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Prognostic Associations of Metastatic Site at Diagnosis in Neuroendocrine Neoplasms

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BACKGROUND

Metastatic site at diagnosis may capture clinically important heterogeneity in neuroendocrine neoplasms (NENs), but real-world patterns and site-specific survival associations remain incompletely characterized.

METHODS

We analyzed patient-level records from a single-institution retrospective NEN dataset. Tumor class was grouped as NEC/poorly differentiated NEC, NET/well-differentiated NET, mixed/MiNEN, or unknown/other. Metastatic sites at diagnosis were abstracted as liver, brain, bone, lung, distant lymph node, or other; review further categorized other-site entries. Overall survival (OS) was evaluated using Kaplan-Meier/log-rank methods and exploratory Cox models adjusted for tumor class, age, sex, and primary site group.

RESULTS

Among 386 patients, 165 (42.7%) had metastatic disease at diagnosis; one patient had missing metastatic-status data. Tumor class included NEC/poorly differentiated NEC (n=198), NET/well-differentiated NET (n=166), mixed/MiNEN (n=12), and unknown/other (n=10). The most common metastatic sites were liver (n=90; 23.3% of all patients; 54.5% of metastatic patients), other (n=56; 14.5%; 33.9%), bone (n=44; 11.4%; 26.7%), brain (n=43; 11.1%; 26.1%), distant lymph node (n=38; 9.8%; 23.0%), and lung (n=14; 3.6%; 8.5%). NEC/poorly differentiated NEC had a higher metastatic-at-diagnosis frequency than NET/well-differentiated NET (119/198, 60.1% vs 38/166, 22.9%; p<0.001) and higher liver, brain, bone, distant lymph node, and other-site involvement. Other-site review found 36 definite/probable and 20 unclear entries; leading categories were peritoneal/abdominal serosal, pleural/effusion, adrenal, and soft tissue/skin.

OS analyses included 386 patients and 150 deaths. Median OS was 64.0 months overall. In unadjusted analysis, median OS was 12.4 months with metastatic disease versus not reached without metastatic disease (p<0.001). Increasing metastatic burden was associated with shorter OS (0 sites: not reached; 1 site: 47.9 months; ≥2 sites: 5.36 months; p<0.001). In exploratory adjusted Cox models, any metastasis (HR 2.10, 95% CI 1.48–2.98), liver metastasis (HR 2.23, 95% CI 1.55–3.22), and bone metastasis (HR 2.84, 95% CI 1.91–4.22) remained associated with worse OS; the bone model had proportional-hazards concern.

CONCLUSIONS

Metastatic patterns differed substantially by tumor class in this real-world NEN cohort. Metastatic disease, multisite burden, liver metastasis, and bone metastasis were associated with worse OS, supporting cautious incorporation of metastatic pattern into future risk-stratification models. Findings remain vulnerable to residual confounding by grade, treatment, and disease biology.

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