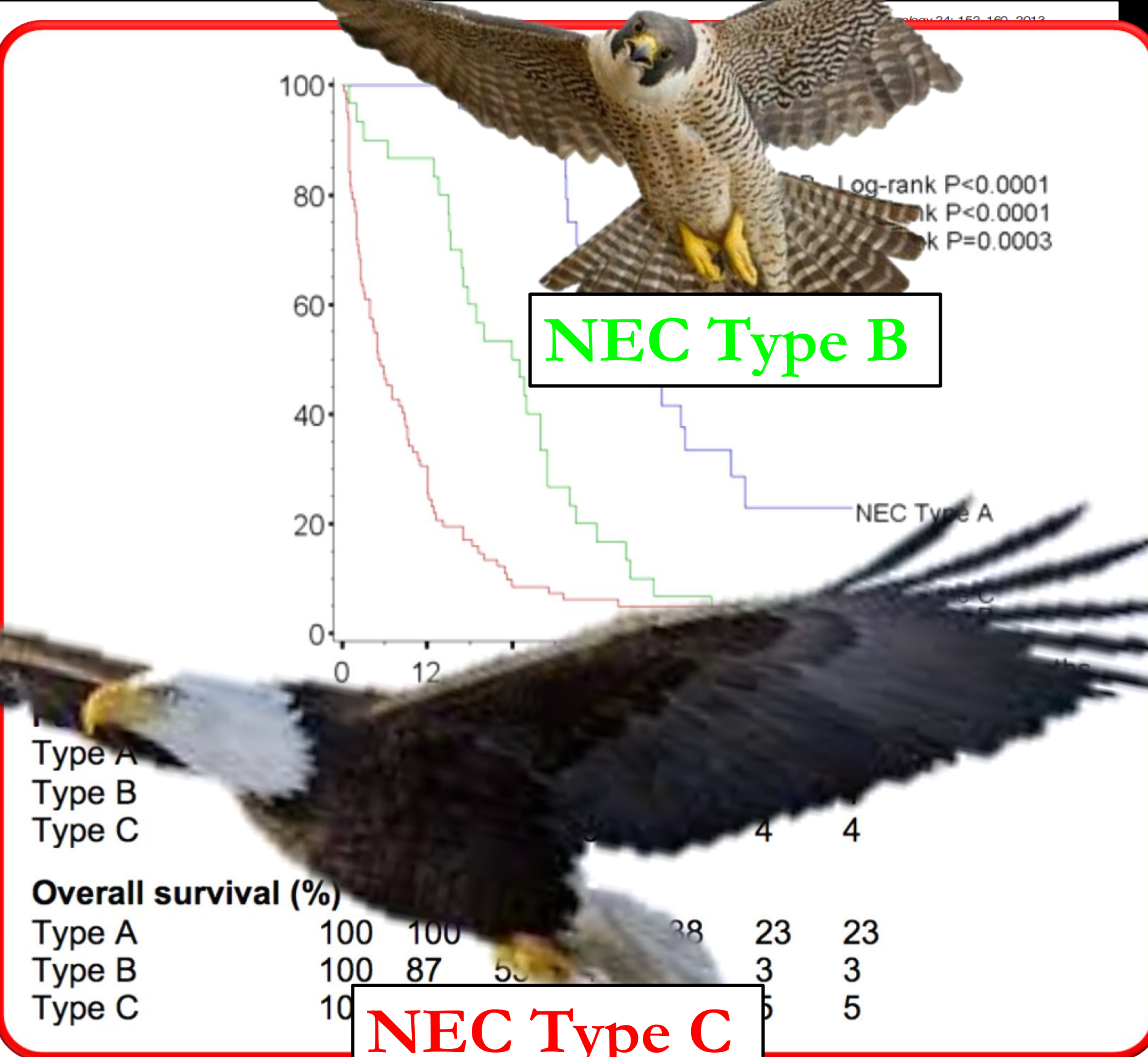
NET G3
(NEC Type A)

Neuro
endocrinology

The Clinicopatho Gastroenteropan Morphological Di Identify Different

Massimo Milione^a Patrick
Paola Spaggiari^f Luca Alba
Alessandro Vanoli^h Robert
Fausto Sessaⁱ Enrico Solcia

Type A (Ben Differenziato+Ki-67 21-55%)-MOS: 43,6
Type B (Scarsamente Differenziato+Ki-67 21-55%)-MOS: 24,5
Type C (Scarsamente Differenziato+Ki-67 >55%)-MOS: 5,3



