WHO 2017

Neuroendocrine Tumour Grading System

An update from the new WHO classification

4th Edition 2017

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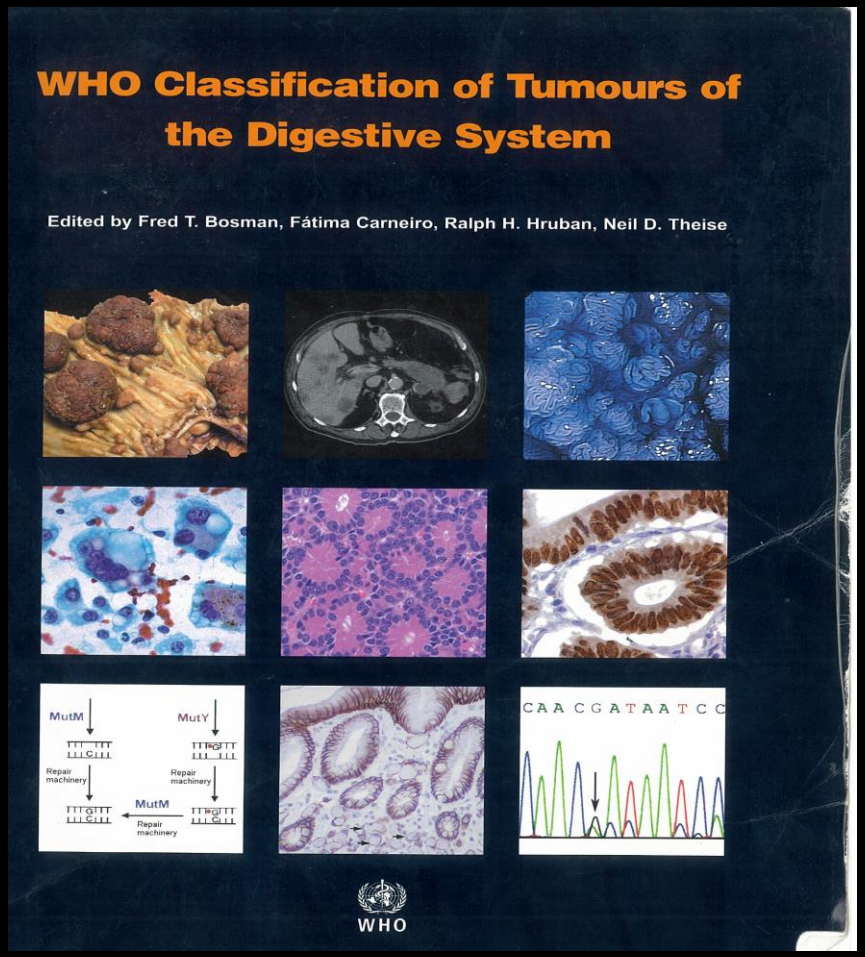
WHO 2010 NET Grading System



Nomenclature and classification of neuroendocrine neoplasms of the digestive system

G. Rindi
R. Arnold
F.T. Bosman
C. Capella

D.S. Klimstra
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E. Solcia

Introduction

One of the major problems in the management of patients with gastrointestinal (neuro)endocrine tumours (NETs) is the lack of universally accepted standards, both for nomenclature (i.e. the clinical significance of current definitions) and for staging of disease [2114]. Based on a wealth of evidence, the most recent WHO classification of 2000 [3013] provided a rational approach to the nomenclature and classification of NETs of the digestive system, developing a coherent terminology and allowing the prognostic stratification of these neoplasms. This WHO classification has served as a basis for establishing criteria for practical management, as reflected in the guidelines of many scientific societies [2343–2345, 2567, 2621]. However, while most institutions in the European Union (EU) adhere to the WHO 2000 classification scheme, the scheme has not achieved widespread acceptance in diagnostic practice in the United States of America (USA). The reasons for this include: (1) the embedding of stage-related information within a grading system; (2) the complicated clinical–pathological classification schemes; and (3) the category "uncertain behaviour," which has met with resistance from both clinicians and pathologists [850]. In addition, the continued widespread use of the term "carcinoid," with its largely incorrect benign connotation, hampered universal acceptance of this classification system. Taking into account the considerations stated above, the European Neuroendocrine Tumor Society (ENETS) has recently proposed two complementary classification tools – a grading classification and a site-specific staging system [2684, 2685]. The intention was to improve the WHO 2000 classification by strengthening its appreciation of the following concepts: (1) tumour heterogeneity, i.e. tumours differ according to the site of origin; (2) tumour differentiation i.e. tumours differ according to tumour cell differentiation status; and (3) malignancy, i.e. long-term follow-up indicates that NETs as a category are malignant.

Such concepts stem from evidence that biological characteristics and stage at diagnosis largely determine the clinical behaviour of NETS. As it does for other epithelial neoplasms, the ENETS grading and staging system formally recognizes the malignant potential of NETs and organizes their classification according to grade and stage.

WHO 2010 classification

In the present volume of the WHO classification of tumours, we attempt to bridge the above-mentioned classification gap by introducing a grading scheme and applying the terms NET and NEC as widely accepted and used by clinicians in both the EU and USA. The term "neuroendocrine" is adopted here to indicate the expression of neural markers in neoplastic cells with otherwise exquisitely endocrine properties and phenotype. The term "neuroendocrine neoplasm" can be used synonymously with "neuroendocrine tumour".

Grading classification

Grading is performed on the basis of morphological criteria (see individual chapters) and the assessment of proliferation fraction according to the ENETS scheme [2684, 2685]. Evidence that the proliferation fraction has prognostic significance is available for NETs of foregut origin, including stomach and pancreas [250, 850, 1705, 2514, 2676, 2682, 2686]. The proposed grading based on proliferation has three tiers (G1, G2, G3) with the following definitions of mitotic count and Ki67 index:

– G1: mitotic count, < 2 per 10 high power fields (HPF) and/or ≤ 2% Ki67 index;
– G2: mitotic count 2–20 per 10 HPF and/or 3–20% Ki67 index;
– G3: mitotic count > 20 per 10 HPF and/or > 20% Ki67 index.

