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Ki-67 Index Variability in Neuroendocrine Tumors

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Background: The Ki-67 labeling index is well recognized as an integral factor in the identification and treatment of neuroendocrine tumors (NETs). In 2010, the WHO endorsed a grading system of NETs dividing tumors into G1 (Ki-67 <3%), G2 (Ki-67 3-20%), and G3 (Ki-67>20%) classes. Studies have shown that higher Ki-67 scores are associated with greater morbidity, with G3 tumors behaving particularly aggressively. Currently Ki-67 is determined from a single biopsy in a majority of cases and no consensus guidelines exist on taking multiple biopsy specimens through the disease course.

Aims: To compare Ki-67 variability among multiple biopsy samples taken at different times in individual patients.

Methods: The Sunnybrook Odette NETs database (n=327) was retrospectively reviewed for patients with a confirmed diagnosis of NET and multiple (>=2) biopsy or surgical pathologic specimens at variable times. Changes in WHO classification between specimens were determined.

Results: Forty-three patients were identified for inclusion in the analysis. Thirty-nine patients had pathology on their primary tumor as well as a metastatic focus, while 4 had pathology on multiple metastatic foci only. Sixteen of 43 patients (37.2%) were identified who had enough variability between Ki-67 indices resulting in differing WHO classification grades. Twelve of 43 (27.9%) resulted in a second sample that increased the WHO grade by at least one level. Seven of 43 (16.3%) resulted in a new WHO classification of G3.

Conclusion: The Ki-67 labeling index in NETs may change throughout the disease course, may differ between primary tumor and metastases, and may behave more aggressively later in the disease. Given the reliance on this index for management decisions, multiple biopsies through the disease course may be required to effectively treat these heterogeneous malignancies.