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inside insights

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GIT neuroendocrine tumours

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Introduction: The 5th (2019) edition of the "WHO Classification of Tumours – Digestive System Tumours" has introduced several changes to the classification of neuroendocrine tumours.

The major change is related to the distinction of well differentiated neuroendocrine tumours (NET) from neuroendocrine carcinomas (NEC). It is increasingly clear that, although they share expression of neuroendocrine markers, these entities are unrelated from a genetic and clinicopathological perspective and should be separated.

Table 1. *Former* Classification System (2010)

Terminology	Ki67 proliferative index
NET G1	<2%
NET G2	3-20%
NEC (small and large cell types)	>20%

Table 2. *Revised* Classification System (2019)

Terminology	Ki67 proliferative index
NET G1	<3%
NET G2	3-20%
NET G3	>20%
NEC (small and large cell types)	>20%

The specific changes are:

- NET G1 now explicitly includes NETs with a proliferative index of 2-3%. Previously, it was unclear how these tumours should be graded although most pathologists would default to a grade 1 designation.
- The introduction of the subgroup of grade 3 well-differentiated neuroendocrine tumour. Previously tumours with well-differentiated morphology (i.e. architectural and cytological features resembling a low-grade NET) but with a high mitotic rate or Ki67 proliferative index >20% were designated as neuroendocrine carcinoma. However, recent studies have demonstrated that these tumours are genetically and clinically more aligned with the well-differentiated NETs (see Table 3).

Table 3. Comparison of grade 3 neuroendocrine tumour (G3 NET) with neuroendocrine carcinoma (NEC)

	Grade 3 NET	NEC
Genetics	Mutations in MEN1, PAXX, ATRX	Mutations in p53 and RB1
Histology	Well-differentiated (look like G1 or G2 NETs) Ki67 proliferative index often 20-40%	Poorly differentiated (look like high grade malignancy) Ki67 proliferative index usually >60%
Diagnostic	DOTATATE PET avid	FDG PET avid
Predictive	May respond better to non-cisplatin / etoposide chemotherapy	May respond better to cisplatin / etoposide chemotherapy
Prognostic	Median survival often several years	Median survival typically less than one year

*Because this is a new classification, aspects relating to treatment response and survival are currently under investigation.

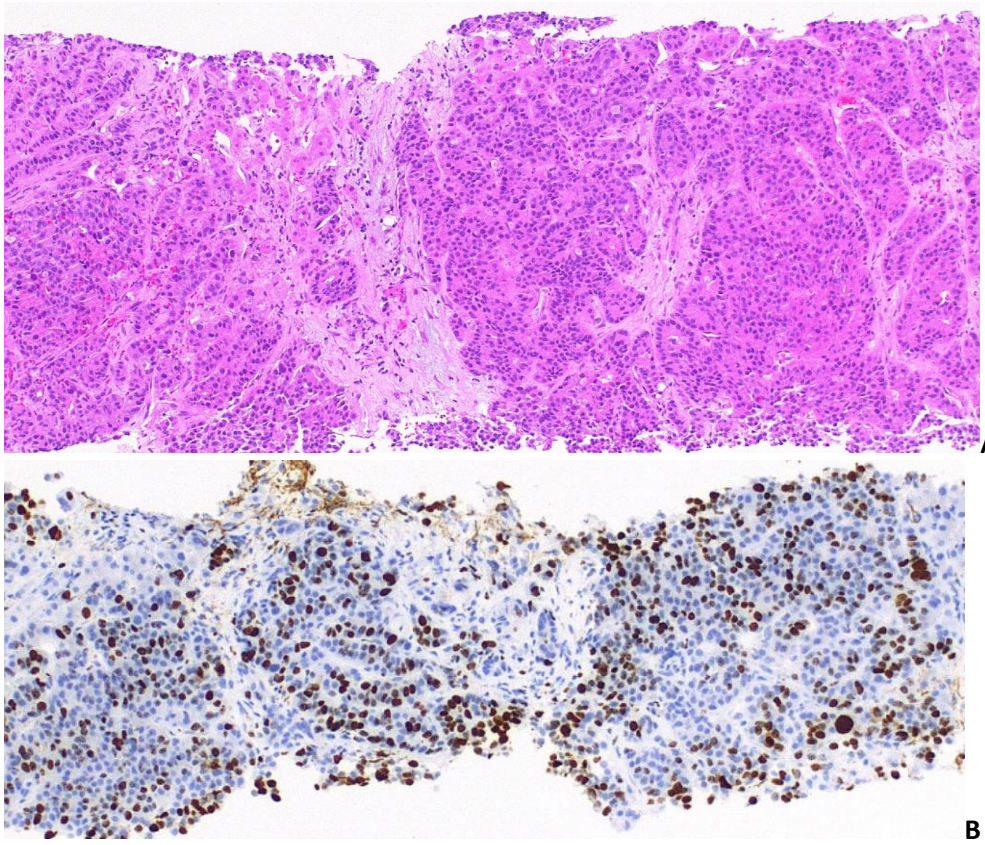

Figure 1. (A) H&E stained section of a grade 3 neuroendocrine tumour metastatic to the liver showing well-differentiated morphology with retention of pseudo-acinar and nested growth pattern **(B)** Ki67 immunohistochemistry showing a proliferation index of 34.5%.

References:

Basturk et al; The high-grade (WHO G3) pancreatic NET category include both well-differentiated and poorly-differentiated neoplasms. AJSP 2015 39(5):683-690

WHO Classification of Tumours (5h edition) Digestive System Tumours; 2019.