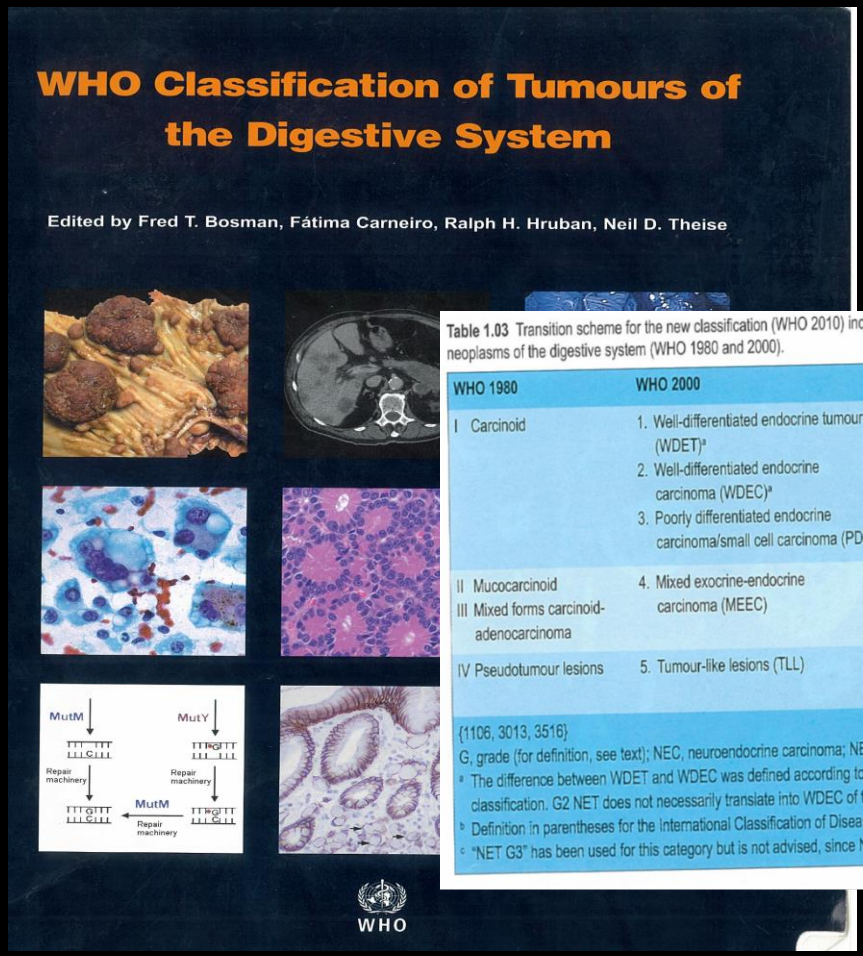
The grading requires mitotic count in at least 50 HPFs (1 HPF = 2 mm²) and Ki67 index using the MIB antibody as a percentage of 500–2000 cells counted in areas of strongest nuclear labelling ("hot spots"). If grade differs for mitotic count compared with Ki67 index, it is suggested that the higher grade be assumed. Evidence to support this grading scheme is available for the stomach, duodenum and pancreas NETs [772, 868, 1705, 2449], but is still lacking for NETs of the intestine.

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)[a]
	2. Well-differentiated endocrine carcinoma (WDEC)[a]	2. NET G2[a]
	3. Poorly differentiated endocrine carcinoma/small cell carcinoma (PDEC)	3. NEC (large cell or small cell type)[b,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.

WHO 2010 NET Grading System



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WHO 2010 Grading System

World Health Organization Classification 2010 for Neuroendocrine Neoplasms

Well differentiated NENs	**Ki67index|**	**Mitotic index**
Neuroendocrine tumour (NET) G1	≤ 2 %	<2/10 HPF
Neuroendocrine tumour (NET) G2	3-20 %	2-20/10 HPF
Poorly differentiated NENs		
Neuroendocrine carcinoma (NEC) G3*	>20 %	>20/10 HPF
Mixed adenoneuroendocrine carcinoma (MANEC)		

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WHO 2017 Grading System

TABLE 1

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)

* Ki67 index is based on at least 500 cells in areas of higher nuclear labeling ("hot spots"); mitoses in 50 high power fields (HPF, 0.2mm^2) in areas of higher density and expressed per 10 HPF (2.0 mm^2); the final grade based on which ever index (mitotic rate or Ki67) places the tumor in the highest grade category. For assessing Ki67, casual visual estimation ("eyeballing") is not recommended; manual counting of printed images is suggested {25412850}.

The changes

The changes

- Alteration in set point of Ki67 cut offs

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Poorly differentiated NENs		
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Grade 1 cut of <3%

- Because this was always the intention of WHO 2010. That is ki67 proliferative indices were to be rounded up or down to nearest whole number
- Partly in recognition that the G1 cut off is too low

Debate- Should grade 1 cut off be changed to 5%?

- Studies based on large patient cohorts have revealed that in the subgroup of patients with G1 to G2 tumours, a significant higher risk of progression was observed when 5% was used as cutoff level in stead of 2%.

Ref:

Scarpa A et al Pancreatic endocrine tumors: improved TNM staging and histopathological grading permit a clinically efficient prognostic stratification of patients. Mod Pathol. 2010 Jun;23:824-33.

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The changes

- Alteration in set point of Ki67 cut offs
- Subdivision of tumours with ki67>20% into well differentiated G3 NETS and poorly differentiated G3 NECS

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POORLY DIFFERENTIATED NENs		
Neuroendocrine Carcinoma (NEC) G3	>20%	>20/10 HPF
Mixed adenoneuroendocrine carcinoma (MANEC)		

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PNETs with ki67>20%

- Since 2010 it has been recognised that grade 3 NETs at the lower range of proliferative index are more like G2 NETS than aggressive carcinoma

Nordic NEC study

Sorbye H, Welin S, Langer SW, et al. Predictive and prognostic factors for treatment and survival in 305 patients with advanced gastrointestinal neuroendocrine carcinoma (WHO G3): the NORDIC NEC study. *Ann Oncol*. 2013;24:152 160.

- <55% less responsive to platinum based chemo
- >55% more responsive (but still recurred quicker and worse survival)

However pathology in this study not well evaluated.

