NEN del pancreas:stato dell'arte

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Classificazione WHO 2017

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Modern Pathology
https://doi.org/10.1038/s41379-018-0110-y

….next future?

USCAP

ARTICLE

Check for updates

A common classification framework for neuroendocrine neoplasms: an International Agency for Research on Cancer (IARC) and World Health Organization (WHO) expert consensus proposal

Guido Rindi[1] · David S. Klimstra[2] · Behnoush Abedi-Ardekani[3] · Sylvia L. Asa[4] · Frederik T. Bosman[5] · Elisabeth Brambilla[6] · Klaus J. Busam[2] · Ronald R. de Krijger[7] · Manfred Dietel[8] · Adel K. El-Naggar[9] · Lynnette Fernandez-Cuesta[3] · Günter Klöppel[10] · W. Glenn McCluggage[11] · Holger Moch[12] · Hiroko Ohgaki[3] · Emad A. Rakha[13] · Nicholas S. Reed[14] · Brian A. Rous[15] · Hironobu Sasano[16] · Aldo Scarpa[17] · Jean-Yves Scoazec[18] · William D. Travis[2] · Giovanni Tallini[19] · Jacqueline Trouillas[20] · J. Han van Krieken[21] · Ian A. Cree[3]

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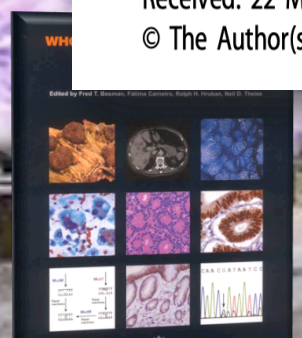
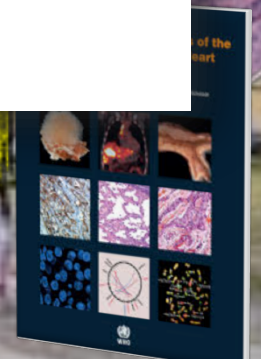
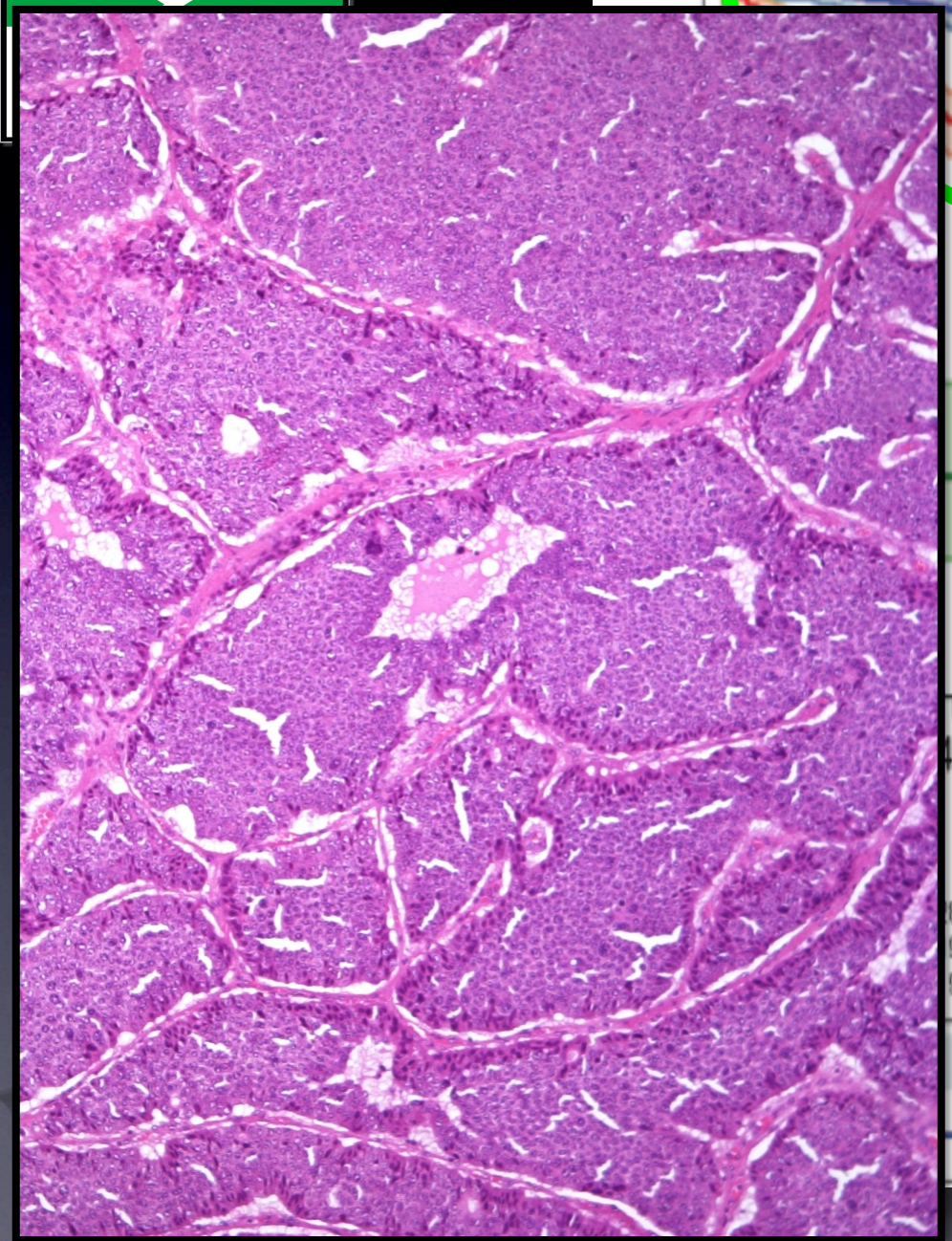


