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Liver Metastases Independently Predict Worse Overall Survival in Neuroendocrine Carcinoma: A Differentiation-Stratified Analysis

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BACKGROUND

Liver metastases are an established adverse prognostic factor in neuroendocrine neoplasms (NEN). However, prior registry analyses conflate poorly differentiated neuroendocrine carcinoma (NEC) and well-differentiated neuroendocrine tumors (NET) — biologically distinct entities. Whether this survival effect is class-uniform or concentrated in NEC has not been examined in a WHO-annotated cohort.

METHODS

We conducted a single-institution retrospective analysis of 469 NEN patients at a CoC-accredited community cancer center (2018–2025). WHO-aligned differentiation class was chart-abstracted for 386 patients; this analysis includes 197 NEC and 165 NET patients with available survival data. Liver metastasis at diagnosis was coded from SEER collaborative stage fields. Stratified Cox proportional hazards regression was performed within each differentiation subgroup, adjusted for age, and in a combined model including NEC status.

RESULTS

Liver metastasis prevalence was higher in NEC (31.0%, 61/197) than NET (16.4%, 27/165). In NEC, liver metastases independently predicted markedly worse OS: HR 2.01 (95% CI 1.39–2.91, p<0.001); median OS 4.0 vs. 16.0 months (log-rank p=0.0001). In NET, the effect was directionally consistent but underpowered: HR 2.67 (95% CI 1.00–7.11, p=0.050); with only 19 events across 165 patients, median OS estimates are unreliable. In the overall adjusted model (n=362), liver metastasis remained independently significant (HR 2.12, 95% CI 1.50–2.99, p<0.001) after controlling for NEC status (HR 7.87) and age.

Table 1. Liver Metastasis and OS by Differentiation Stratum

Stratum	LM+ (n/total)	Median OS (LM+ vs LM−)	HR (95% CI)
NEC	61/197 (31.0%)	4.0 vs. 16.0 mo	2.01 (1.39–2.91)**
NET	27/165 (16.4%)	Not estimable†	2.67 (1.00–7.11)*
Overall (adj.)	88/362	—	2.12 (1.50–2.99)**

**p=0.050; **p<0.001. †19 events across 165 NET patients (including 27 LM+) preclude reliable median OS estimation. Overall model adjusted for age and NEC status (HR 7.87).*

CONCLUSIONS

In this WHO-annotated cohort, synchronous liver metastases robustly predict worse OS in NEC (median 4.0 vs. 16.0 months) but the NET effect remains underpowered with 19 events. Pooled NEN analyses without differentiation stratification risk generating liver metastasis effect estimates driven by NEC case-mix. These findings support differentiation-stratified analysis as a methodological standard for NEN prognostic research and suggest that the clinical significance of hepatic involvement — and by extension, the urgency and expected benefit of liver-directed intervention — may differ substantially between NEC and NET.

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