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**

TABLE 3. Comparison of Survival (All Stages)

	Grade-concordant (Mitotic G2/Ki67 G2) PanNETs (n = 53)	Grade-discordant (Mitotic G2/Ki67 G3) PanNETs (n = 19)	Poorly Differentiated NECs (n = 43)
Median survival (95% confidence interval) (mo)	67.8 (51.8-93.8)	54.1 (30.5-117.9)	11 (6-18)
2-y survival (mean ± SD) (%)	86.7 ± 5.1	74.9 ± 11	22.5 ± 6.9
5-y survival (mean ± SD) (%)	62.4 ± 8.3	29.1 ± 16	16.1 ± 6.3
P	0.2	0.002	

Median survival of grade discordatnt PNETS was less than Concordant but this did not reach statistical significance

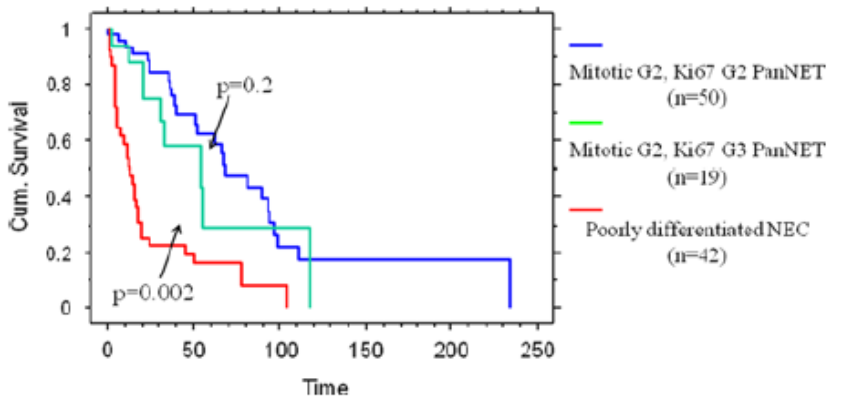


FIGURE 4. The Kaplan-Meier analysis comparing the overall disease-specific survivals of all grade-concordant PanNETs, grade-discordant PanNETs, and poorly differentiated NECs (all cases).

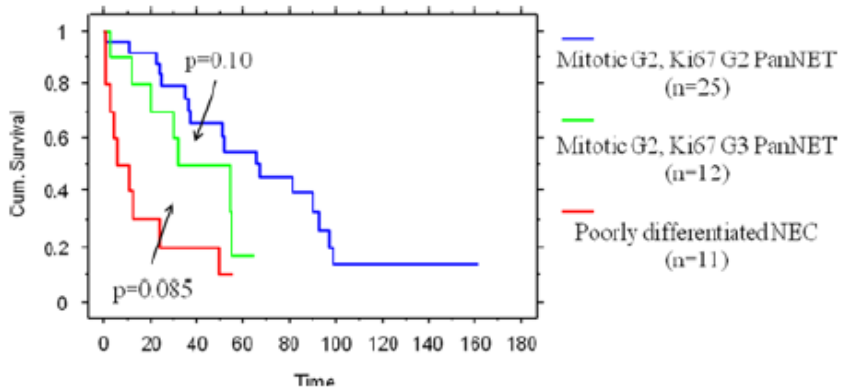


FIGURE 5. The Kaplan-Meier analysis comparing the overall disease-specific survivals of grade-concordant PanNETs, grade-discordant PanNETs, and poorly differentiated NECs (cases with distant metastasis only).

PNETs with ki67>20%

- Strong evidence that not just ki67/mitotic rate but also morphological differentiation is important.
- LCNEC, SCUC should be considered completely different entities to PNETs