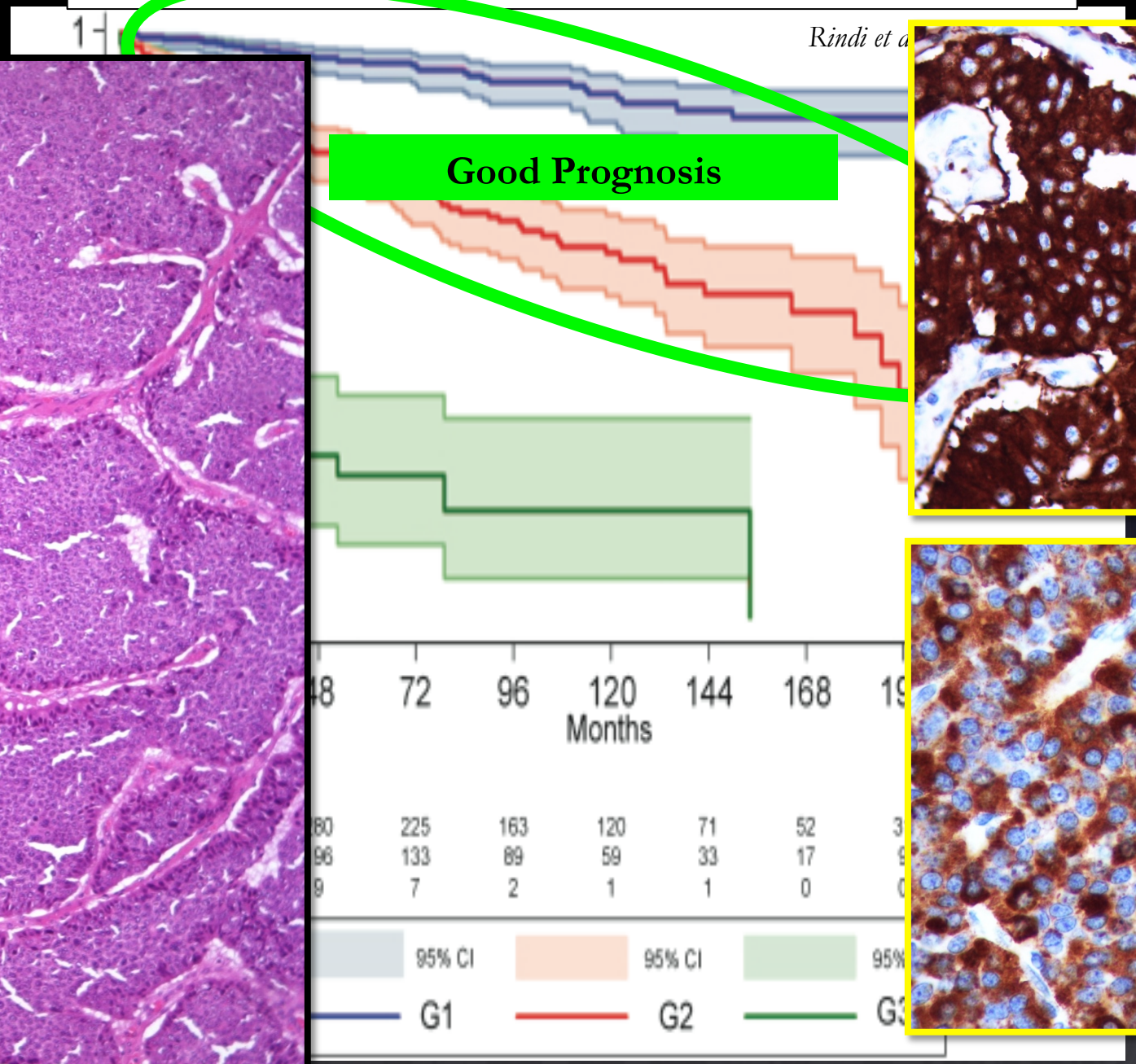
2017 GEP

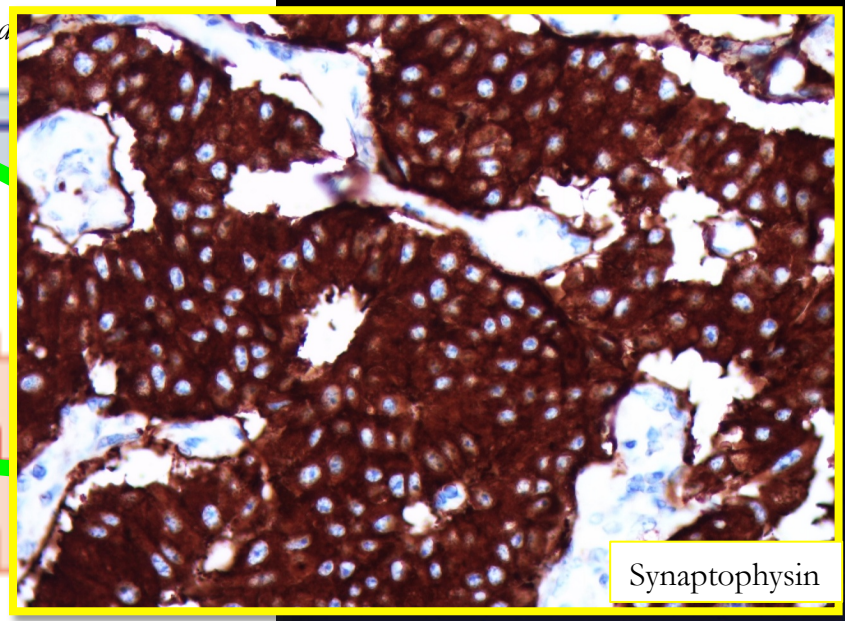
2015 LUNG

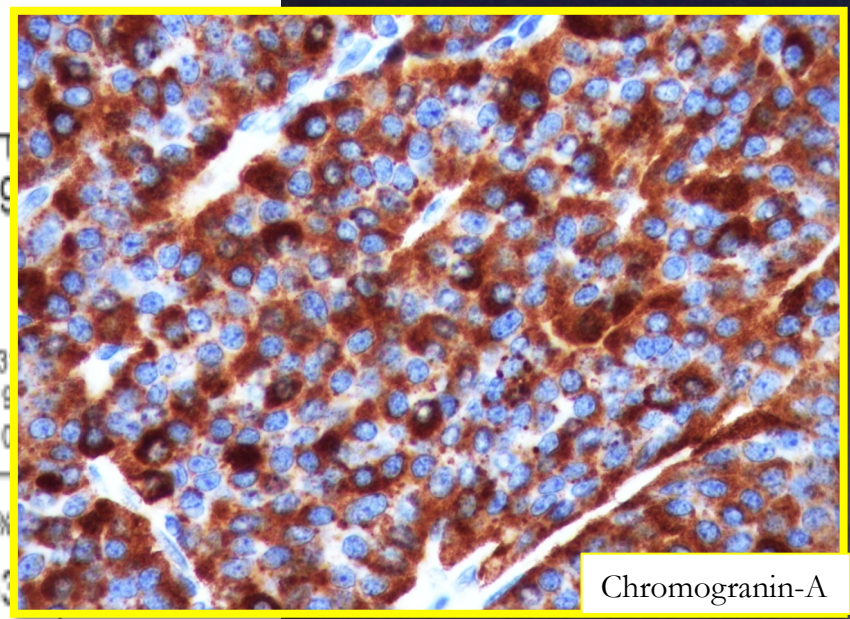


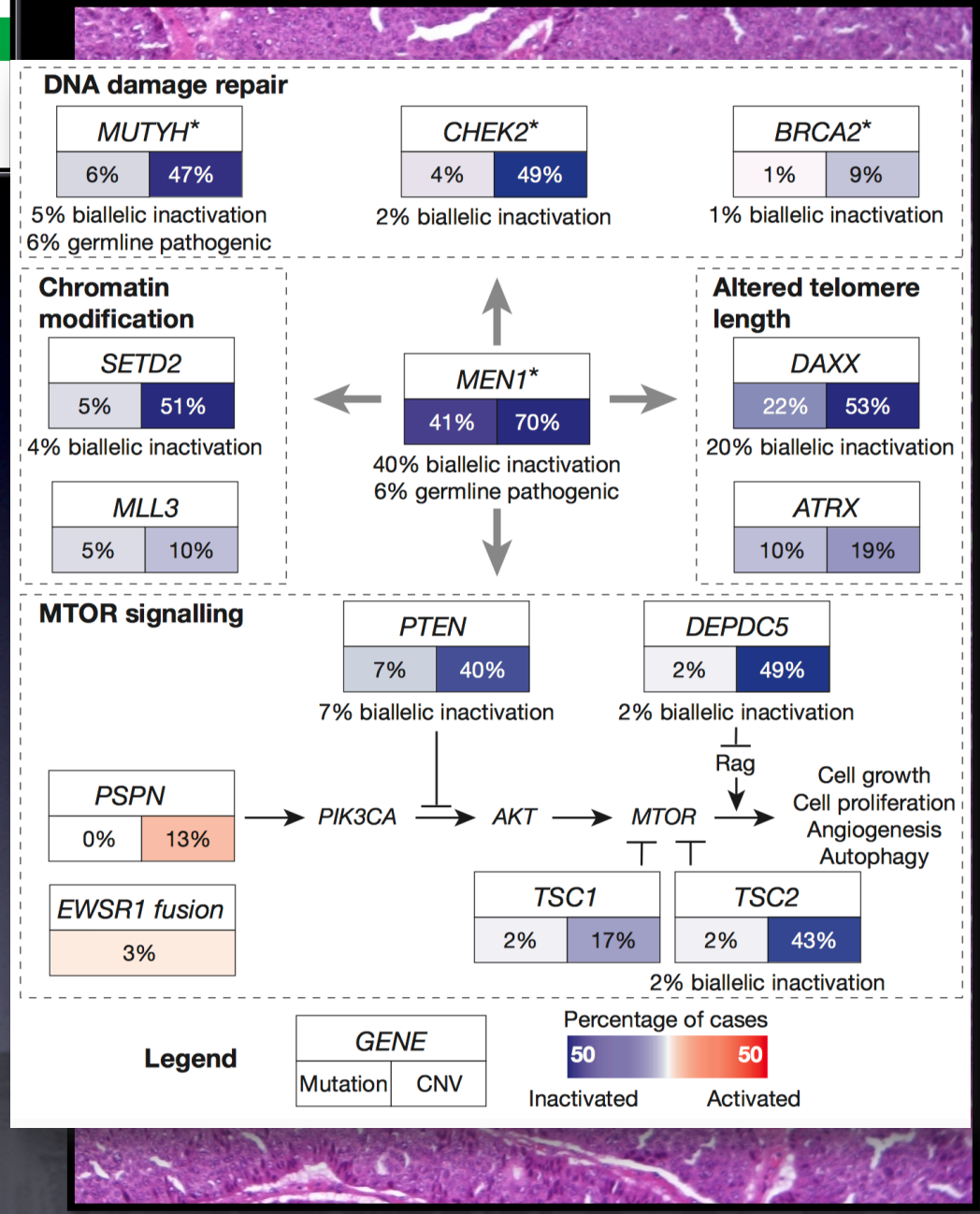
Well Differentiated Neuroendocrine Tumors











Scarpa A. et al Nature 2017 Mar 2;543(7643):65-71

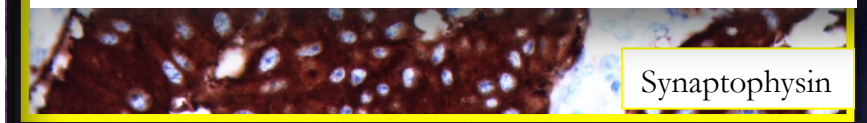
ARTICLE

doi:10.1038/nature21063

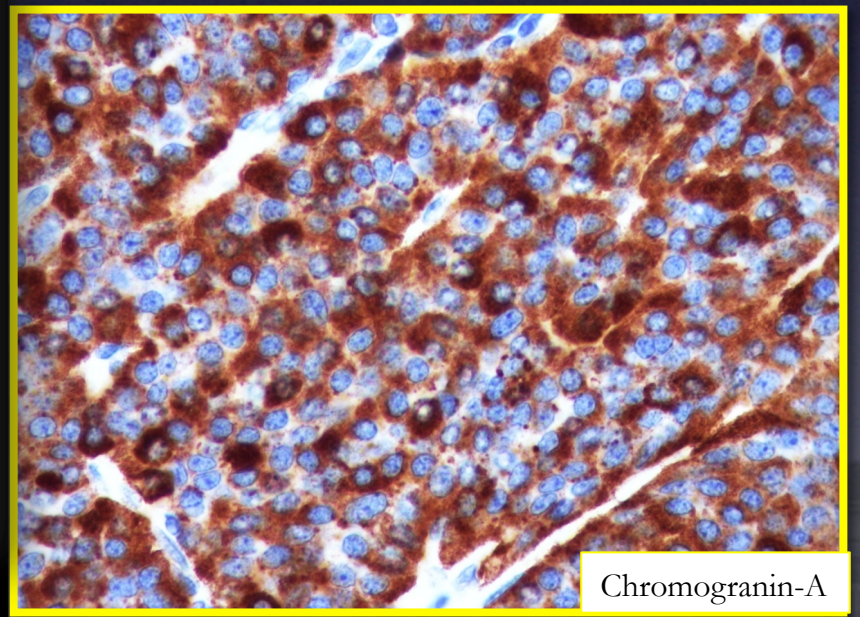
Whole-genome landscape of pancreatic neuroendocrine tumours

A list of authors and their affiliations appears at the end of the paper

The diagnosis of pancreatic neuroendocrine tumours (PanNETs) is increasing owing to more sensitive detection methods, and this increase is creating challenges for clinical management. We performed whole-genome sequencing of 102 primary PanNETs and defined the genomic events that characterize their pathogenesis. Here we describe the mutational signatures they harbour, including a deficiency in G:C>T:A base excision repair due to inactivation of *MUTYH*, which encodes a DNA glycosylase. Clinically sporadic PanNETs contain a larger-than-expected proportion of germline mutations, including previously unreported mutations in the DNA repair genes *MUTYH*, *CHEK2* and *BRCA2*. Together with mutations in *MENI* and *VHL*, these mutations occur in 17% of patients. Somatic mutations, including point mutations and gene fusions, were commonly found in genes involved in four main pathways: chromatin remodelling, DNA damage repair, activation of mTOR signalling (including previously undescribed *EWSRI* gene fusions), and telomere maintenance. In addition, our gene expression analyses identified a subgroup of tumours associated with hypoxia and HIF signalling.