NEC Type B

Type A
Type B
Type C

Overall survival (%)

Type A	100	100	38	23	23
Type B	100	87	53	3	3
Type C	100	10	5	5	5

NEC Type C

- **for treatment and reduced gastrointestinal G3): The NORDIC**

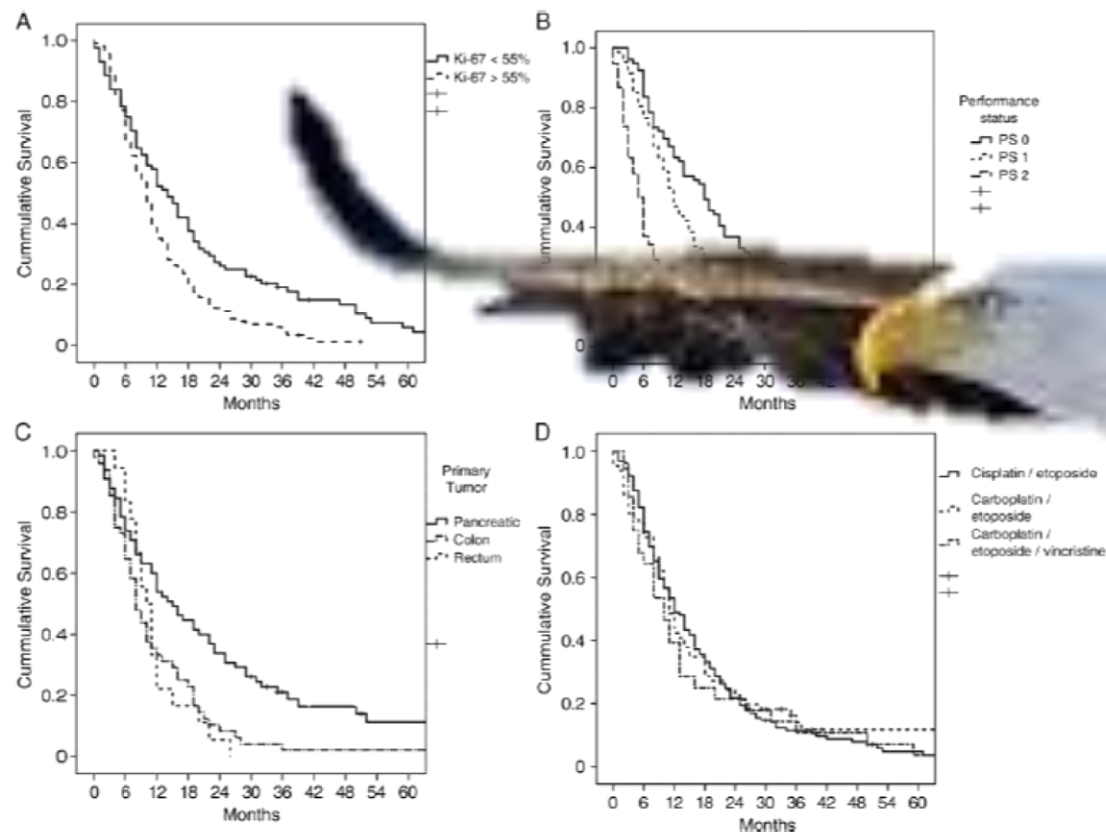
¹Department of Oncology, Haukeland University Hospital, Bergen, Norway; ²Department of Medical Sciences, Uppsala University, Uppsala, Sweden; ³Department of Oncology, Rigshospitalet, University of Copenhagen; ⁴Department of Oncology, Odense University Hospital, Odense; ⁵Department of Oncology and Medical V, Aarhus University Hospital, Aarhus, Denmark; ⁶Department of Oncology, Helsinki University Central Hospital, Helsinki, Finland; ⁷Department of Oncology, Oslo University Hospital, Radium Hospital, Oslo; ⁸Department of Oncology, St Olavs Hospital, University of Trondheim, Trondheim; ⁹Department of Oncology, Ullevål Hospital, Oslo University Hospital, Oslo, Norway; ¹⁰Department of Oncology, Karolinska University Hospital, Stockholm, Sweden; ¹¹Department of Oncology, Stavanger University Hospital, Stavanger; ¹²Department of Gastroenterology, Oslo University Hospital, Rikshospitalet, Oslo, Norway; ¹³Department of Pathology, Odense University Hospital, Odense; Departments of ¹⁴Surgery & ¹⁵Pathology, Rigshospitalet, University of Copenhagen, Denmark; ¹⁶Center for Clinical Research, Haukeland University Hospital, Bergen, Norway

