

## Tumor Heterogeneity in Small Intestine Neuroendocrine Tumors Metastatic to the Liver

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**Background:** Tumor heterogeneity is present in many malignancies including neuroendocrine tumors (NETs). Ki67 index, a major prognostic factor of NETs, has been used to grade gastroenteropancreatic NETs by the World Health Organization (WHO), and is frequently based on a single biopsy of an easily accessible lesion. Patients with small intestine NET (SI-NET) often present with multiple liver metastatic lesions at the time of diagnosis and the predictive power of a single biopsy is unknown. In this study, we would examine tumor heterogeneity within individual patients by analyzing Ki67 index.

**Study Design:** Seventeen patients with SI-NET who had 2 or more liver lesions resected were included in the study. Immunohistochemical labeling for Ki67 was performed on all resected available tumors.

**Results:** The 17 patients included 8 males and 9 females, with a mean age of 58 years, ranging from 44 to 75 years. Eleven subjects had a primary tumor available for Ki67 labeling: 10 G1 and 1 G2 tumors. A total of 126 liver lesions were resected from 17 patients. The average tumor number per patient was 7, ranging from 2 to 17. Based on Ki67 index, 79 (63%) tumors were G1, 37 (29%) G2, and 10 (8%) G3. Six patients had only G1 tumors, 6 G2 with/without G1 tumor, and 5 G3 with or without G1/G2 tumors. We also confirmed frequent tumor heterogeneity within each tumor, especially G2 and G3 tumors. Within most G3 tumors, Ki67 ranged from <1% in one area to >20% in another.

**Conclusions:** While most primary SI-NETs are G1 tumors, their liver metastatic tumors are mostly G2 or above. In addition to intratumoral heterogeneity, different liver metastatic SI-NETs in the same patient can range from G1 to G3 tumor. These tumors may grow at different rates. Therefore, in patients with multiple metastatic liver SI-NETs, biopsy from one lesion may not be predictive of prognosis.