C-35

Brain Metastases in Patients with Pulmonary Neuroendocrine Tumors: Clinical Characteristics, Risk Factors, and Outcomes

Skylar Robbins[1], Hayden Stoltzfoos[1], Jonathan Strosberg[1], Taymeyah Al-Toubah[1], Mintallah Haider[1]

[1]H. Lee Moffitt Cancer Center and Research Institute

BACKGROUND

Brain metastases are an uncommon but clinically important complication of pulmonary neuroendocrine tumors (NETs) and are associated with poor prognosis. Risk factors for brain metastases in this population remain poorly defined, and current surveillance practices are not standardized. We aimed to identify clinical and pathologic factors associated with the development of brain metastases in patients with well-differentiated pulmonary NETs.

METHODS

We performed a retrospective study of 206 patients with metastatic, histologically confirmed, well-differentiated pulmonary NETs treated at Moffitt Cancer Center between 2008 and 2024. Patients with other neuroendocrine neoplasms were excluded. Clinical, imaging, pathology, and treatment data were collected. Of these patients, 94 underwent at least one brain MRI, and 29 developed brain metastases. Survival was estimated using Kaplan-Meier methods. Continuous variables were compared using independent t-tests and categorical variables using chi-squared tests. Receiver operating characteristic (ROC) analysis was performed to evaluate Ki-67 as a predictor of brain metastasis risk, identifying a threshold of 19% for risk discrimination.

RESULTS

Among 206 patients, 29 (14%) developed brain metastases. Median age at brain metastasis diagnosis was 58 years, and 23 patients (79.3%) had stage IV disease at initial pulmonary NET diagnosis. Mean[SJR1] Ki-67 index was higher in patients who developed brain metastases than in those who did not (22.0% vs 11.67%, $p<0.001$), and higher histologic grade was also significantly associated with brain metastasis development ($p<0.001$). A Ki-67 threshold of 19% discriminated[SJR2] patients at higher risk for brain metastases. Median time from pulmonary NET diagnosis to brain metastasis was 18 months. At brain metastasis diagnosis, 22 patients (75.9%) had multiple lesions, and 16 (55.2%) ultimately developed more than five brain metastases. Stereotactic radiosurgery was the most common initial brain-directed therapy (48.3%). Median overall

survival was 45 months from pulmonary NET diagnosis and 19 months from brain metastasis diagnosis.

CONCLUSIONS

Brain metastases in pulmonary NETs are relatively common and associated with poor survival. Ki-67 of at least 19% and higher histologic grade at diagnosis were associated with increased brain metastasis risk and may help identify patients who could benefit from closer neurologic surveillance and earlier brain imaging. Prospective studies are needed to define optimal screening and management strategies for this high-risk subgroup.

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