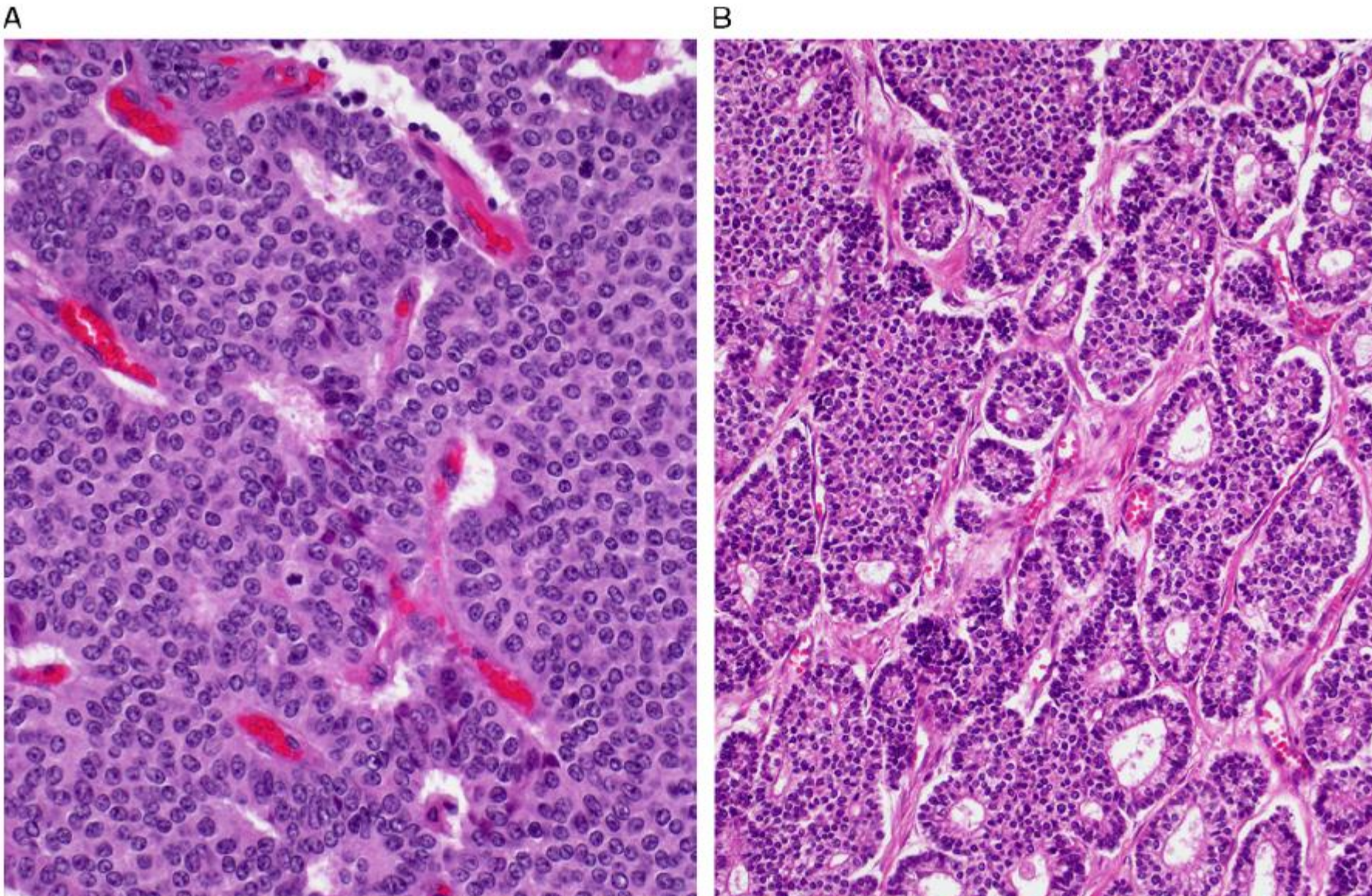
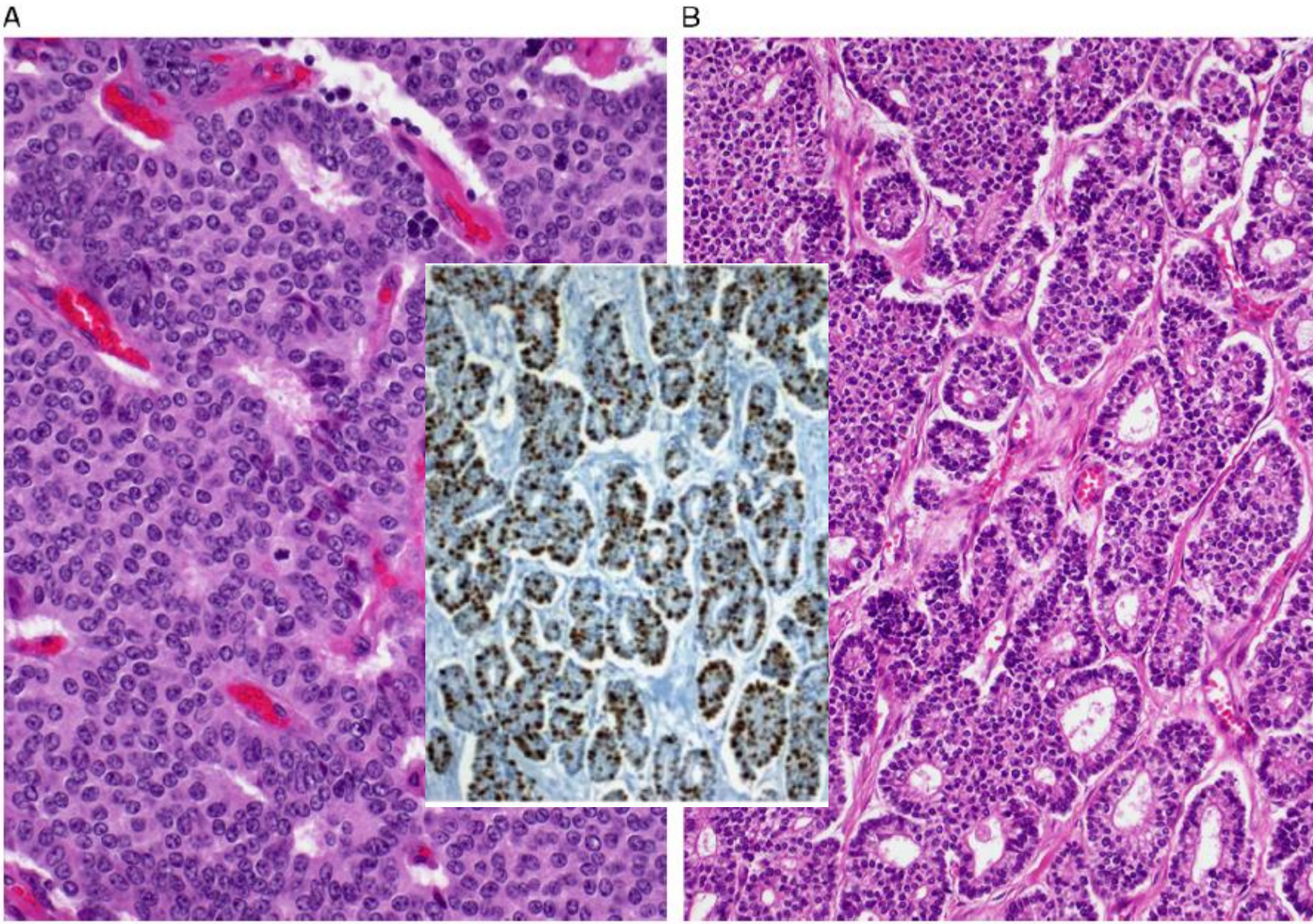


FIGURE 1. Well differentiated NETs may reveal different growth patterns ([A] diffuse and [B] glandular growth patte depicted here). The cells vary in size but usually have a moderate amount of eosinophilic cytoplasm, and nuclei are uniform and shape. Mitotic figures are rare (by definition, between 2 and 20/10 HPF for grade 2).