Morfologia...discrimina

649–657

Logrank: $\chi^2 = 0.88$
 $P = 0.35$

At risk



657-664

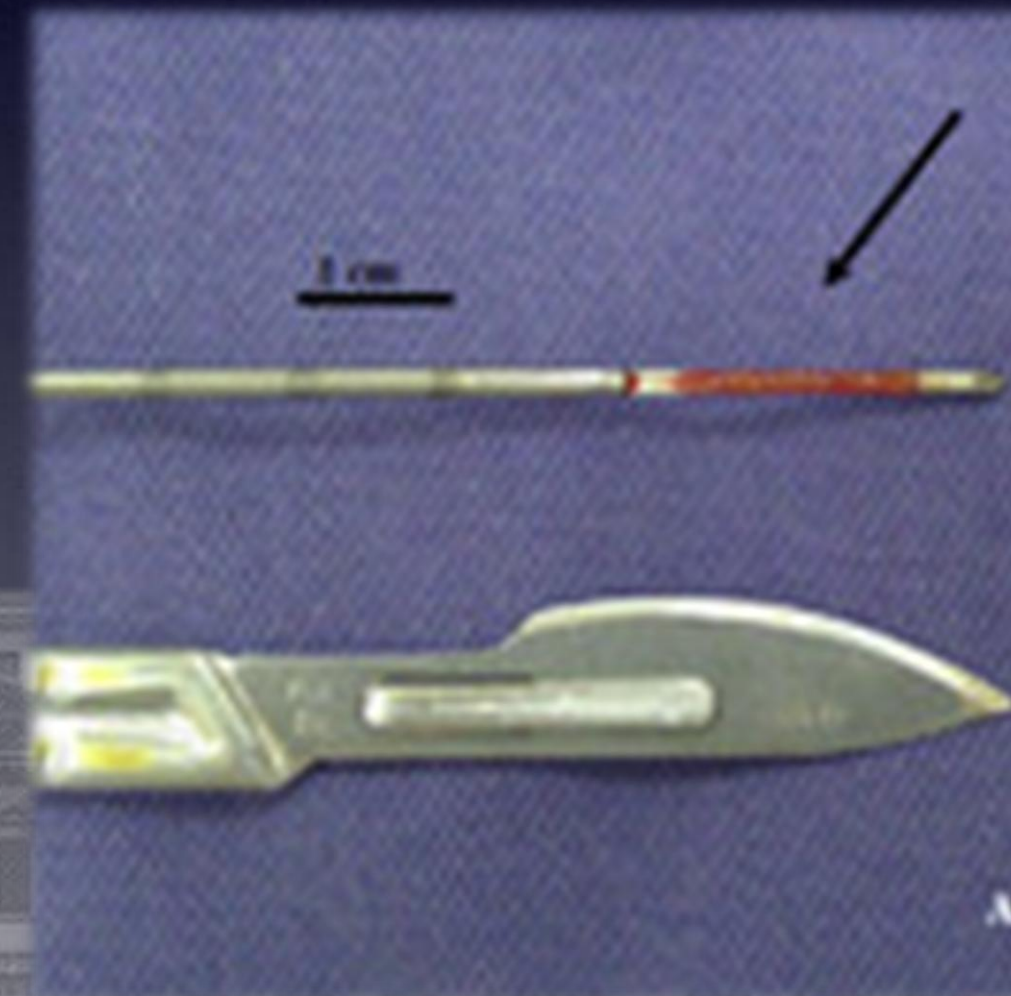
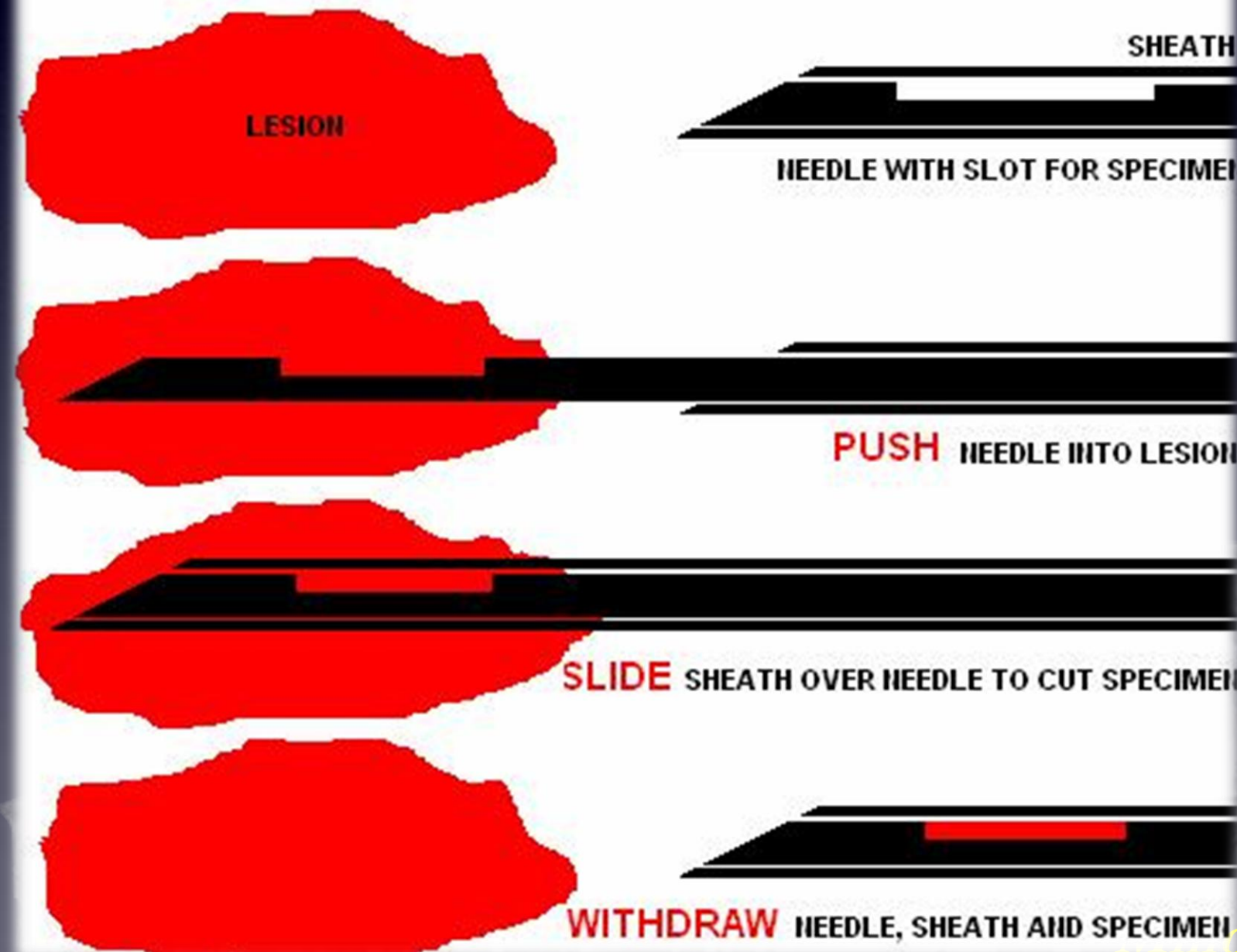
Figure 1 consists of three Kaplan-Meier survival curves. Panel (a) shows overall survival for NET G3 (dotted line) and NEC (solid line). Panel (b) shows overall survival for NET G3 (dotted line) and NEC (solid line). Panel (c) shows overall survival for Stage I+II, Stage III, and Stage IV. All plots show survival probability over 120 months.