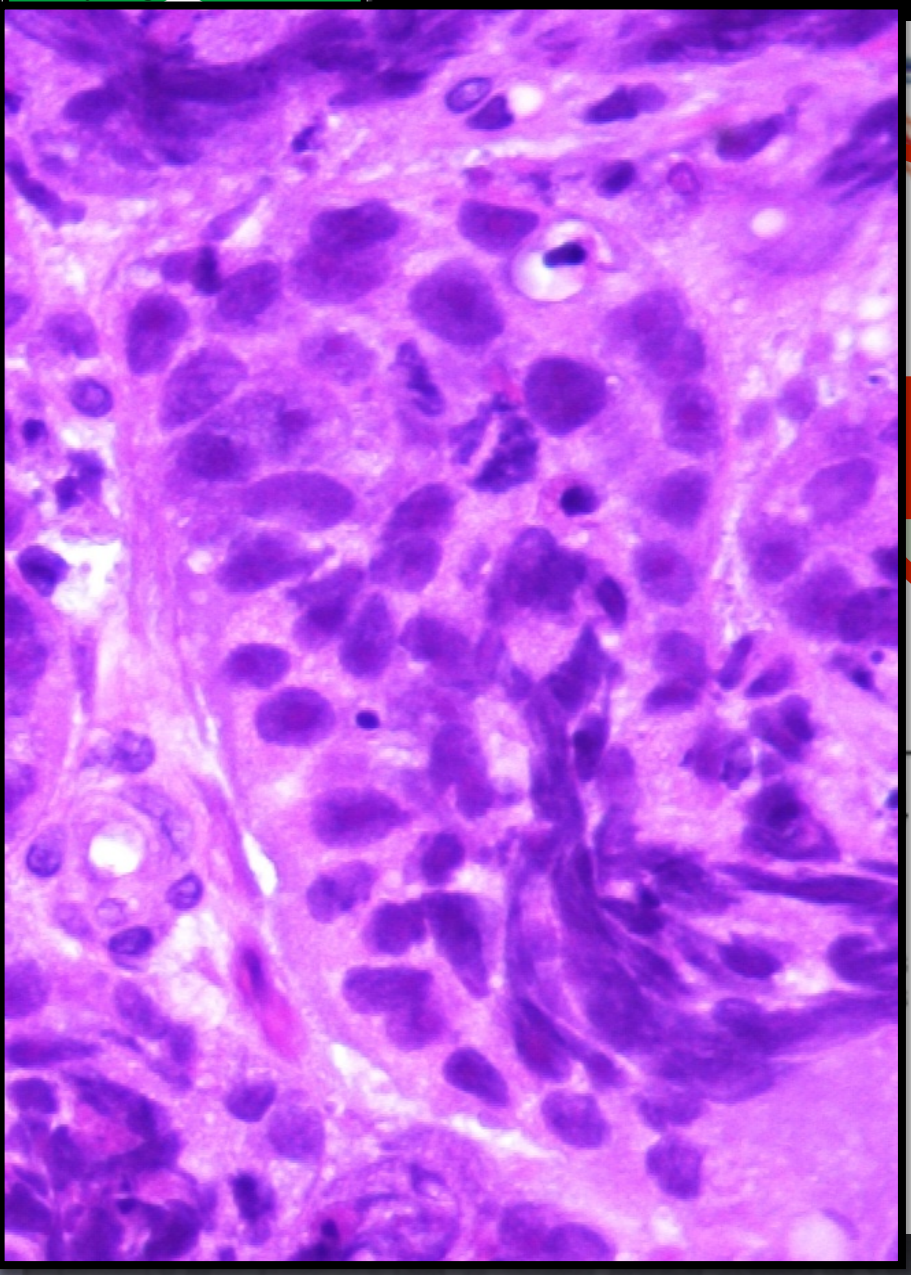
Synaptophysin

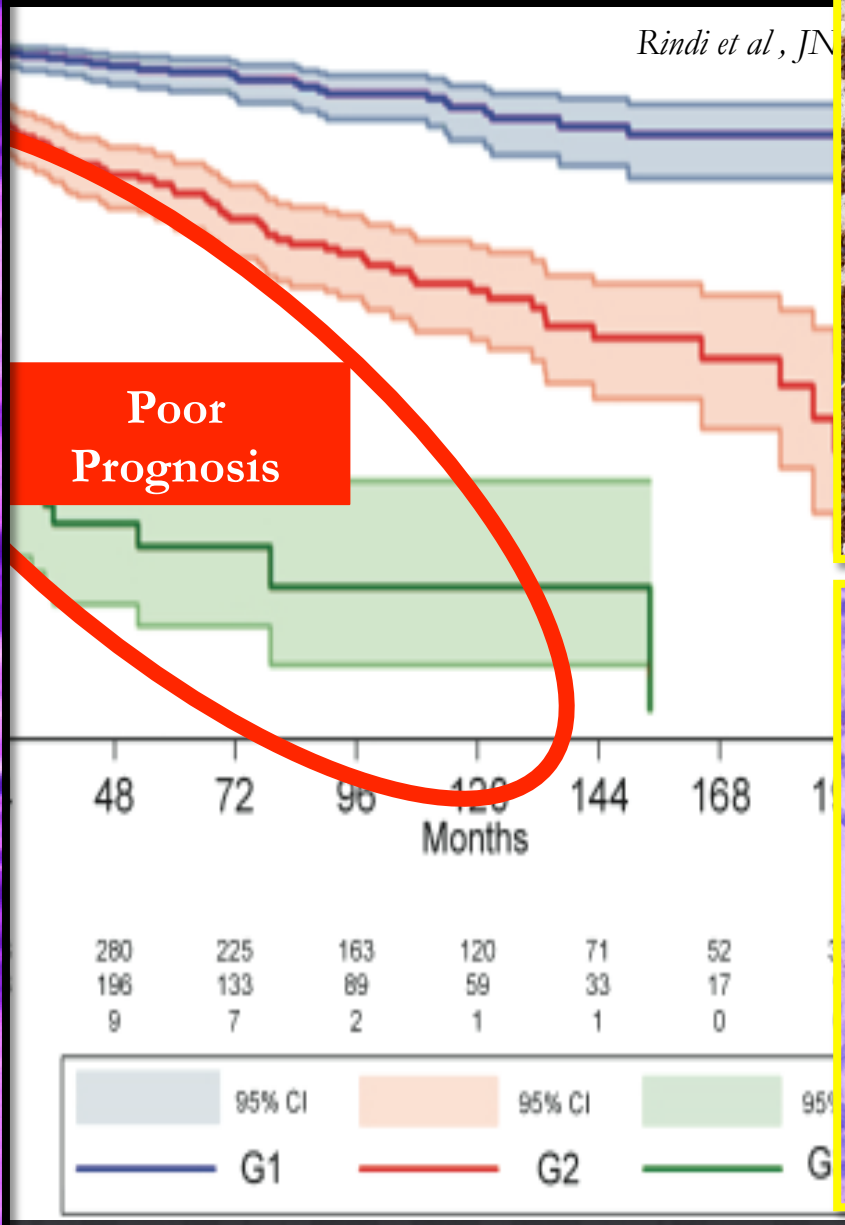


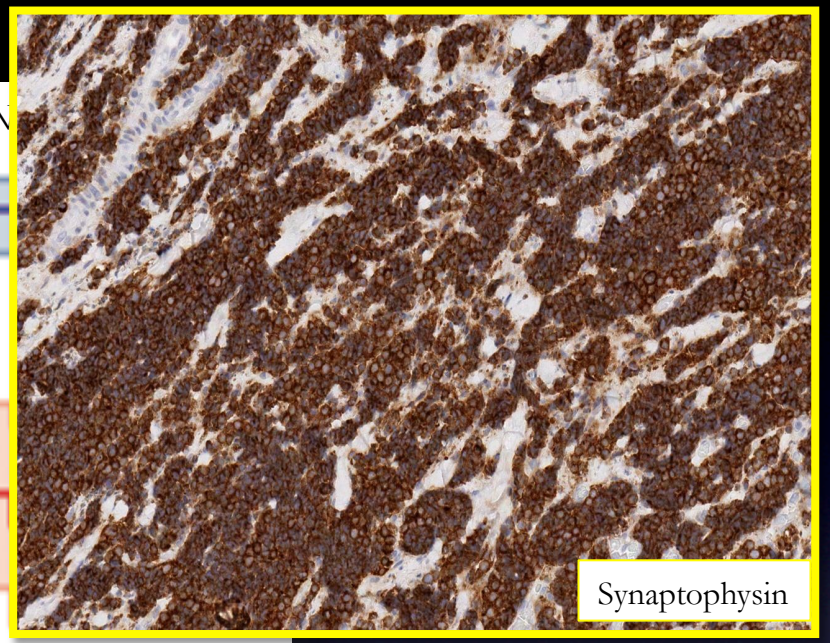
Chromogranin-A

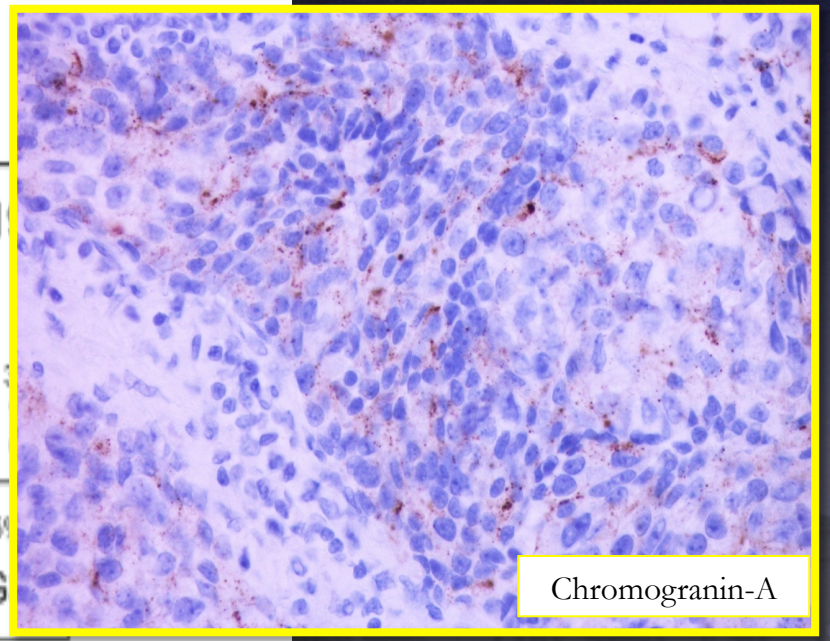
Poorly Differentiated Neuroendocrine Carcinomas

Am J Surg Pathol 2012









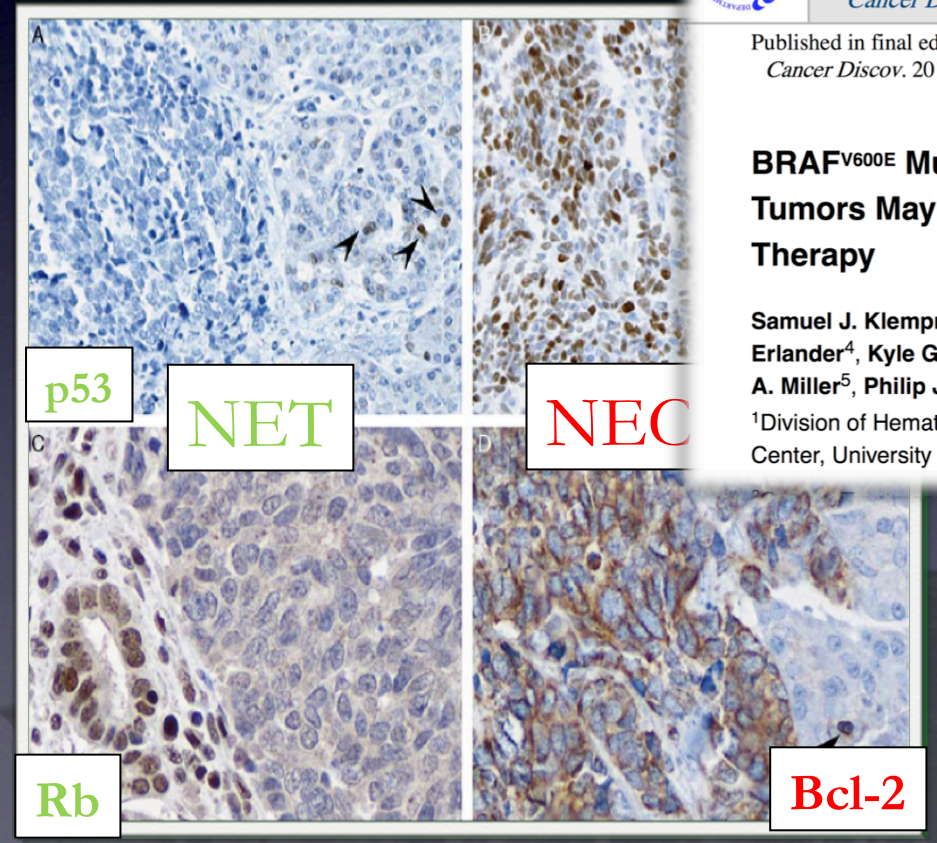
Poorly Differentiated Neuroendocrine Carcinomas

Am J Surg Pathol 2012

ORIGINAL ARTICLE

Small Cell and Large Cell Neuroendocrine Carcinomas of the Pancreas are Genetically Similar and Distinct From Well-differentiated Pancreatic Neuroendocrine Tumors

Shinichi Yachida, MD, PhD, Efsevia Vakiani, MD, PhD,† Catherine M. White, BS,* Yi Zhong, MD, PhD,* Tyler Saunders, HS,* Richard Morgan, MS,* Roeland F. de Wilde, MD,* Anirban Maitra, MBBS,* Jessica Hicks, BS,* Angelo M. DeMarzo, MD, PhD,*† Chanjuan Shi, MD, PhD,§ Rajni Sharma, PhD,* Daniel Laheru, MD,‡ Bar… Christopher L. Wolfgang, MD, PhD,‖ Richard D. Schulick, MD,‖ Ralph H… Laura H. Tang, MD, PhD,† David S. Klimstra, MD,† and… Christine A. Iacobuzio-Donahue, MD, PhD*‡‖*



Cancer 2003

1273

Genetic Alterations in Poorly Differentiated Endocrine Carcinomas of the Gastrointestinal Tract

Silvia Pizzi, Ph.D.
Cinzia Azzoni, Ph.D.
Daniela Bassi, M.D.

BACKGROUND. The molecular pathogenesis of poorly differentiated endocrine carcinomas of the gastrointestinal tract (GI PDECs) remains unclear. It has been suggested that these lesions either originate from multipotent stem cells that also can serve as the origin of nonendocrine adenocarcinomas or arise due to the dedifferentiation of well-differentiated endocrine carcinomas (WDECs).

METHODS. Ten gastric and 9 colorectal PDECs, 9 gastric WDECs, and 12 colorectal carcinomas (CRCs) were analyzed for loss of heterozygosity (LOH) at 11q13 (*MEN1*), 17p13.1 (*p53*), 3p14.2 (*FHIT*), 3p21.3 (*RASSF1A*), and 18q23 (*DCC/DPC4/Smad2*), and for immunohistochemical expression of p53, FHIT, Rb, and p16.

RESULTS. PDECs exhibited high fractional allelic loss (FAL; 0.49), with frequent

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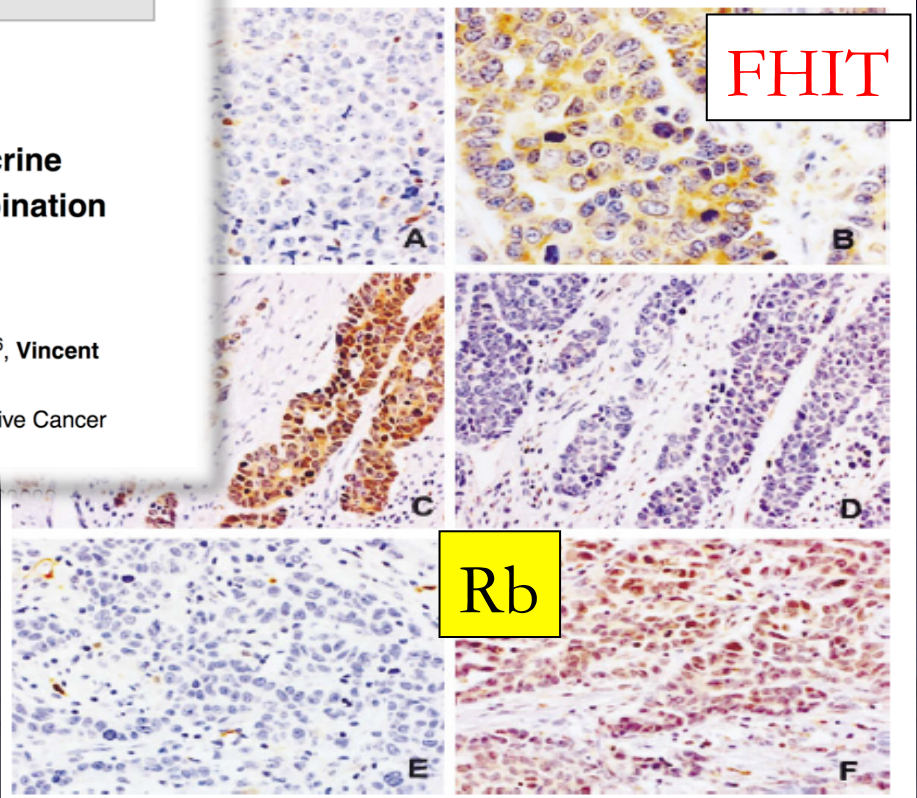
Cancer Discov. 2016 June ; 6(6): 594–600. doi:10.1158/2159-8290.CD-15-1192.