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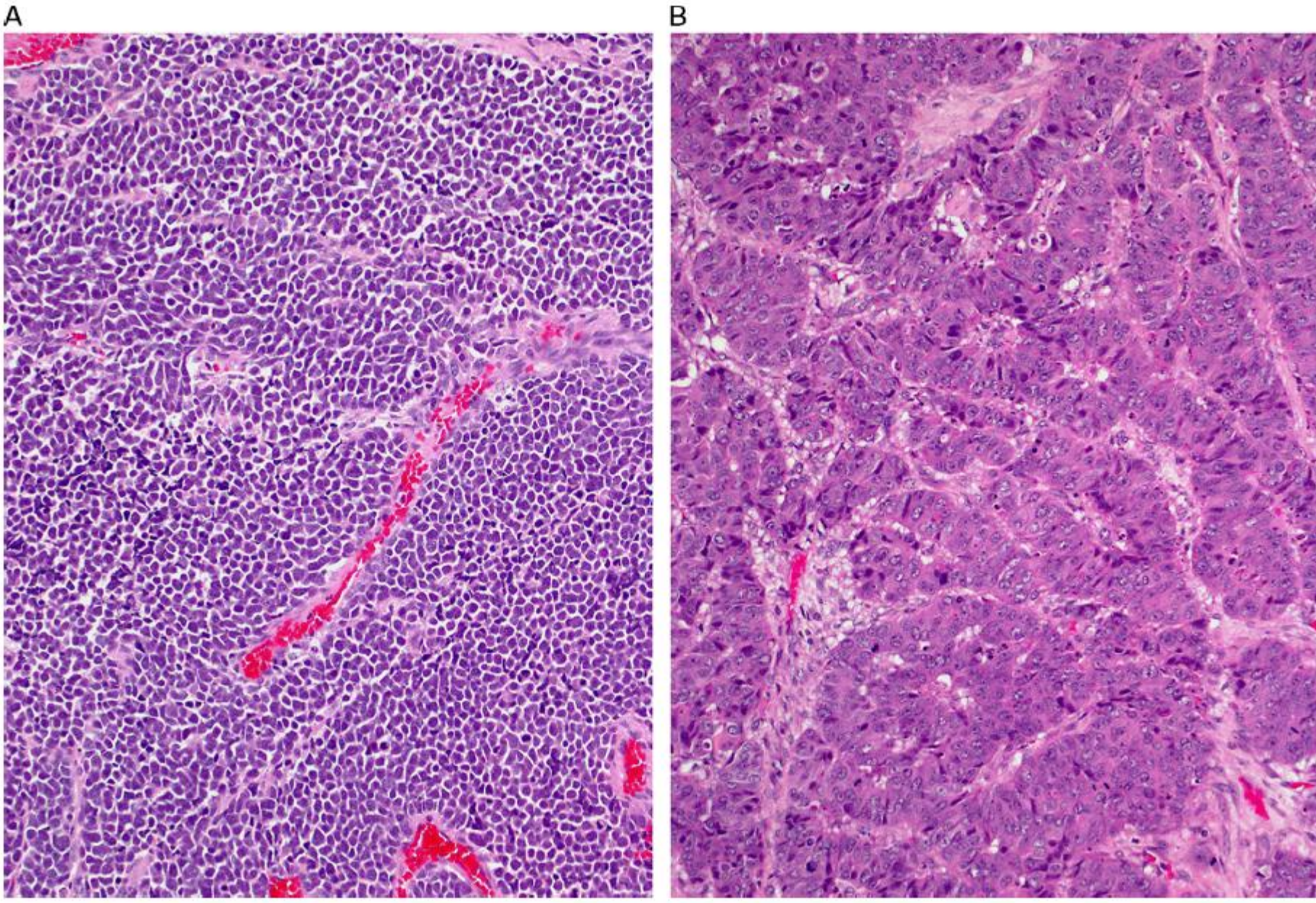
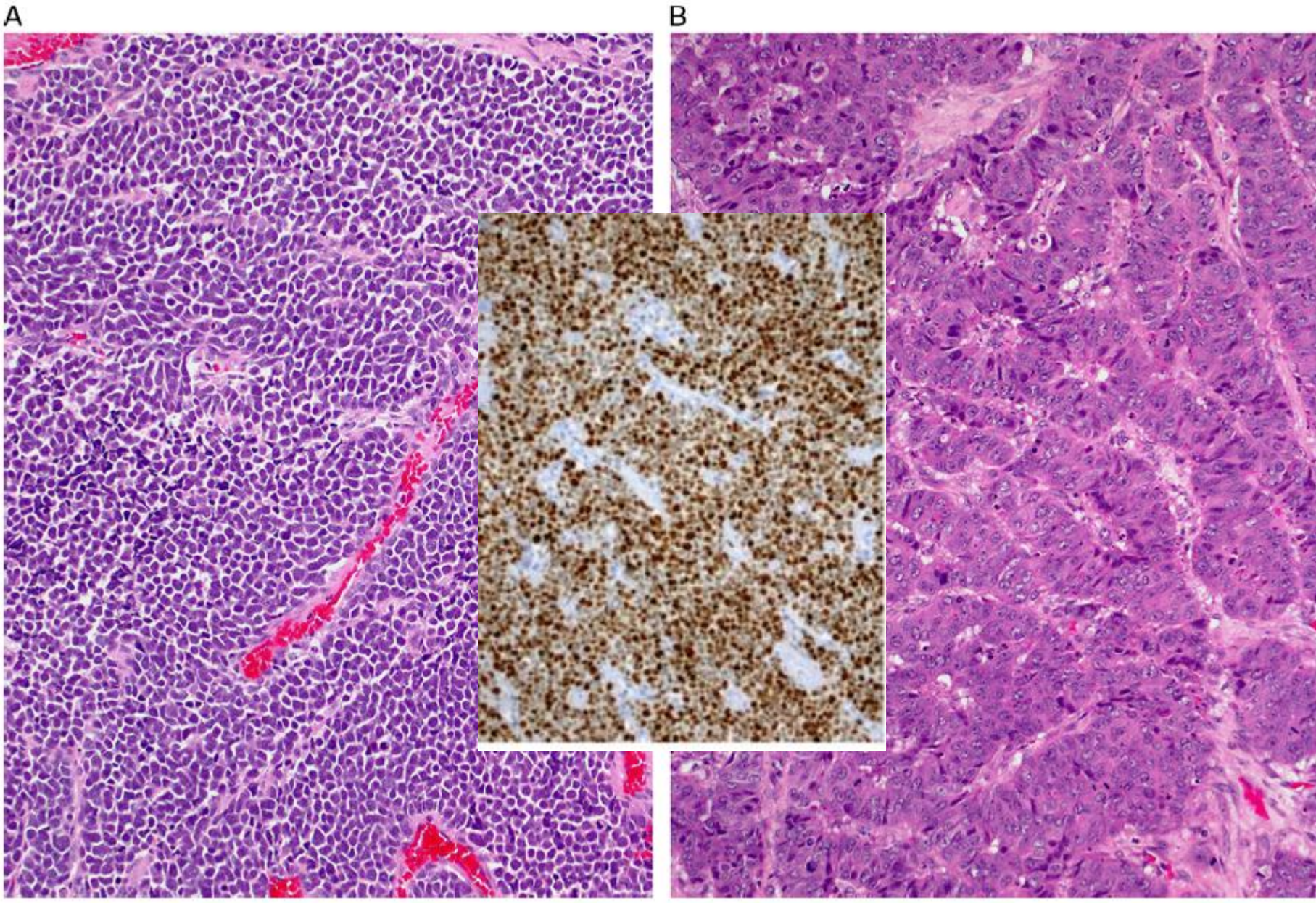