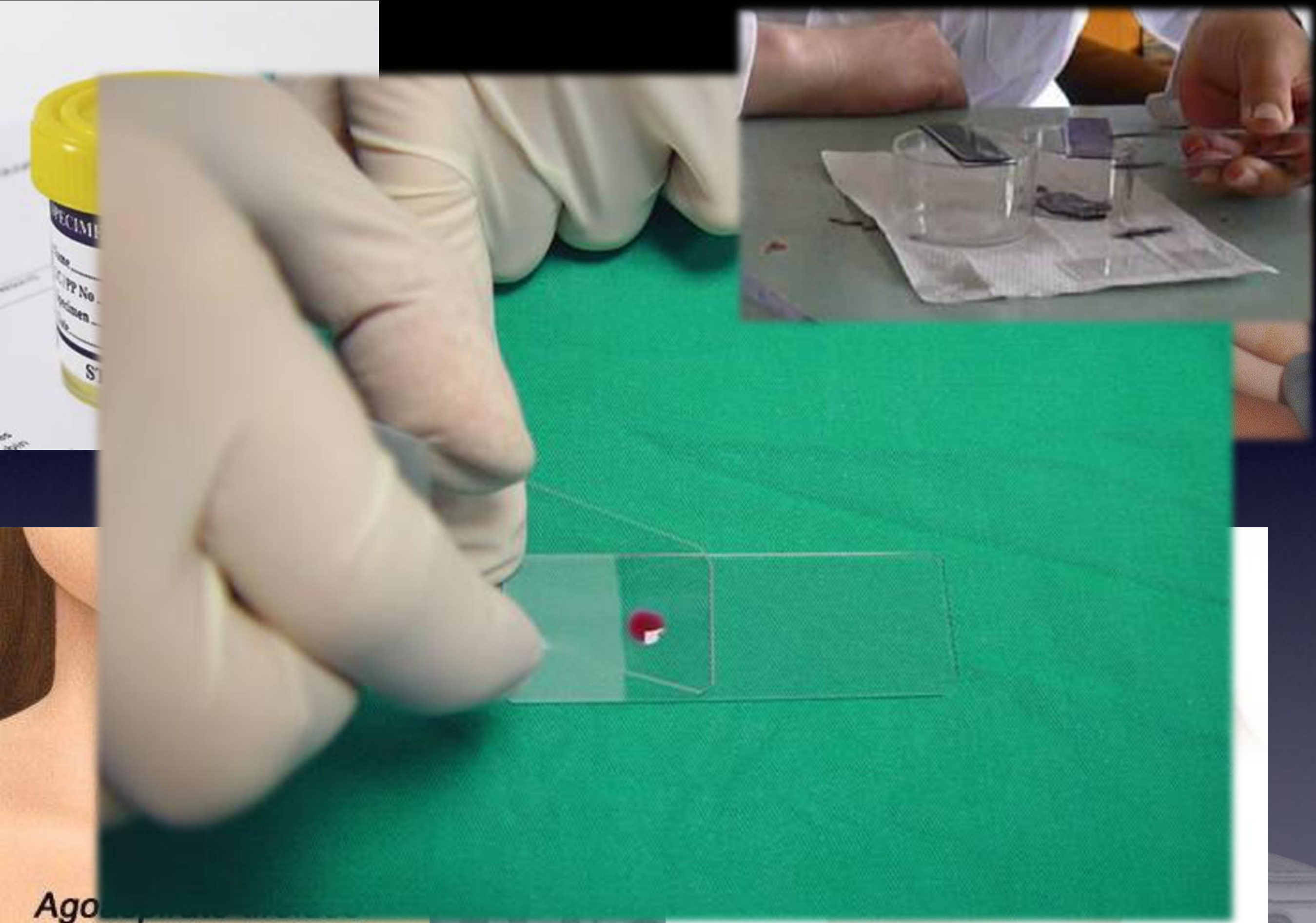
Survival in patients with Grade 3 neuroendocrine neoplasm, in the whole population (a) and according to differentiation (b), and TNM stage (c) after multivariate analysis.