BRAF^{V600E} Mutations in High Grade Colorectal Neuroendocrine Tumors May Predict Responsiveness to BRAF-MEK Combination Therapy

Samuel J. Klempner[1,*], **Bruce Gershenhorn**[2], **Phu Tran**[1], **Thomas K. Lee**[3], **Mark G. Erlander**[4], **Kyle Gowen**[5], **Alexa B. Schrock**[5], **Deborah Morosini**[5], **Jeffrey S. Ross**[5,6], **Vincent A. Miller**[5], **Philip J. Stephens**[5], **Sai-Hong Ignatius Ou**[1], and **Siraj M. Ali**[5]

[1]Division of Hematology-Oncology, Department of Medicine, Chao Family Comprehensive Cancer Center, University of California Irvine School of Medicine, Orange, CA 92868, USA



Ki-67: The Prognosis Pillar

Virchows Arch (1996) 429:323–333

ORIGINAL ARTICLE

Stefano La Rosa · Fausto Sessa · Carlo Capella
Cristina Riva · Biagio Eugenio Leone
Catherine Klersy · Guido Rindi · Enrico Solcia

Prognostic criteria in nonfunctioning pancreatic endocrine tumours

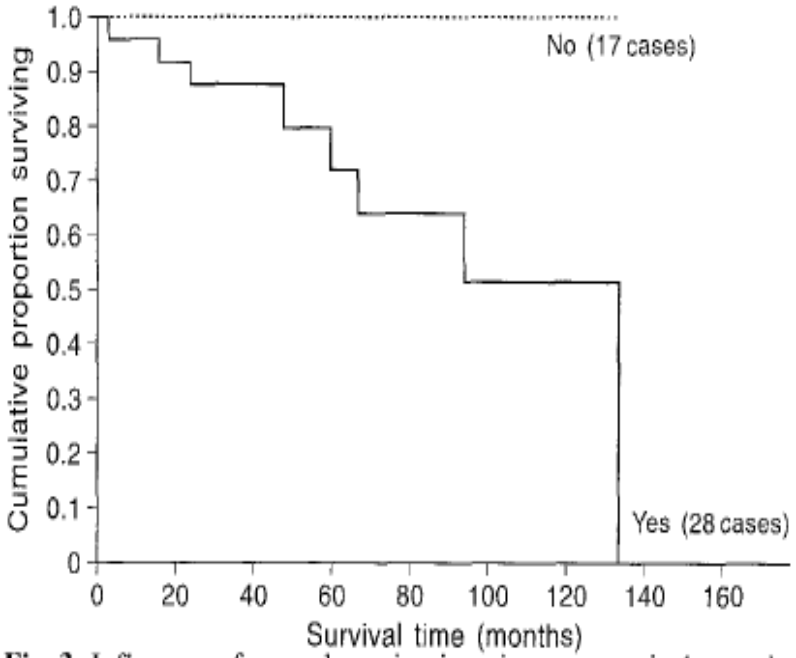
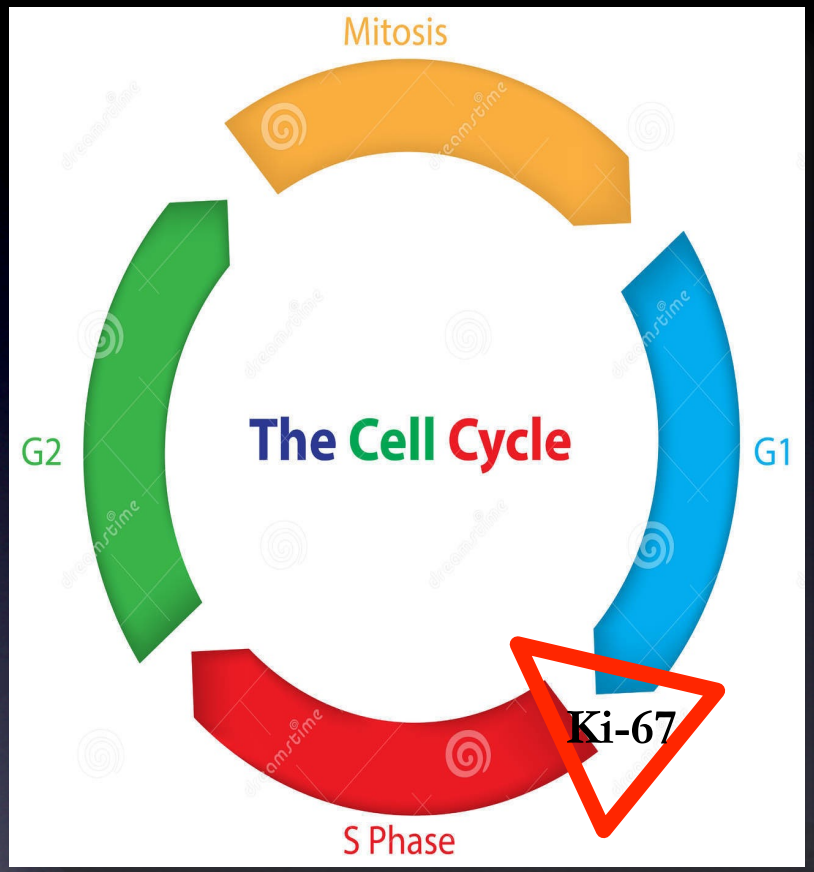


Fig. 3 Influence of vascular microinvasion on survival rate in 45 well-differentiated endocrine tumours. Univariate analysis $P = 0.025$



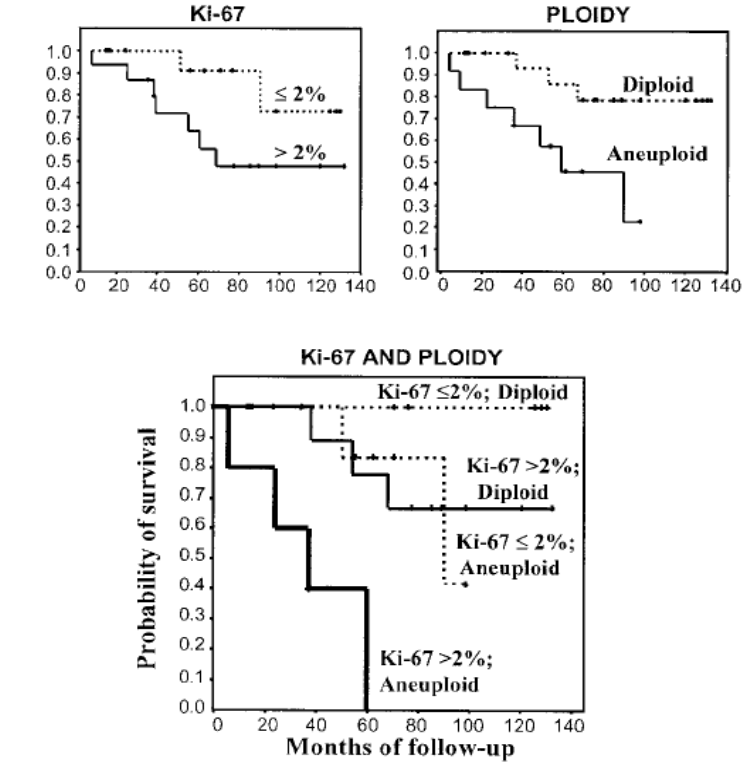
Cancer Research

AACR

High Resolution Allelotype of Nonfunctional Pancreatic Endocrine Tumors: Identification of Two Molecular Subgroups with Clinical Implications

Gildas Rigaud, Edoardo Missiaglia, Patrick S. Moore, et al.

Cancer Res 2001;61:285-292.



MORPHOLOGY

+

Ki-67%

=

WHO (2017) CLASSIFICATION

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}.

regarding therapeutics

WELL DIFFERENTIATED

NEC

POORLY DIFFERENTIATED

NET G1

NET G2

NET G3

Ki67 LI = N°positive nuclei per 2mm^2 → 2mm^2 = 200 nuclei → N°positive nuclei / 2000 nuclei % = Ki67 LI

3%

20%

Ki67 LI=0,3%

Ki67 LI= 4%

Ki67 LI= 40%

Ki67 LI= 90%

Neuro-endocrinology

Neuroendocrinology (DOI:10.1159/000464292)
(Accepted, unedited article not yet assigned to an issue)

Advanced Release: February 25, 2017

Received: December 14, 2016
Accepted after revision: February 19, 2017

ENETS Consensus Guidelines for Standard of Care in Neuroendocrine Tumours: Surgery for Small Intestinal and Pancreatic Neuroendocrine Tumours

Stefano Partelli[1]*, Detlef K. Bartsch[2]*, Jaume Capdevila[3], Jie Chen[4], Ulrich Knigge[5], Bruno Niederle[6], Els J.M. Nieveen van Dijkum[7], Ulrich-Frank Pape[8], Andreas Pascher[9], John Ramage[10], Nick Reed[11], Philippe Ruszniewski[12], Jean-Yves Scoazec[13], Christos Toumpanakis[14], Reza Kiamanesh[15]^, Massimo Falconi[1]^, *all other Antibes Consensus Conference participants*

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Neuroendocrinology. 2016 ; 103(2): 153–171. doi:10.1159/000443171.

Consensus guidelines update for the management of functional p-NETs (F-p-NETs) and non-functional p-NETs (NF-p-NETs)

M Falconi[a,*], B Eriksson[b,*], G Kaltsas[c,*], DK Bartsch[d], J Capdevila[e], M Caplin[f], B Kos-Kudla[g], D Kwekkeboom[h], G Rindi[i], G Klöppel[j], N Reed[k], R Kianmanesh[l], RT Jensen[m], and all other Vienna Consensus Conference participants[n]

