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Predicting Metastatic Potential in Pheochromocytoma and Paraganglioma: A Comparison of PASS and GAPP Scoring Systems

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BACKGROUND: Although approximately 25% of pheochromocytoma and paragangliomas (PCC/PGL) develop metastases, there are no definitive predictors of metastatic potential. The Pheochromocytoma of the Adrenal Gland Scaled Score (PASS) and the Grading System for Adrenal Pheochromocytoma and Paraganglioma (GAPP) are histopathologic scoring systems to predict metastatic potential in PCC/PGL. The goal of this study is to assess PASS and GAPP as metastatic predictors and to correlate with survival outcomes.

METHODS: The cohort included PCC/PGL with ≥5 years of follow-up or known metastases. Surgical pathology slides were re-reviewed. Ki-67 immunostaining was performed on FFPE tumor sections and scored by computer automated method. Per published criteria, PASS and GAPP scores were assigned. Univariate and multivariate logistic regression, Kaplan Meier survival analysis, and Cox proportional hazards were performed to assess recurrence free survival (RFS) and disease specific survival (DSS).

RESULTS: From 143 subjects, 106 tumors were PCC, and 37 were PGL. Metastases developed in 24%. Germline genetic testing was performed in 65% of subjects; 37% were sporadic tumors. The median PASS score was 6.5 (IQR:4.0-8.0) and median GAPP score was 3.0 (IQR:2.0-4.0). Interrater reliability was low-moderate for PASS (ICC:0.5232). Older age (OR:0.969, p=0.0170) was associated with longer RFS. Germline SDHB pathogenic variant (OR:8.205, p=0.0049), extra-adrenal tumor (OR:6.357, p<0.0001), Ki-67 index 1-3% (OR:4.810, p=0.0477), and higher GAPP score (OR:1.537, p=0.0047) were associated with shorter RFS. PASS score was not associated with RFS (p=0.1779). On Cox regression, a GAPP score in the moderately-differentiated range was significantly associated with disease recurrence (HR:3.367, p=0.0184) compared to well-differentiated score.

CONCLUSION: Higher GAPP scores were associated with metastatic PCC/PGL suggesting correlation with aggressive histopathologic features. PASS score was not associated with metastases and demonstrated significant inter-observer variability, limiting clinical utility. Stronger scoring systems for metastatic prediction likely will require a combination of histopathology, germline and somatic molecular markers and clinical data.

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