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Grade Creep and the Importance of Tissue Sampling: Changes in Ki-67 and Grade in Serial Neuroendocrine Tumor Samples

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BACKGROUND

Neuroendocrine tumor (NET) grade, which utilizes Ki-67 expression, is a useful prognostic tool and aids in treatment decisions. However, it is not well known how these measures evolve over time. This retrospective review evaluates changes in Ki-67 and grade over time in patients with multiple NET tissue samples.

METHODS

77 patients were included (44M; mean age 58±9.5 years at first sample). Primary NET sites included 46 small bowel, 21 pancreatic, 3 rectal, 2 colonic, 2 lung, 1 appendiceal, 1 biliary, and 1 unknown. Surgical resection and biopsy histology, including Ki-67 immunohistochemistry, were reviewed. NETs were graded using the 2017 WHO classification. Statistical analysis was performed using the paired Student t test.

RESULTS

Among 77 initial samples, 69% were from biopsy and 31% from surgical resection; 75% were from metastatic and 25% from primary tumor. Median Ki-67 was 4% (range 1-20%), with 39% grade 1 and 61% grade 2. Second samples were obtained a median of 0.6 (range 0-7.6) years after initial pathology. 68% were from surgical resection and 32% from biopsy; 57% from metastatic disease and 43% from primary tumor or resection bed recurrence. Median Ki-67 was 5.2% (range 1-64%), with 39% grade 1, 51% grade 2, and 10% grade 3. No significant increase in Ki-67 was observed between first and second samples (p=0.1); grade increased in 26%. Thirty-two patients had third samples a median of 3.0 (range 0-11.3) years after initial pathology. 53% were from biopsy and 47% from surgical resection; 81% from metastasis and 19% from primary site. Median Ki-67 was 6.9% (range 1-36%), with 25% grade 1, 66% grade 2, and 9% grade 3. No significant increase in Ki-67 was observed between second and third samples (p=0.172); grade increased in 28%. Six patients had fourth samples and two patients had fifth samples a median of 3.6 (range 0.5-5.4) years after initial sampling, all from metastasis. Five of 8 samples were grade 3 (63%). Among all patients, grade increased between initial and final samples in 31% (n=24). A statistically significant increase in Ki-67 was seen between initial and final samples (p=0.004). Ki-67 increased at an overall rate of 1.2% annually.

CONCLUSIONS

Serial NET sampling demonstrates an increase in Ki-67 over time, resulting in grade increase in 31%. Improved understanding of these changes may have important diagnostic and therapeutic implications, including guidance for frequency of re-biopsy.

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