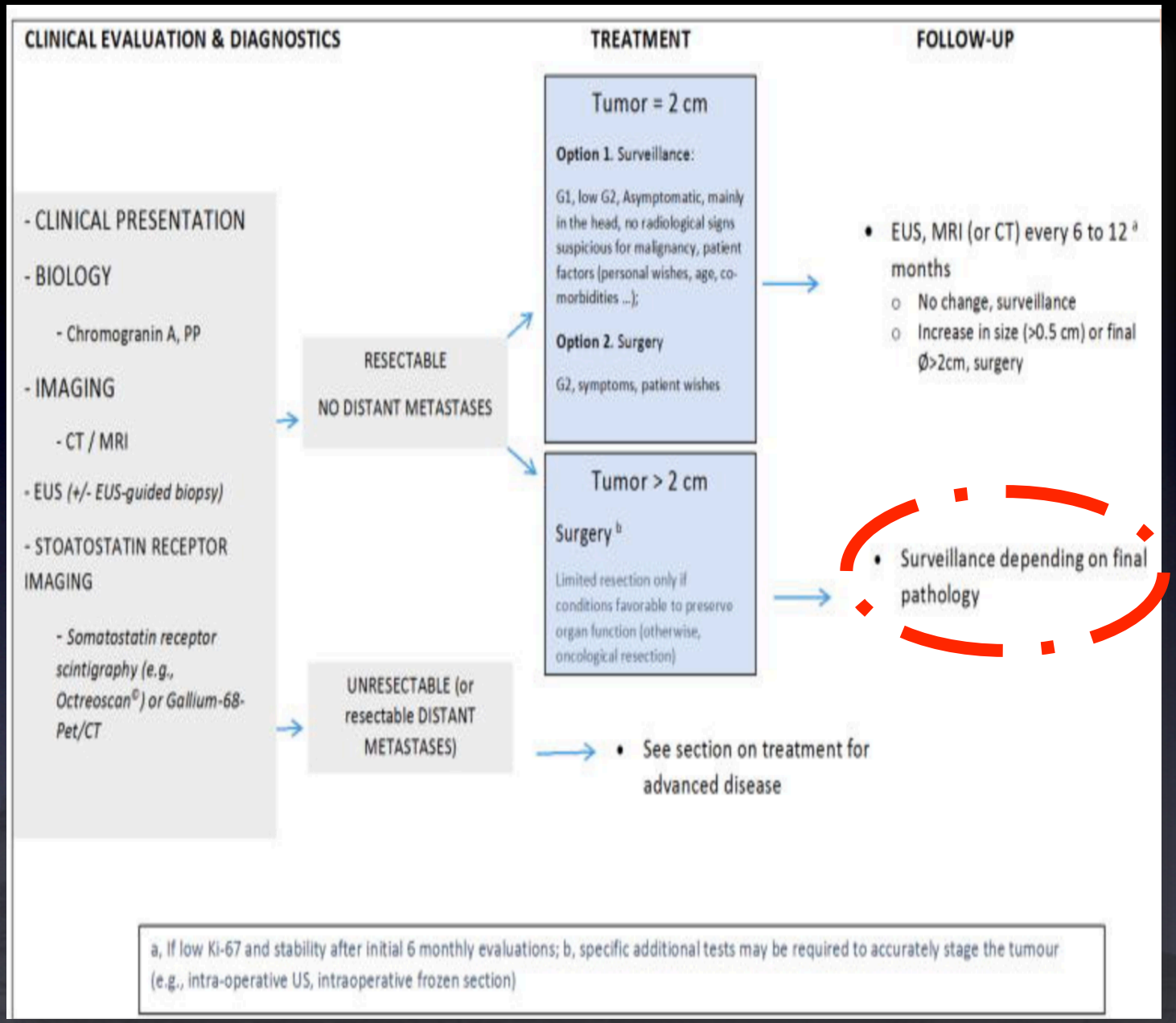
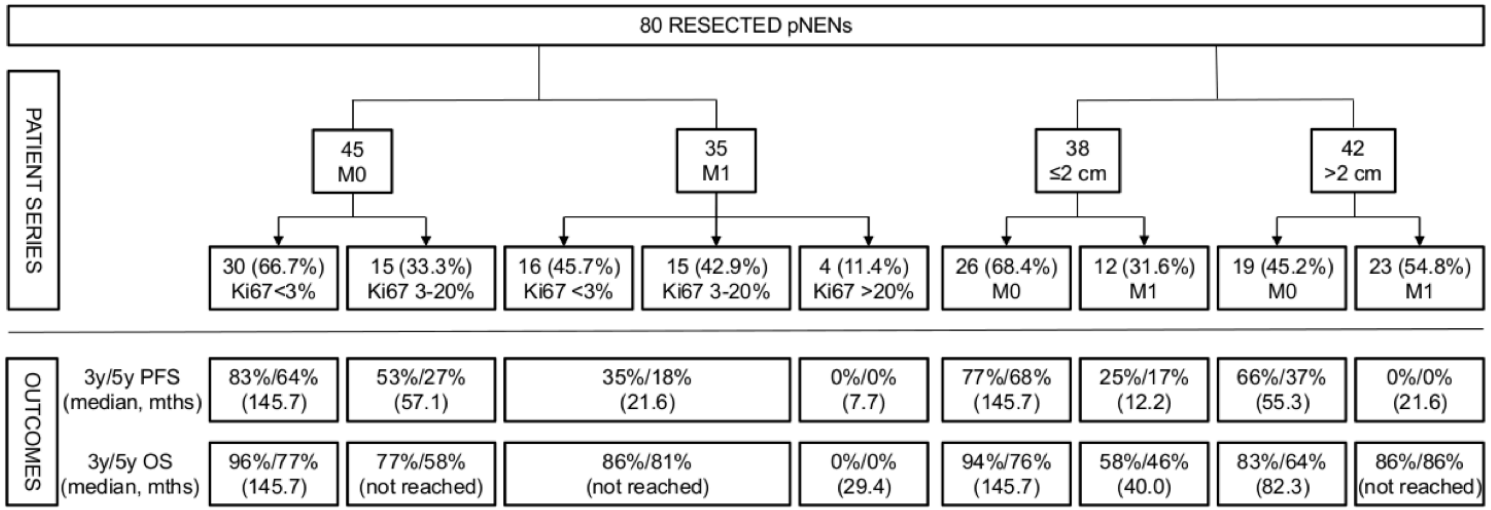


Figure 1. Distribution of Ki67, primary tumor size, presence of liver metastases and main outcome of 80 consecutive patients with pNENs who underwent pancreatic resection.



M1 patients had a significantly lower PFS as compared to M0 patients (multivariable p=0.0008); patients with Ki67 <3% had significantly better PFS than the ones with Ki67 ≥3% (multivariable p=0.01); there were no significant differences in PFS according to tumor size ≤2 cm or >2 cm (multivariable p=0.66).

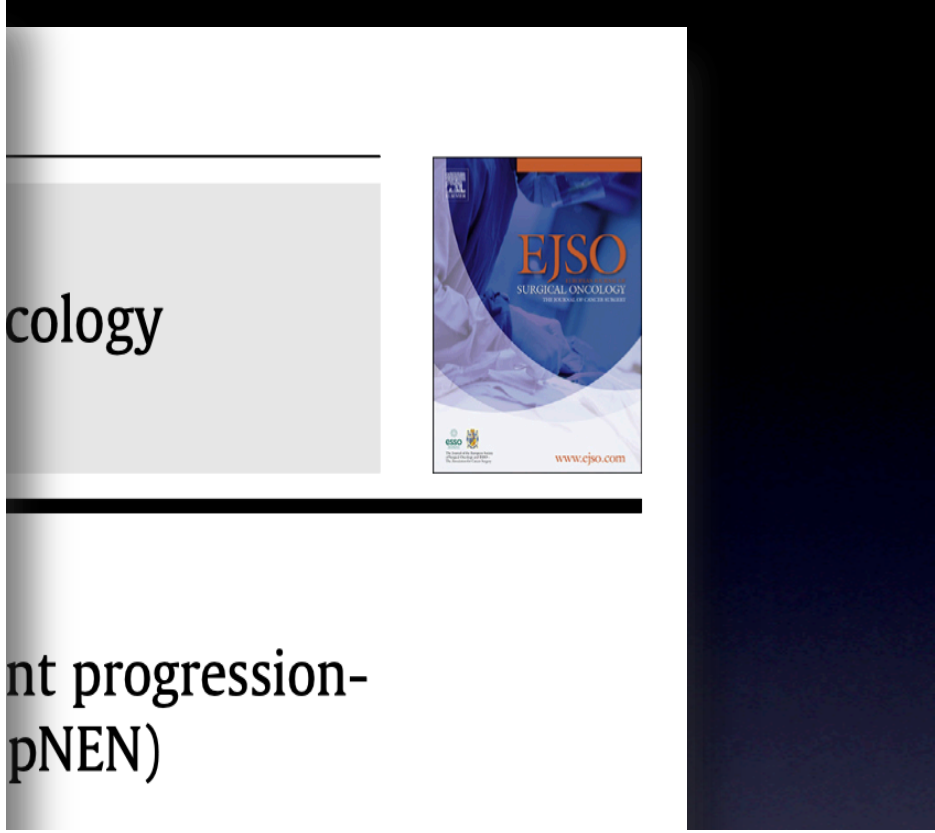
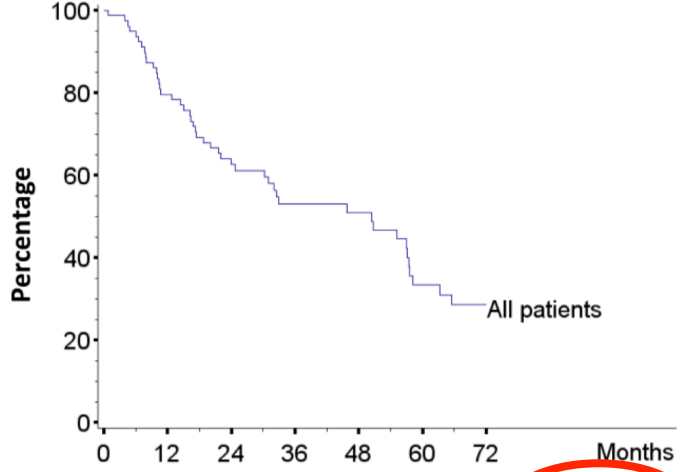


Table 2. Univariable and multivariable analysis of risk factors associated with cancer progression

	Univariable analysis N=80		Multivariable analysis N=76		Reduced model	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Body/tail vs. head	1.18 (0.64-2.18)	0.60	1.09 (0.54-2.23)	0.81		
>2 cm vs. ≤2 cm	1.58 (0.88-2.84)	0.12	1.18 (0.58-2.39)	0.66		
Multifocal vs. unifocal	0.53 (0.13-2.19)	0.38	0.80 (0.19-3.49)	0.77		
Ki-67 ≥3% vs. <3%	**2.57 (1.43-4.61)**	**0.002**	**2.97 (1.26-7.02)**	**0.01**	**2.09 (1.16-3.76)**	**0.01**
MI >2 vs. <2	1.33 (0.75-2.35)	0.33	0.66 (0.27-1.56)	0.34		
Parenchymal invasion	**2.23 (1.11-4.49)**	**0.02**	1.43 (0.58-3.56)	0.44		
Vascular invasion	1.53 (0.86-2.75)	0.15	0.62 (0.28-1.37)	0.24		
Perineural invasion	**1.98 (1.11-3.53)**	**0.02**	1.32 (0.60-2.92)	0.49		
Necrosis of primary tumor	1.52 (0.71-3.26)	0.28	0.53 (0.21-1.35)	0.18		
Lymph node metastases	**1.90 (1.07-3.36)**	**0.03**	0.94 (0.45-1.97)	0.86		
Liver metastases	**3.63 (1.98-6.64)**	**<.0001**	**3.60 (1.70-7.61)**	**0.0008**	**3.20 (1.74-5.91)**	**0.0002**
Stage II vs. I (ENETS/AJCC)	1.96 (0.46-8.26)	0.36	-			
Stage III vs. I (ENETS/AJCC)	**4.18 (1.60-10.9)**	**0.003**	-			
Stage IV vs. I-III (ENETS/AJCC)	**5.24 (1.88-14.6)**	**0.001**	-			



Number at risk

All patients	80	62	45	30	24	15	9

Median PFS 50.5 months

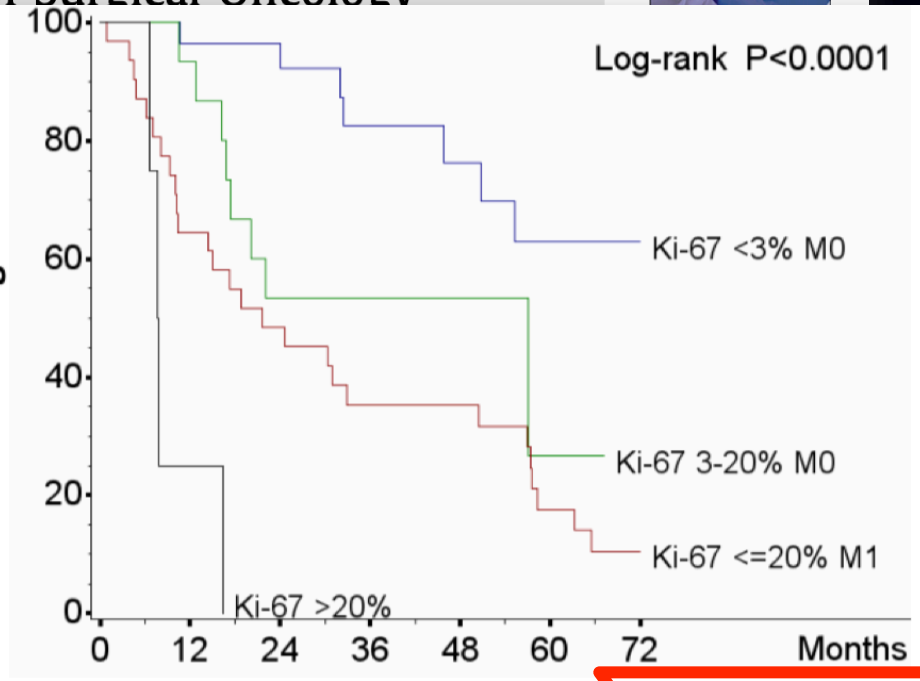
European Journal of Surgical Oncology xxx (2018) 1–6

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

Ki-67 and presence of l risk classes in pancreat undergoing resection

Massimo Milione [a], Patrick M
Giovanni Centonze [a], Jorgelina
Oleksandra Lanhazo [g], Gianca



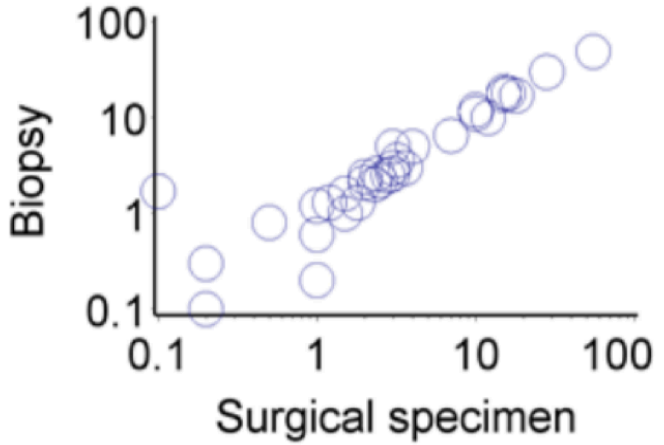
Number at risk								Median PFS	HR (95% CI)
Ki-67 <3% M0	30	27	22	16	12	9	6	145.7 months	1.00
Ki-67 3-20% M0	15	14	8	4	2	1	0	57.1 months	3.21 (1.18-8.74)
Ki-67 ≤20% M1	31	20	15	10	10	5	3	21.6 months	5.06 (2.29-11.2)
Ki-67 >20%	4	1	0	0	0	0	0	7.7 months	24.3 (6.64-89.2)

Figure 4. Concordance (weighted Kappa) and intra-class correlation among different pathologists on pre-surgical pNEN biopsy and post-surgical pathology of the same tumor.