FIGURE 2. Poorly differentiated NEC. A, Small cell type is composed of relatively small tumor cells with a high nucleu cytoplasm ratio, hyperchromatic nuclei, and nuclear molding. B, Large cell type is characterized with cells that are often roun polygonal, and the nuclei have either vesicular chromatin or prominent nucleoli. Note multiple mitotic figures.



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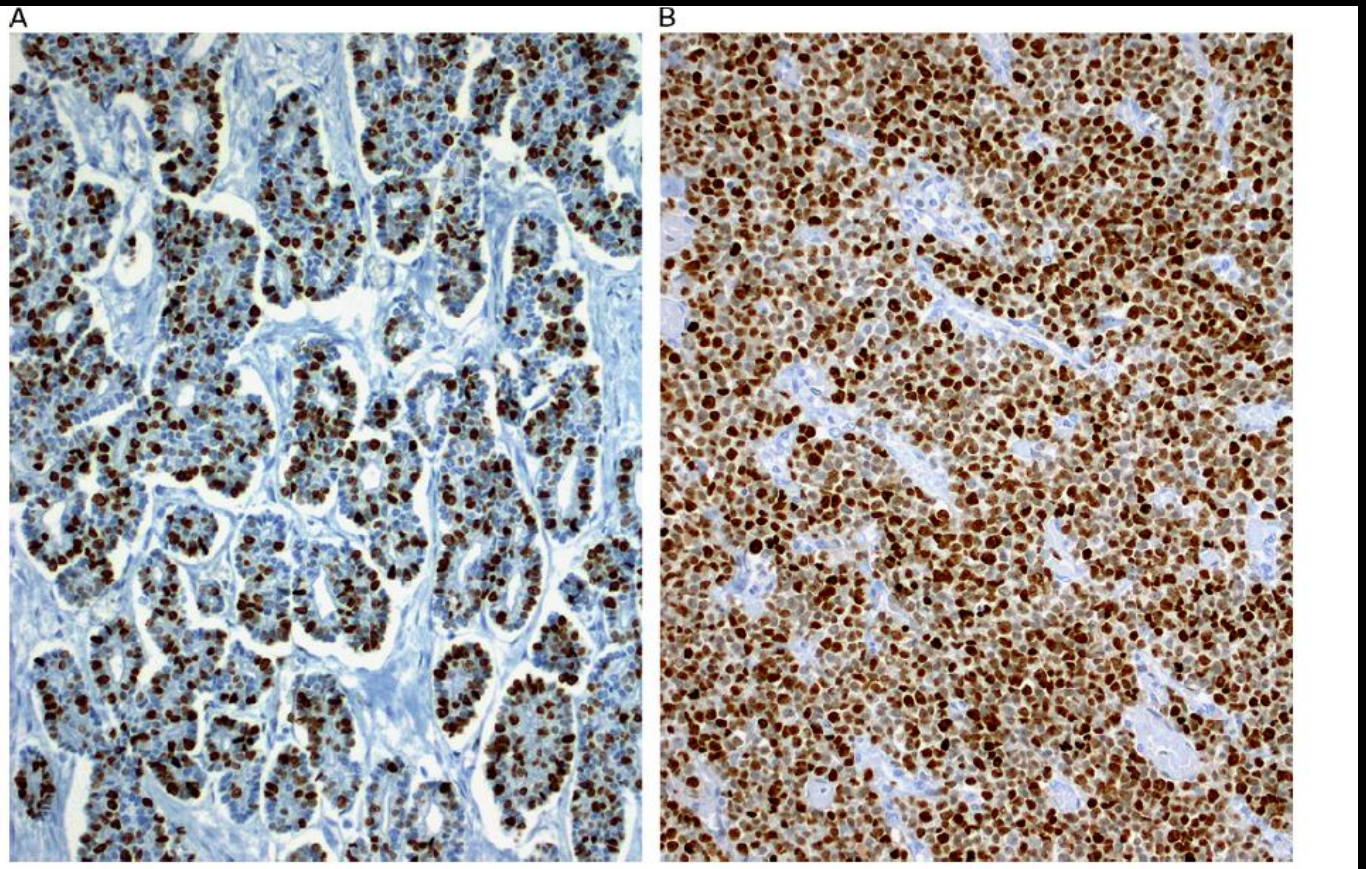

FIGURE 3. A, Average Ki67 proliferation index of grade-discordant PanNETs was 40% (as opposed to 74% of small cell–type and 66% of large cell–type poorly differentiated NECs). B, A small cell carcinoma with a Ki67 proliferation index of >95% is depicted here.

