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Time to Treatment Initiation (TTI) and Survival Outcomes in Metastatic Extrapulmonary Neuroendocrine Carcinoma (EP-NEC)

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BACKGROUND

Advanced EP-NEC is typically treated with platinum plus etoposide, yet outcomes remain poor. Early systemic therapy is commonly pursued given the aggressiveness; however, data from small-cell lung cancer suggest that shorter TTI does not necessarily improve overall survival. The impact of TTI in advanced EP-NEC remains poorly defined.

METHODS

We conducted a multicenter retrospective study of adults with biopsy-confirmed stage IV EP-NEC treated across three Mayo Clinic sites from 2005–2025. TTI was defined as days from pathologic diagnosis to first-line systemic therapy and analyzed using a receiver operating characteristic–derived cutoff of ≤14 versus >14 days and as a continuous variable. Overall survival (OS) and progression-free survival (PFS) were evaluated using Kaplan–Meier and multivariable Cox models.

RESULTS

Among 248 patients, median age was 61 years and median TTI was 19 days. Median OS was 13.9 months (95% CI, 11.7–16.7), and median PFS was 5.7 months (95% CI, 5.3–6.3). Patients with TTI >14 days had longer median OS than those treated within ≤14 days (16.4 vs 10.1 months), with improved OS on unadjusted analysis (HR, 0.69; 95% CI, 0.50–0.96; p=0.028), although this was not significant after multivariable adjustment (HR, 0.74; 95% CI, 0.53–1.05; p=0.097). TTI >14 days was also associated with longer median PFS (6.5 vs 4.8 months), with improved PFS on unadjusted analysis (HR, 0.67; 95% CI, 0.51–0.88; p=0.0038) and after multivariable adjustment (HR, 0.75; 95% CI, 0.56–1.00; p=0.047). When analyzed as a continues variable, TTI was not independently associated with OS (HR, 0.99; 95% CI, 0.98–1.00; p=0.173) or PFS (HR, 0.99; 95% CI, 0.98–1.00; p=0.089).

CONCLUSIONS

In this large multicenter cohort of stage IV EP-NEC, earlier systemic therapy initiation (≤14 days) was not associated with improved OS. Although TTI >14 days was associated with

improved PFS, continuous TTI showed no significant association with OS or PFS, suggesting that this finding may reflect patient selection or clinical context rather than a direct effect of delayed treatment. These findings may provide reassurance when short delays are needed for biomarker testing or clinical trial enrollment.

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