Biopsy \ Surgical specimen	Ki-67 <3%	3-20%	>20%
<3%	18	-	-
3-20%	1	14	-
>20%	-	-	2

Weighted Kappa (95% CI)

0.98 (0.94-1.00)



Intra-class correlation coefficient (95% CI)

0.989 (0.978-0.994)

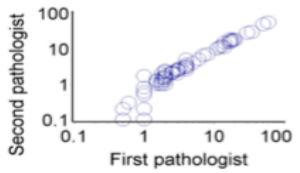
vs

Table S2. Concordance between pathologists and automated system for the evaluation of Ki-67 expression considering all samples, only biopsy samples, or surgical samples

First vs. second pathologist

Ki-67	<3	3-20	>20
<3	30	7	-
3-20	-	29	-
>20	-	-	4

	Weighted Kappa (95% CI)
All samples	0.94 (0.88-1.00)
Biopsies	0.97 (0.91-1.00)
Surgical	0.92 (0.83-1.00)

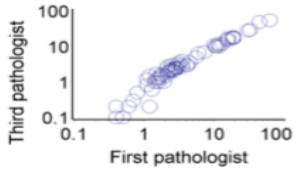


Intra-class correlation (95% CI)
0.993 (0.989-0.996)
0.994 (0.988-0.997)
0.992 (0.985-0.996)

First vs. third pathologist

Ki-67	<3	3-20	>20
<3	35	2	-
3-20	2	27	-
>20	-	-	4

	Weighted Kappa (95% CI)
All samples	0.97 (0.93-1.00)
Biopsies	0.97 (0.91-1.00)
Surgical	0.97 (0.91-1.00)

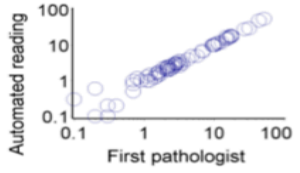


Intra-class correlation (95% CI)
0.991 (0.986-0.995
0.990 (0.980-0.995)
0.994 (0.989-0.997)

First pathologist vs. Automated

Ki-67	<3	3-20	>20
<3	36	1	-
3-20	4	25	-
>20	-	-	4

	Weighted Kappa (95% CI)
All samples	0.95 (0.89-1.00)
Biopsies	0.94 (0.85-1.00)
Surgical	0.96 (0.90-1.00)

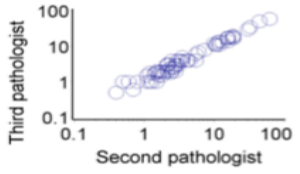


Intra-class correlation (95% CI)
0.996 (0.994-0.998)
0.998 (0.997-0.999)
0.994 (0.989-0.997)

Second vs. third pathologist

Ki-67	<3	3-20	>20
<3	30	-	-
3-20	7	29	-
>20	-	-	4

	Weighted Kappa (95% CI)
All samples	0.94 (0.88-1.00)
Biopsies	0.93 (0.84-1.00)
Surgical	0.95 (0.88-1.00)

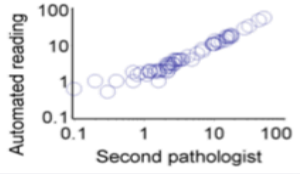


Intra-class correlation (95% CI)
0.994 (0.990-0.996)
0.997 (0.993-0.998)
0.991 (0.982-0.995)

Second pathologist vs. Automated

Ki-67	<3	3-20	>20
<3	30	-	-
3-20	10	26	-
>20	-	-	4

	Weighted Kappa (95% CI)
All samples	0.90 (0.81-0.98)
Biopsies	0.90 (0.78-1.00)
Surgical	0.91 (0.79-1.00)

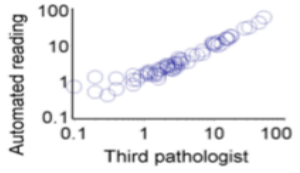


Intra-class correlation (95% CI)
0.987 (0.980-0.992)
0.988 (0.976-0.994)
0.987 (0.975-0.993)

Third pathologist vs. Automated

Ki-67	<3	3-20	>20
<3	37	-	-
3-20	3	26	-
>20	-	-	4

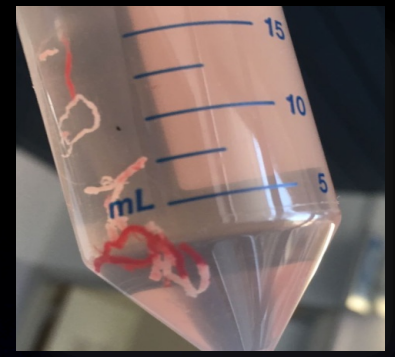
	Weighted Kappa (95% CI)
All samples	0.97 (0.93-1.00)
Biopsies	0.98 (0.94-1.00)
Surgical	0.96 (0.90-1.00)



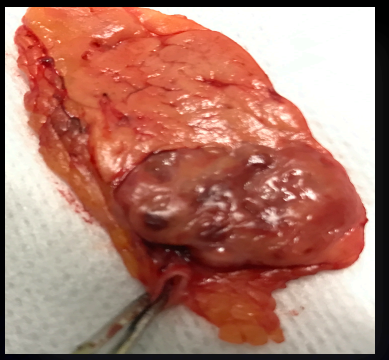
Intra-class correlation (95% CI)
0.988 (0.980-0.992)
0.981 (0.964-0.990)
0.997 (0.993-0.998)


European Journal of Surgical Oncology

Ki-67 and presence of liver metastases identify different progression-risk classes in pancreatic neuroendocrine neoplasms (pNEN) undergoing resection



vs



vs

vs

vs

regardi

Format: Abstract

Send to

Neuroendocrinology. 2018 Oct 9. doi: 10.1159/000494355. [Epub ahead of print]

COMPETITIVE TESTING THE WHO 2010 VS THE WHO 2017 GRADING OF PANCREAS NEUROENDOCRINE NEOPLASIA: DATA FROM A LARGE INTERNATIONAL COHORT STUDY.

Rindi G, Klersy C, Albarello L, Baudin E, Bianchi A, Büchler MW, Caplin M, Couvelard A, Cros J, de Herder WW, Delle Fave G, Doglioni C, Federspiel B, Fischer L, Fusai G, Gavazzi F, Hansen C, Inzani F, Jann H, Komminoth P, Knigge U, Landoni L, La Rosa S, Lawlor R, Luong T, Marinoni I, Panzuto F, Pape UF, Partelli S, Perren A, Rinzivillo M, Rubini C, Ruszniewski P, Scarpa A, Schmitt AM, Schinzari G, Scoazec JY, Sessa F, Solcia E, Spaggiari P, Toumpanakis C, Vanoli A, Wiedenmann B, Zamboni G, Zandee W, Zerbi A, Falconi M.

Abstract

Background: the World Health Organization (WHO) and the American Joint Cancer Committee (AJCC) modified the grading of pancreatic neuroendocrine neoplasms from a three-tiers (WHO-AJCC 2010) to a four-tiers system by introducing the novel category of NET G3 (WHO-AJCC 2017).

OBJECTIVES: This study aims at validating the WHO-AJCC 2017 and identifying the most effective grading system.

METHOD: 2102 patients were enrolled; entry criteria were i) performed surgery; ii) at least two years of follow-up; iii) observation time up to 2015. Data from 34 variables were collected; grading was assessed and compared for efficacy by statistical means including Kaplan Meier method, Cox regression analysis, Harrell's C statistics and Royston's explained variation in univariable and multivariable analyses.

RESULTS: At descriptive analysis, the two grading systems demonstrated statistically significant differences for the major category sex but not for age groups. At Cox regression analysis, both grading systems showed statistically significant differences between grades for OS and EFS, however no statistically significant difference was observed between the two G3 classes of WHO-AJCC 2017. At multivariable analysis for the two models fitted to compare efficacy, the two grading systems performed equally well with substantially similar optimal discrimination and well-explained variation for both OS and EFS. The WHO-AJCC 2017 grading system retained statistically significant difference between the two G3 classes for OS but not for EFS.

CONCLUSIONS: the WHO-AJCC 2017 grading is at least equally performing as the WHO-AJCC 2010 but allows the successful identification of the most aggressive PanNET subgroup. Grading is confirmed as probably the most powerful tool for patient survival prediction.
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NEC

LY DIFFERENTIATED

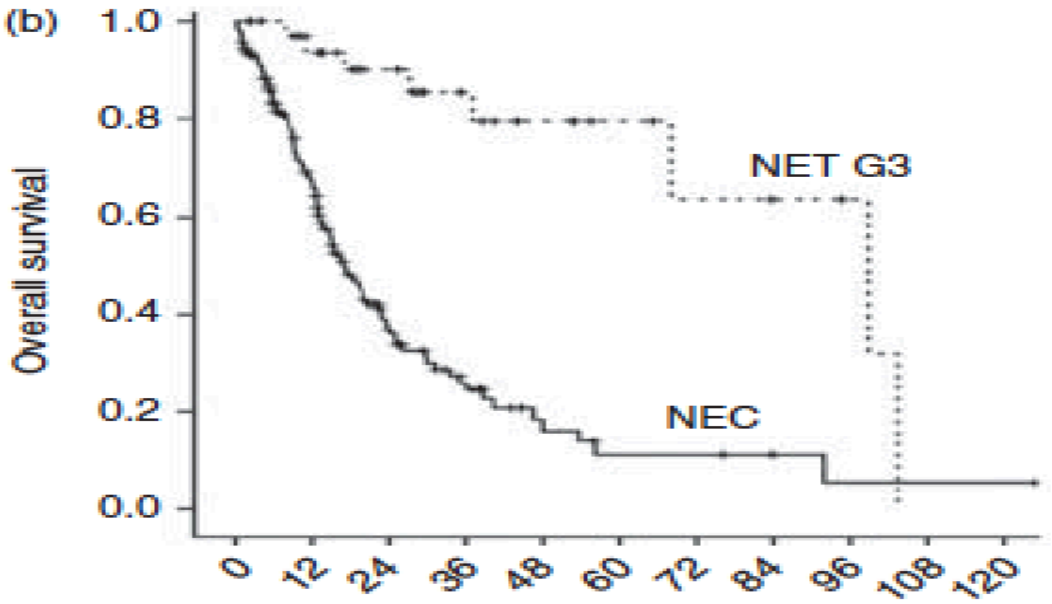
67 LI

Ki67 LI= 40%

Ki67 LI= 90%

Morphology

Well Diferentiated *vs* Poorly Differentiated



Heetfeld et al Endocr Relat Cancer Oncol 2015

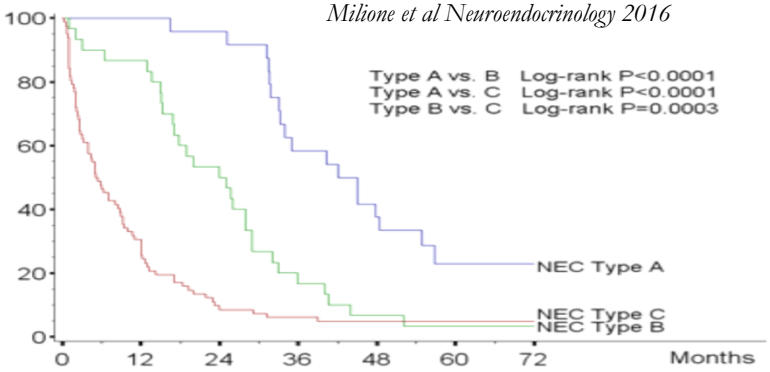
Table 4 Efficacy of platinum-etoposide first-line chemotherapy according to differentiation of Grade 3 neuroendocrine neoplasms

	NET G3	NEC	*P*
Number of patients	12	113	
OR, *n* (%)	2 (17)	39 (35)	0.18
SD, *n* (%)	1 (8)	25 (22)	0.24
PD, *n* (%)	6 (50)	30 (27)	0.09
NA, *n* (%)	3 (25)	19 (17)	0.36
DCR (%)	3 (33%)	64 (68%)	0.036
Median PFS (95% CI), months	2.4 (1.1–3.8)	5.0 (4.0–6.1)	0.049
Median OS (95% CI), months	NR	16.4 (13.4–19.5)	0.003

OR, objective response; SD, stable disease; PD, progressive disease; NA, not available; DCR, disease control rate; PFS, progression free survival; OS, overall survival; NR, not reached.