G3 NETS vs G3 NECs

Low grade NETs	**Poorly Diff NECs**
MEN1, DAX, ATRX mutations	P53, RB1mutations
Recognisable as NETS	Small cell or large cell type
Often evolve from a recognisable lower grade component	No lower grade component
No upper limit given, but usually ki67 <40 to 55%, mitotic count <20/10hpf	Must have ki67 index >20%, no lower limit given but usually >55%

Summary

- NETs with a ki67>20% are divided into two groups by WHO 2017

1. Well diff NET with high mitotic rate/ki67 – usually have ki67 40%
2. Poorly differentiate SCUC.LCNEC – usually have a ki67 70%

Definitions

Pancreatic neuroendocrine tumour:

Well differentiated, low, intermediate, or high-grade neuroendocrine neoplasm, composed of cells showing minimal to moderate atypia, displaying organoid patterns, lacking necrosis, and expressing general markers of neuroendocrine differentiation (diffuse and intense synaptophysin and usually also chromogranin A staining) and hormones (usually intense but not necessarily diffuse), either orthotopic or ectopic to the pancreas. PanNETs are graded by their proliferative activity into either G1 (mitoses<2/10 HPF and Ki67 index d 2%), G2 (mitoses 2-20/10 HPF or Ki67 index 3-20%), or G3 (mitoses >20/10 HPF or Ki67 index >20%)

Poorly differentiated neuroendocrine carcinoma:

Poorly differentiated, high-grade neuroendocrine neoplasm, composed of highly atypical small cells or large to intermediate cells expressing the general markers of neuroendocrine differentiation (diffuse or faint synaptophysin, faint or focal chromogranin A staining) and rarely hormones, and lacking expression of exocrine enzyme markers (trypsin, chymotrypsin, etc.). PanNECs are graded based on their proliferative activity as G3 (mitoses >20/10 HPF or Ki67 index >20%)

WHO 2010 Grading System

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The changes

- Alteration in set point of Ki67 cut offs
- Subdivision of tumours with ki67>20% into well differentiated G3 NETS and poorly differentiated G3 NECS
- MANEC (mixed adenoneuroendocrine carcinoma) becomes MENEN/MINEN

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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

MINEN (mixed endocrine neuroendocrine carcinoma)

*"NET G3" has been used for this category but is not advised since NETs are by definition well differentiated

MINEN

Mixed endocrine non-endocrine neoplasms

Recognises that MINENs may occasional be well differentiated

MINENs may have a non-endocrine component other than adenocarcinoma (eg: squamous cell carcinoma, acinar cell carcinoma)

To qualify as MENEN each component must have at least 30%

Definitions

Definition of mixed endocrine-nonendocrine neoplasm – MINEN/MENEN

- A mixed neoplasm with components of a nonendocrine carcinoma (mostly ductal adenocarcinoma or acinar cell carcinoma) combined with a neuroendocrine neoplasm. Usually both components are high grade malignant carcinomas (G3), but ocasionally one of the two or both components may belong to the G1/G2 category. Therefore, the components should be individually graded, using the respective grading systems for each. To qualify for a MENEN, each component should comprise at least 30% of the tumour cell population. Nonendocrine carcinomas with scattered neuroendocrine cells by immunohistochemistry do not qualify for this definition and should be called “ nonendocrine carcinoma with neuroendocrine component”.

WHO 2010 Grading System

World Health Organization Classification 2010 for Neuroendocrine Neoplasms

Well differentiated NENs	3%	**Mitotic index**
Neuroendocrine tumour (NET) G1		<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
Mixed adenoneuroendocrine carcinoma (MANEC)		

*"NET G3" has been used for this category but is not advised since NETs are by definition well differentiated

WHO 2010 Grading System

World Health Organization Classification 2010 for Neuroendocrine Neoplasms

Well differentiated NENs		**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

MENEN (mixed endocrine neuroendocrine carcinoma)

*"NET G3" has been used for this category but is not advised since NETs are by definition well differentiated

The changes

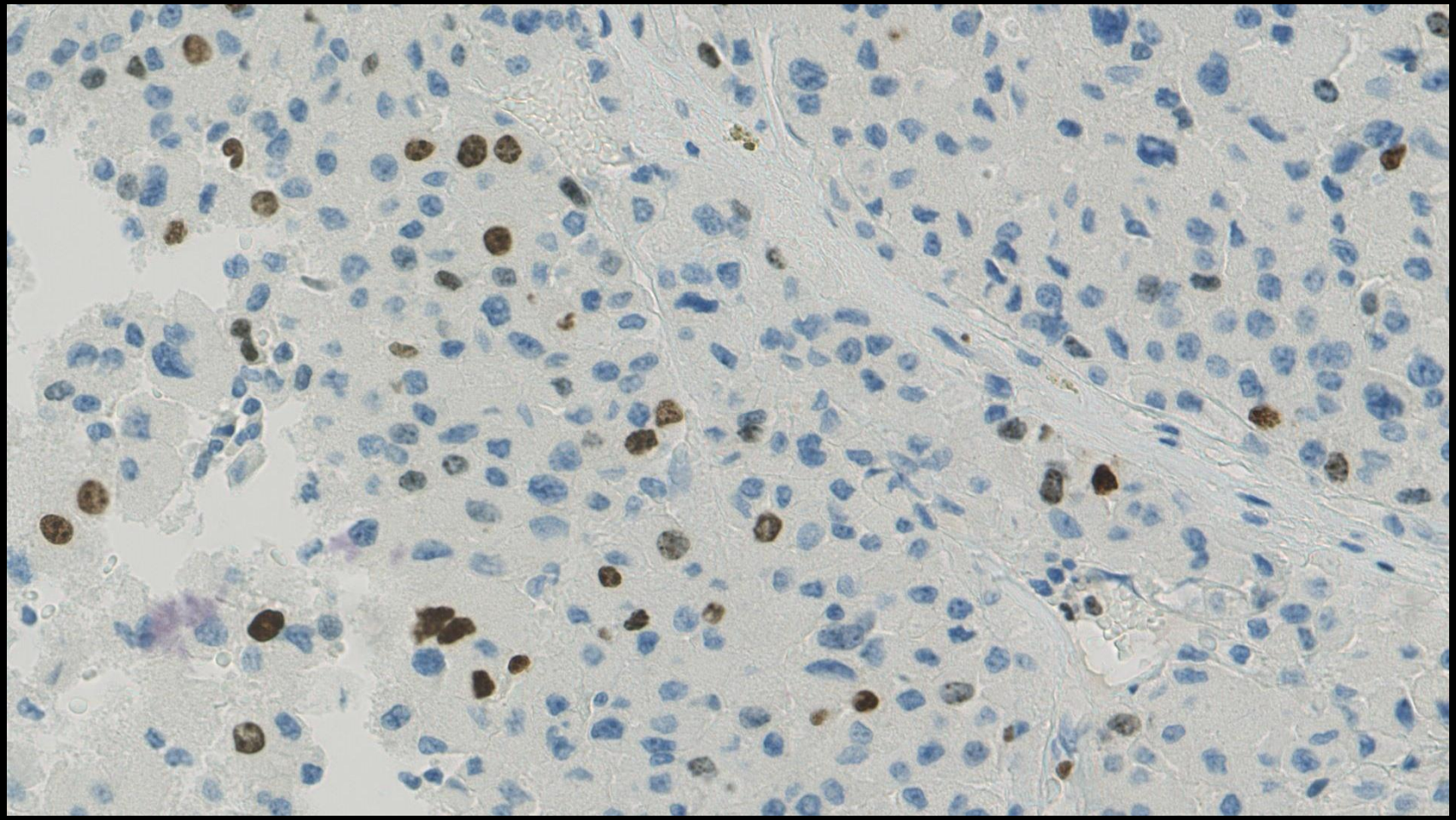
- Alteration in set point of Ki67 cut offs
- Subdivision of tumours with ki67>20% into well differentiated G3 NETS and poorly differentiated G3 NECS
- MANEC (mixed adenoneuroendocrine carcinoma) becomes MENEN/MINEN
- Recommendations on performing and interpreting Ki67

