

## KI-67 Heterogeneity in Gastro-Entero-Pancreatic Neuroendocrine Tumors

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**Background:** The neuroendocrine tumor (NET) proliferation-based grading system (ENETs) has proved reliable for prognostic stratification, however concerns exist on Ki67 heterogeneity. Our aim was to evaluate intratumor Ki67 index heterogeneity in primary and metastatic sites.

**Methods:** A total of 170 GEP-NETs (between 1993-2011) were identified, 50 of them with clinical follow-up (mean follow up was 59 months, range 2-168 months). Twenty-five cases had multiple paraffin blocks on which Ki67 immunohistochemistry was performed.

**Results:** Thirteen out of 21 (62%) primary sites presented exactly the same Ki67 percentage and therefore the same grade in each paraffin block. Six (29%) tumors presented different Ki67 indices between paraffin blocks, but with no change in grade. Two (10%) tumors showed Ki67 index discrepancy (7% vs 2% and 4% vs 2%) which was enough to change grade (G1 to G2). Out of 14 patients with primary NET and synchronous metastases, 9 (64%) presented exactly the same Ki67 index between sites while 2 (14%) showed variability in their Ki67 index, but not in grade. Three (21%) cases showed discrepancy between primary tumor and metastases. In particular two cases showed an increase in proliferation index in nodal metastases (1% vs 5% and 17% vs 31%) and one case showed increased Ki67 index in a mesenteric localization (1% vs 5%). One case with multiple hepatic metastases showed discrepancy between each metastasis (7% vs 1%). Six patients underwent surgical excision of metachronous metastases during follow up. Three (50% - 1 nodal and 2 hepatic metastases) patients showed an increase in Ki67 rate in the metastatic site and a change in grade, from G1 to G2 (1% vs 10%; 2% vs 5%; 1% vs 7%).

**Conclusion:** Differences in grade between primary and synchronous/metachronous metastatic sites are important and evaluation of Ki67 at all sites may be significant for patient management.