TESSUTI



PRINCIPLE OF TRUCUT BIOPSY





Ago

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Ki-67 cut off 55% discrimina



Annals of Oncology 24: 152–160, 2013
doi:10.1093/annonc/mds276
Published online 11 September 2012

Predictive and prognostic factors for treatment and survival in 305 patients with advanced gastrointestinal neuroendocrine carcinoma (WHO G3): The NORDIC NEC study

H. Sorbye^{1*}, S. Welin^{2,†}, S. W. Langer^{3,†}, L. W. Vestermark⁴, N. Holt⁵, P. Osterlund⁶, S. Dueland⁷, E. Hofslø⁸, M. G. Guren⁹, K. Ohrling¹⁰, E. Birkemeyer¹¹, E. Thiis-Evensen¹², M. Biagini¹³, H. Gronbaek⁵, L. M. Soveri⁶, I. H. Olsen¹⁴, B. Federspiel¹⁵, J. Assmus¹⁶, E. T. Janson^{2,‡} & U. Knigge^{14,‡}

¹Department of Oncology, Haukeland University Hospital, Bergen, Norway; ²Department of Medical Sciences, Uppsala University, Uppsala, Sweden; ³Department of Oncology, Rigshospitalet, University of Copenhagen; ⁴Department of Oncology, Odense University Hospital, Odense; ⁵Department of Oncology and Medical V, Aarhus University Hospital, Aarhus, Denmark; ⁶Department of Oncology, Helsinki University Central Hospital, Helsinki, Finland; ⁷Department of Oncology, Oslo University Hospital, Radium Hospital, Oslo; ⁸Department of Oncology, St Olavs Hospital, University of Trondheim, Trondheim; ⁹Department of Oncology, Ullevål Hospital, Oslo University Hospital, Oslo, Norway; ¹⁰Department of Oncology, Karolinska University Hospital, Stockholm, Sweden; ¹¹Department of Oncology, Stavanger University Hospital, Stavanger; ¹²Department of Gastroenterology, Oslo University Hospital, Rikshospitalet, Oslo, Norway; ¹³Department of Pathology, Odense University Hospital, Odense; Departments of ¹⁴Surgery C; ¹⁵Pathology, Rigshospitalet, University of Copenhagen, Denmark; ¹⁶Center for Clinical Research, Haukeland University Hospital, Bergen, Norway

Received 13 April 2012; revised 19 June 2012; accepted 20 June 2012

Morfologia...discrimina

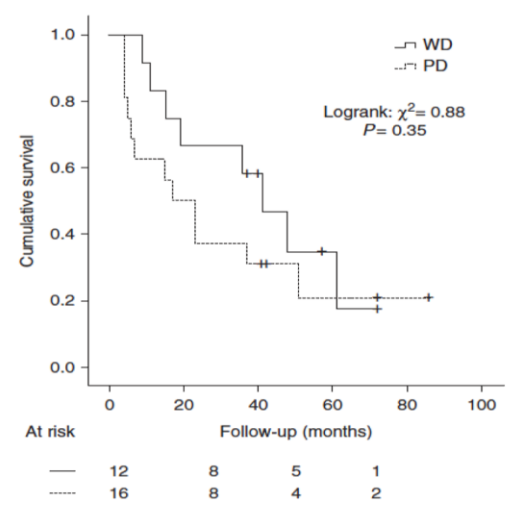
Research

F-L Vélouydom-Céphise et al. Features of grade 3 ENETS neuroendocrine tumors 20:5 649–657

Are G3 ENETS neuroendocrine neoplasms heterogeneous?

Fritz-Line Vélouydom-Céphise¹, Pierre Duvillard², Lyd Cecile N Chougnat¹, Sophie Lebouilleux¹, David Malka⁴, Thierry Debaere⁷, Caroline Caramella⁷, Martin Schlumb Dominique Elias⁶, Michel Ducreux^{4,8}, Jean-Yves Scoaze

Departments of ¹Nuclear Medicine and Endocrine Oncology ²Pathology, I Desmoulin, 94805 Villejuif Cedex, France ³Department of Biostatistics and Epidemiology, Research Group ECM, Université de la Guadeloupe, France ⁴Gastroenterology ⁵Thoracic Oncology ⁶Digestive Surgery, Institut Gustave Roussy, Villejuif, France ⁸Faculté de Médecine Paris Sud, Université Paris 11, Le Kremlin-Bicêtre, France



Research

M Heetfeld et al. Characteristics and treatment of gastroenteropancreatic G3 NEN 22:4 657–664

Characteristics and treatment of patients with G3 gastroenteropancreatic neuroendocrine neoplasms

M Heetfeld, C N Chougnat¹, I H Olsen², A Rinke³, I Borbath⁴, G Crespo⁵, J Barriuso⁶, M Pavel, D O'Toole⁷, T Walter⁸ and other Knowledge Network members*

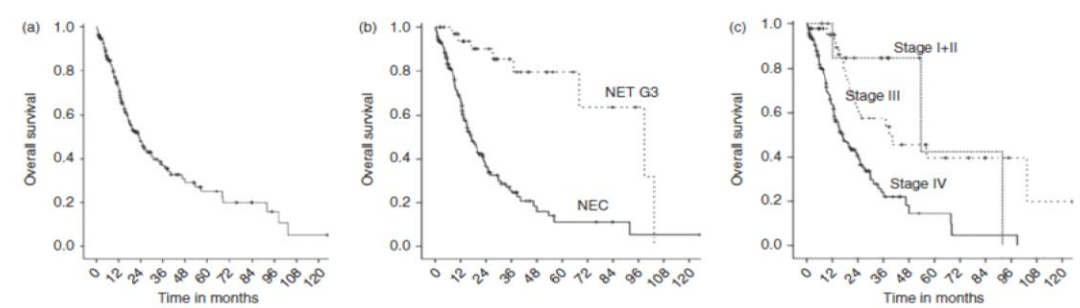


Figure 2 Survival in patients with Grade 3 neuroendocrine neoplasm, in the whole population (a) and according to differentiation (b), and TNM stage (c) after multivariate analysis.

