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Toward a Ki-67 -Informed Grading Framework for Metastatic Pulmonary Neuroendocrine Tumors

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BACKGROUND

Ki-67 is routinely reported in pulmonary neuroendocrine tumors (NETs) and widely used to estimate proliferative activity, yet it is not incorporated into current histopathologic grading, which relies on mitotic rate and necrosis. This gap is increasingly relevant as emerging data and recent WHO/ENETS discussions recognize a subset of well-differentiated pulmonary NETs with higher proliferative indices. However, clinically applicable Ki-67-based stratification, particularly in metastatic disease, remains undefined. We evaluated multiple Ki-67-based stratification approaches to inform the development of a clinically relevant grading framework in stage IV pulmonary NETs.

METHODS

We performed a retrospective cohort study of patients with stage IV well-differentiated pulmonary NETs treated at Moffitt Cancer Center (2008-2024). Clinicopathologic variables, including Ki-67 index, mitotic rate, metastatic sites, imaging findings, treatments, and survival outcomes, were collected. Ki-67 was analyzed using gastrointestinal NET-style strata (<3%, 3–20%, >20%), WHO/ENETS-informed lung NET strata (≤5%, 6–20%, >20%), and binary thresholds (5%, 10%, 15%, and 20%). Mitotic rate-based classification was evaluated as a comparator. Survival was estimated using the Kaplan–Meier method and compared using the log-rank test, with Cox proportional hazards models used for multivariate analysis.

RESULTS

The cohort included 205 patients; Ki-67 was available in 169 (82.4%) and mitotic rate in 152 (74.1%). Median age at diagnosis was 62 years, and median OS was 68 months. Ki-67-based stratification demonstrated consistent prognostic value across multiple schemas, with separation driven by higher proliferative categories. Both gastrointestinal-style and WHO/ENETS-informed grouping significantly stratified OS (p=0.02), largely reflecting worse outcomes in tumors with Ki-67 >20% (median OS ~51 months) compared with lower-proliferation groups (~91-95 months). Binary thresholds of 5% and 10% did not significantly stratify OS (p>0.3), whereas 15% was the lowest threshold associated with a significant separation (median OS 95 vs 68 months, p=0.018). A 20% cutoff provided the strongest discrimination (p=0.006) and remained independently associated with worse

OS (HR 1.78, 95% CI 1.17-2.69; p=0.007). In contrast, conventional mitotic rate-based categories did not significantly stratify OS (log-rank p=0.404; Cox p=0.410).

CONCLUSIONS

Ki-67 offers reproducible, clinically meaningful prognostic stratification in metastatic well-differentiated pulmonary NETs and outperforms mitotic-rate–based grading in this cohort. Prognostic separation occurs at higher Ki-67 values, with 15% as the lowest significant binary cutoff and 20% providing the most robust discrimination and independent association with survival. These findings support integrating Ki-67 into a refined grading

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