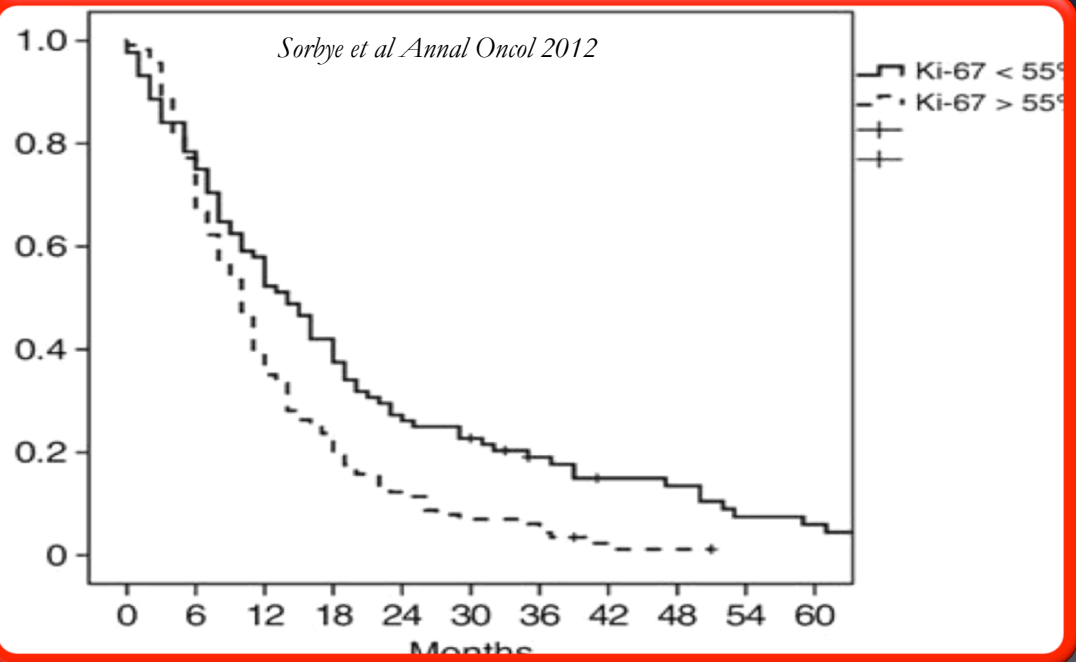
Ki-67 re-evaluation
new cut off? 55%?

Milione et al Neuroendocrinology 2016



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
Overall survival (%)							
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

Sorbye et al Annal Oncol 2012




Ki67 cut off 20%
Ki67 cut off 55%

Endocr Relat Cancer. 2018 May;25(5):583-593

Endocrine-Related Cancer

M Milione et

RESEARCH PRO

Ki67 proliferative i component drives

Massimo Milione[1], Patrick Maisonneuve[2], A
Alessandro Vanoli[6], Giovanna Tagliabue[7], I
Aldo Scarpa[11], Mauro Papotti[12], Marco Vola
Guido Rindi[16], Enrico Solcia[6], Stefano La R

Table 2. Univariate and multivariable analysis for overall survival

	Adjusted for site HR (95% CI) *	P-value	Multivariable [2] HR (95% CI)	P-value	Multivariable [3] HR (95% CI)	P-value
Site						
Colorectal	1.00		1.00		**1.00**	
Gastroesophageal	0.73 (0.50-1.06)	0.10	**0.61 (0.39-0.94)**	**0.02**	**0.64 (0.43-0.96)**	**0.03**
Pancreatobiliary	**0.41 (0.25-0.67)**	**0.0004**	0.54 (0.29-1.03)	0.06	0.58 (0.33-1.04)	0.07
Stage						
I/II/IIIA (pN-)	1.00		1.00		1.00	
IIIB (pN+)	**2.03 (1.20-3.42)**	**0.008**	1.70 (0.90-3.22)	0.10	1.75 (0.95-3.23)	0.07
IV (M+)	1.59 (0.80-3.16)	0.19	1.08 (0.48-2.40)	0.86	1.09 (0.51-2.31)	0.83
MANEC subtype						
Collision	1.00		1.00			
Combined	0.90 (0.63-1.28)	0.56	1.07 (0.72-1.61)	0.73	-	
Amphicrin/Combined	**0.56 (0.33-0.96)**	**0.04**	0.83 (0.45-1.53)	0.55	-	
NEC type						
Large cells	1.00		1.00			
Small cells	1.54 (0.97-2.43)	0.07	1.27(0.77-2.10)	0.35	-	
NEC component						
% NEC component (per 10%)	1.09 (0.96-1.22)	0.18	-		-	
Ki67 (≥55% vs. <55%)	**9.08 (5.13-16.1)**	**<0.0001**	**8.92 (3.96-20.1)**	**<0.0001**	**7.83 (4.17-14.7)**	**<0.0001**
MC (≥50/10HPF vs. <50/10HPF)	**1.81 (1.28-2.58)**	**0.0009**	**1.53 (1.03-2.28)**	**0.04**	**1.51 (1.03-2.20)**	**0.04**
p53 (≥30% vs. <30%)	1.10 (0.78-1.56)	0.58	-		-	
CD117 (positive vs. negative)	**1.59 (1.13-2.24)**	**0.008**	1.45 (0.98-2.15)	0.06	1.42 (0.99-2.04)	0.06
SSTR2a (positive vs. negative)	1.21 (0.87-1.68)	0.25	-			
Non-NEC component						
Ki67 (≥55% vs. <55%)	**1.81 (1.28-2.54)**	**0.0007**	1.29 (0.87-1.92)	0.20	-	
MC (≥50/10HPF vs. <50/10HPF)	1.39 (0.91-2.11)	0.13	-		-	
Nerve infiltration						
Present vs. absent	**3.20 (1.77-5.77)**	**0.0001**	0.88 (0.42-1.82)	0.72	-	
Angioinvasion						
Present vs. absent	0.85 (0.54-1.33)	0.47	-		-	
Budding						
Absent	1.00		1.00			
Mild/moderate	0.82 (0.53-1.27)	0.37	1.29 (0.72-2.28)	0.39	-	
Severe	**1.97 (1.31-2.96)**	**0.001**	1.13 (0.65-1.96)	0.67	-	
Molecular Analysis**						
Wild type	1.00		1.00		1.00	
Mutated	**2.36 (1.41-3.97)**	**0.001**	**2.22 (1.19-4.15)**	**0.01**	**2.68 (1.50-4.81)**	**0.0009**

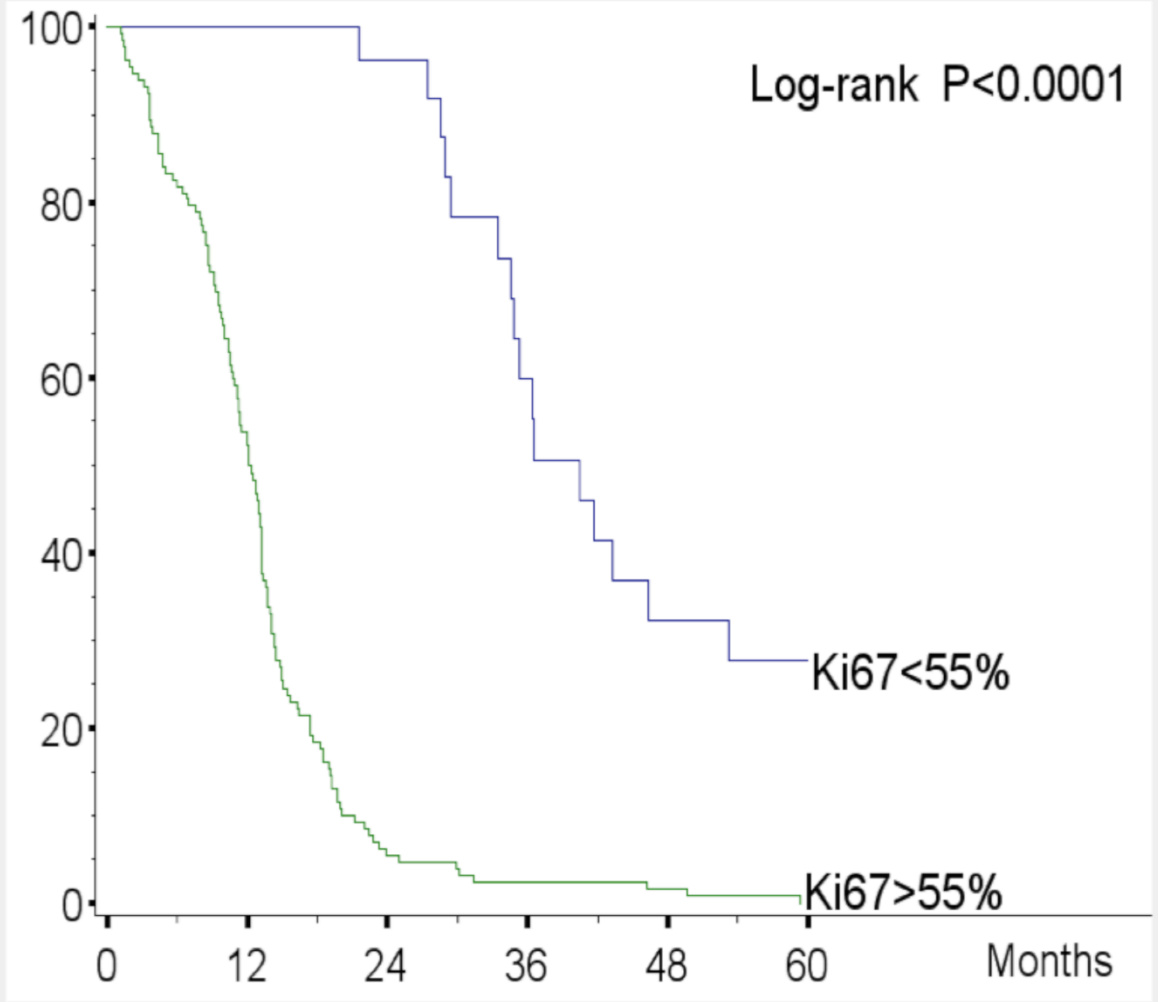
CD117: tyrosine-protein kinase Kit; **Ki67:** Ki67 index; **M+:** Liver metastases; **MANEC:** Mixed adeno-neuroendocrine carcinoma; **MC:** Mitotic count; **N+:** Lymph node metastases; **NEC:** neuroendocrine carcinoma; **SSTR2a**: somatostatin receptor 2a.

Multivariable model 2 includes all factors associated with overall survival after single adjustment for tumor site; Multivariable model 3 retains only variables showing an association (P<0.10) with overall survival.

** Multivariable risk estimates for single gene mutations from alternative model 3: *KRAS* mutated [n=12; HR=2.69 (1.24-5.82); P=0.01]; *BRAF* mutated [n=4; HR=1.81 (0.51-6.39); P=0.36]; *TP53* mutated [n=17; HR=2.90 (1.48-5.68); P=0.002].

