P-14

Composite Metastatic Organ Burden Refines Prognostic Stratification Beyond AJCC M1 Substaging in Neuroendocrine Neoplasms

Joseph Watts[1,2], Sanjay Shankar[1,2], Harry Menon, DO[2], Katharine Thomas, MD[2]

[1]UNR School of Medicine; [2]Renown Health

BACKGROUND

AJCC 8th edition introduced M1 substaging (M1a: hepatic only, M1b: extrahepatic only, M1c: hepatic + extrahepatic) for neuroendocrine neoplasms (NEN). Prior validation studies derive largely from gastrointestinal NET registries and SEER data with limited differentiation granularity. Whether composite metastatic organ burden—operationalized as number of concurrently involved sites—adds discriminative power beyond categorical M1 substaging in a mixed-site cohort enriched for lung primary and poorly differentiated histology remains uncertain.

METHODS

Single-institution CoC-accredited NEN registry, 2018–2025. 469 patients; WHO-aligned differentiation class manually abstracted (NEC 51%, NET G1/G2 28%, Well-differentiated 14%, Mixed 6%). Metastatic site involvement at diagnosis coded from SEER collaborative stage fields (bone, brain, liver, lung, distant lymph nodes, other). M1 subcategory assigned per AJCC 8th edition. Composite metastatic burden operationalized as continuous count of involved organ sites. Cox proportional hazards regression performed with age adjustment. Kaplan-Meier analysis used for subgroup comparisons; log-rank test for pairwise significance

RESULTS

Of 386 patients with linked differentiation and survival data, 164 (42.5%) had distant metastasis. M1 substaging distribution: M1a (liver only) n=35 (21%), M1b (extrahepatic only) n=75 (46%), M1c (hepatic + extrahepatic) n=54 (33%). Median OS by M1 subcategory: M1a 19 months, M1b 12 months, M1c 4 months. All pairwise comparisons were significant (M1a vs M1b p=0.04; M1a vs M1c p=0.002; M1b vs M1c p=0.04). This cohort is notable for lung-predominant primary site with M1b constituting the largest M1 subgroup, reflecting extrahepatic pulmonary spread. Continuous composite burden (sites per patient) independently predicted mortality after age adjustment: HR 1.66 per additional site (95% CI 1.47–1.87, p<0.001). Within M1 patients, those with ≥2 concurrently involved organ sites had significantly worse OS than single-site involvement: median OS 5 vs 17 months; HR 1.88 (95% CI 1.25–2.83, p=0.003).

Table 1. M1 Substaging and Composite Burden: Survival Outcomes

M1 Category	n	Median OS (mo)	HR vs Reference
M1a - Hepatic Only	35	19	reference
M1b - Extrahepatic only	75	12	1.6 (p=0.04)
M1c - Hepatic + extrahepatic	54	4	4.2 (p=0.002)
≥2 organ sites (within M1)	82	5	hr 1.88 (P=0.003)
Single organ site	82	17	Reference

All M1 pairwise OS comparisons significant by log-rank test. Composite burden HR adjusted for age at diagnosis.

CONCLUSIONS

Composite metastatic organ burden provides discrimination beyond AJCC M1 subcategory alone in a community NEN cohort enriched for lung primary and high-grade histology. The M1a-M1b-M1c gradient was preserved, and ≥2 concurrently involved sites identified a subgroup with markedly worse prognosis even after site-based substaging. These findings support prospective collection of site-specific metastatic burden as a standard registry variable, particularly in mixed-site cohorts where extrahepatic (M1b) disease predominates.

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