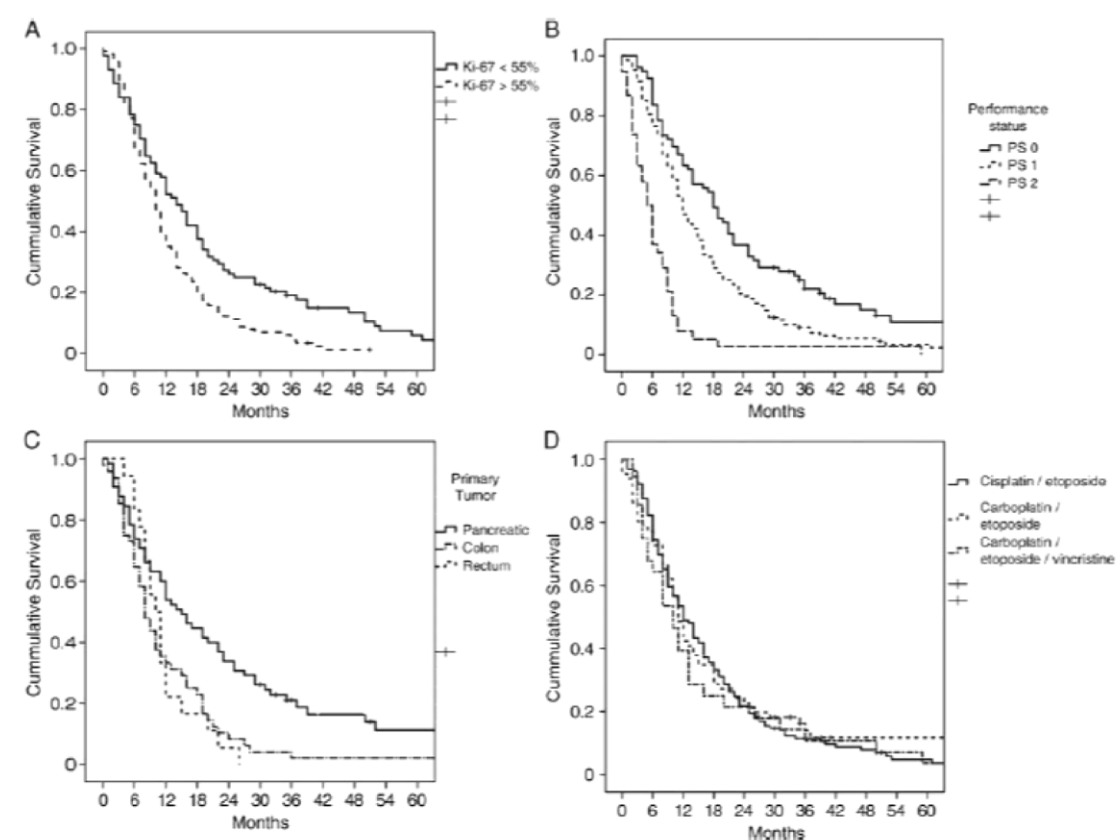


Figure 1. Survival in patients treated with chemotherapy according to (A) Ki-67 index, (B) performance status (PS), (C) location of primary tumor and (D) chemotherapy schedule.

DESCRIZIONE

1. Neoplasia Neuroendocrina ben o scarsamente differenziata
2. Positività immunoistochimica per Sinaptofisina + Cromogranine (%)
3. Indice Mitotico.../10 HPF
4. Indice di proliferazione Ki-67%

DIAGNOSI

- a) Tumore Neuroendocrino ben differenziato :
NET G1, NET G2, NET G3
- b) Carcinoma Neuroendocrino scarsamente differenziato
... a piccole cellule
....a grandi cellule
(NEC G3 con Ki67 > 20%)

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