Higher Tumor Grade in Neuroendocrine Tumor Metastases Negatively Impacts Survival

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Background: Tumor grade is an important predictor of survival in gastroenteropancreatic (GEP) neuroendocrine tumors (NETs), as determined by the percentage of cells expressing Ki-67 and mitotic rate. NETs generally grow indolently, but some cells may acquire traits facilitating metastasis. It is currently unclear how frequently metastases differ in grade from their primary tumors, and whether increasing grade in metastases affects prognosis.

Methods: Ki-67 immunohistochemistry was performed on GEPNETs; data from 270 resected patients were reviewed to identify cases with Ki-67 results for both primary tumors and concurrent metastases. Grade was determined using a modified WHO classification (Ki-67: G1= 0-2%; G2 >2-20%; G3 >20%).

Results: Ki-67 was performed on both the primary tumor and metastases (90 lymph nodes, 61 liver metastases) in 103 patients. Tumor grade was higher in metastases from 25 (24%) patients, 24 from G1 to G2, and 1 from G2 to G3; 68(66%) patients had no change in grade (42 G1 and 26 G2) and 10 (10%) decreased from G2 to G1. No clinicopathologic factors were predictive of higher grade in metastases. The median progression free survival (PFS) and overall survival (OS) for patients with G1 primaries was significantly improved for patients with stable versus increased grade (Table 1). The 5-year PFS was 54.5 % for patients with stable grade vs. 7.8% with increased grade, while 5-year OS was 92% and 54%, respectively. The 5-year OS of patients who had G2 primaries and stable grade was similarly decreased at 64%.

Conclusion: The Ki-67 grade of GEPNETs is an important prognostic tool. One-third of patients had a metastasis with a different grade than their primary, and when grade increased, both PFS and OS significantly decreased. These results suggest the importance of determining grade in both primaries and metastases and reinforce the assertion that increasing grade is related to increasing biological aggressiveness.

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Table 1: Effect of Tumor Grade on Progression Free and Overall Survival

Primary Grade->Metastasis Grade (n)	G1->G1 (42)	G1->G2 (24)	
Median PFS, yrs. (% 5 yr.)	6.46 (54.5%)	0.91 (7.8%)	p = 0.0005*
Median OS, yrs. (% 5 yr.)	11.29 (92%)	7.32 (58%)	p = 0.023*
Primary Grade->Metastasis Grade (n)	G2->G2 (26)	G1->G2 (24)	
Median PFS, yrs. (% 5 yr.)	2.50 (15%)	0.91 (7.8%)	p = 0.548*
Median OS, yrs. (% 5 yr.)	5.75 (64%)	7.32 (58%)	p = 0.319*

*: p-values calculated utilizing Kaplan-Meier method and Log-Rank Test