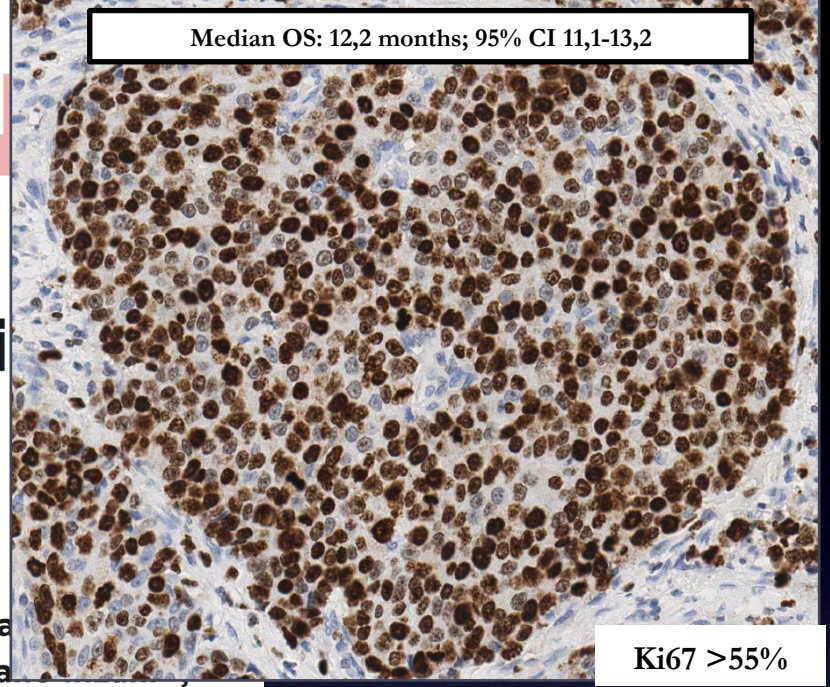
Endocr Relat Cancer. 2018 May;25(5):583-593

Endocrine-Related | M Milione *et al.* | Ki67 in NEC drives MANEC | 25:5

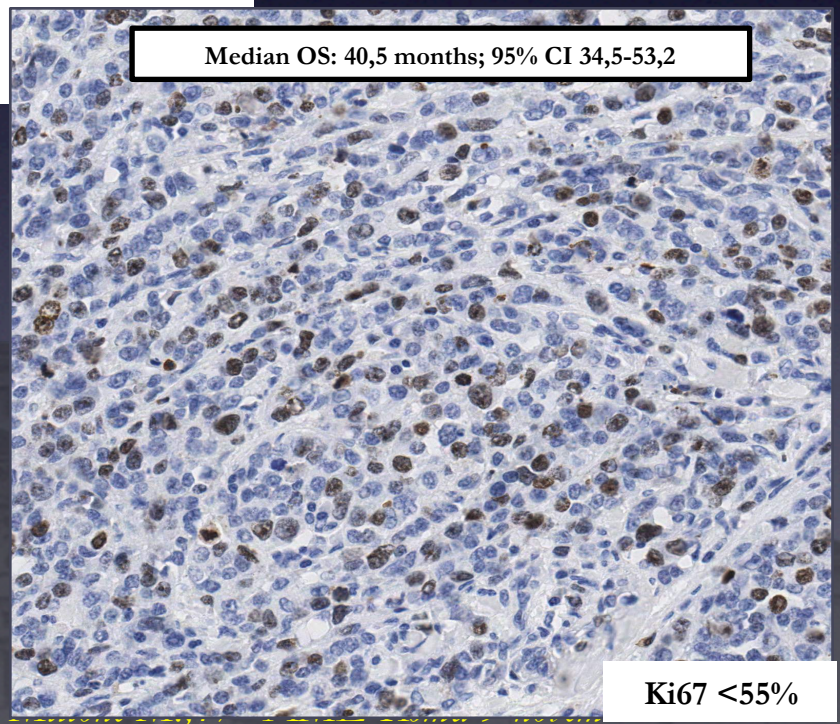


At risk

Ki67<55%	28	28	24	13	7	6
Ki67≥55%	132	69	7	3	2	0

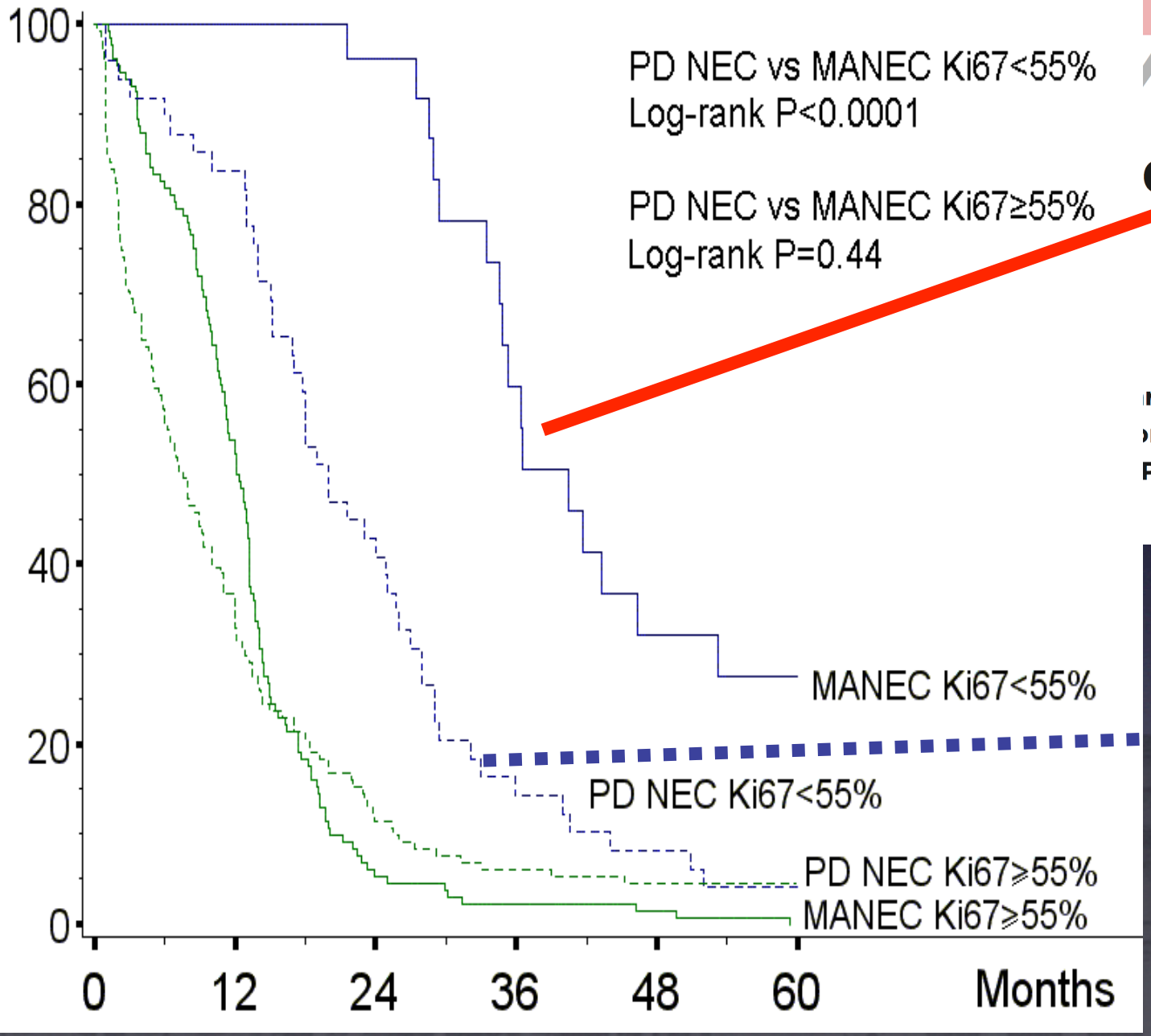


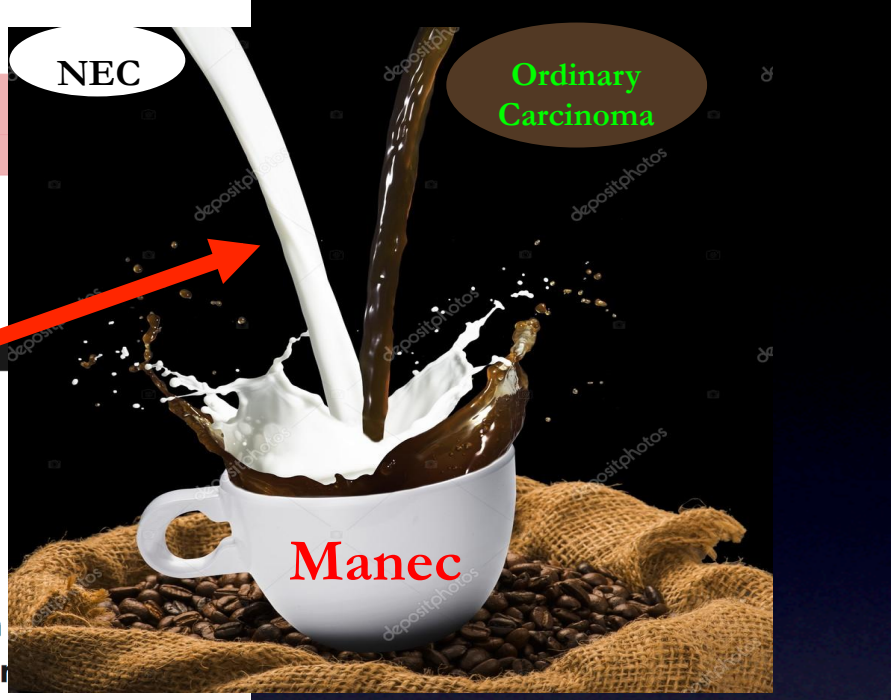
Ki67 >55%

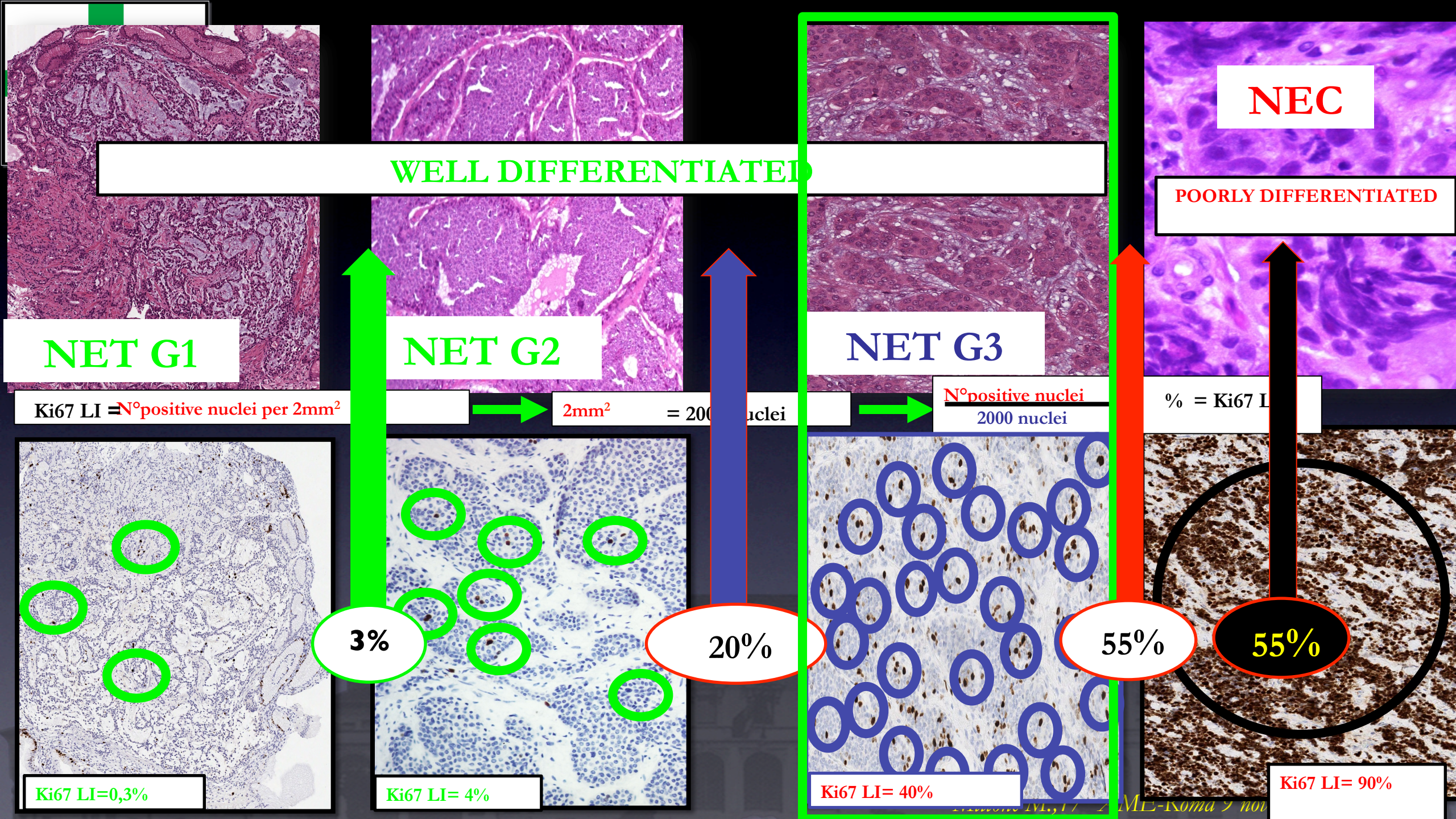


Ki67 <55%

Endocr Relat Cancer. 2018 May;25(5):583-593






WELL DIFFERENTIATED
NEC
POORLY DIFFERENTIATED
NET G1
NET G2
NET G3
Ki67 LI = N°positive nuclei per 2mm²
2mm²
= 200
uclei
N°positive nuclei
2000 nuclei
% = Ki67 L
3%
20%
55%
55%
Ki67 LI=0,3%
Ki67 LI= 4%
Ki67 LI= 40%
Ki67 LI= 90%


massimo.milione@istitutotumori.mi.it
grazie