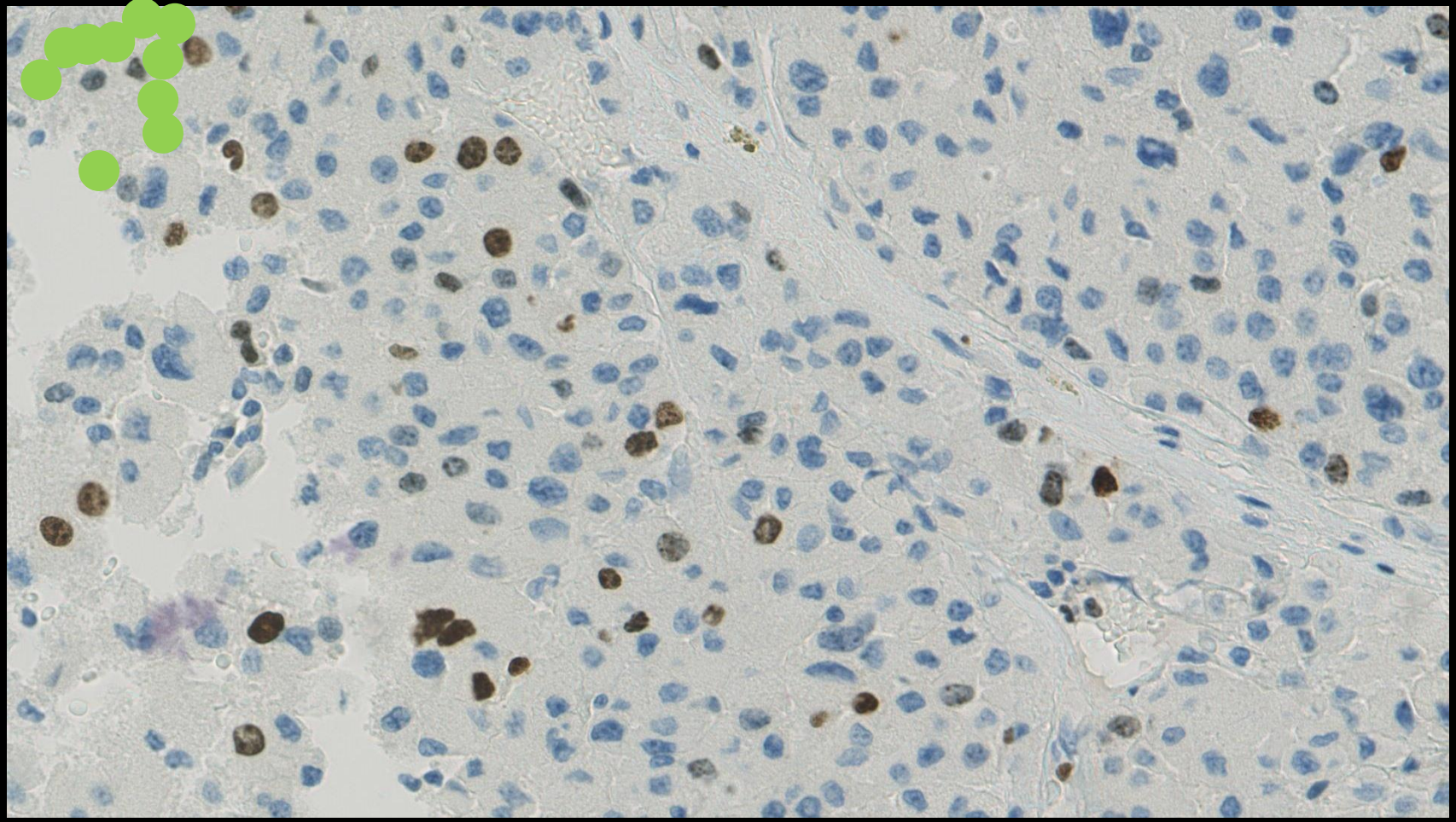
Problems with Ki67

- Remarkable constant, but sill some inter and intralaboratory variation
- Fixation and processing may effect both Ki67 and mitotic rate
- No consensus on some matters like degree of staining required

Recommendations for reporting Ki67

- Assess hotspots
- Round up or down to the nearest whole number
- Count at least 500 cells
- If mitotic count and ki67 are discordant, the higher figure (almost always ki67) is used
- Use photograph and mark methods!!





WHO 2017 Grading System

TABLE 1

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)

* Ki67 index is based on at least 500 cells in areas of higher nuclear labeling ("hot spots"); mitoses in 50 high power fields (HPF, 0.2mm^2) in areas of higher density and expressed per 10 HPF (2.0 mm^2); the final grade based on which ever index (mitotic rate or Ki67) places the tumor in the highest grade category. For assessing Ki67, casual visual estimation ("eyeballing") is not recommended; manual counting of printed images is suggested {25412850}.