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Comparison of pulmonary versus extra-pulmonary small cell neuroendocrine carcinomas demonstrate distinct genomic alterations

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BACKGROUND

Small cell neuroendocrine carcinomas (SC-NECs) are uncommon but aggressive tumors with poor prognosis. Although both small cell lung cancer (SCLC) and extrapulmonary small cell NEC (EP-SC-NEC) have similar histological and morphological characteristics, whether they are biologically distinct is still unknown. We assessed and compared the genomic profiles of SCLC and EP-SC-NECs to identify distinct mutations that may allow for more personalized therapeutic options.

METHODS

Patients with a histological diagnosis of SC-NEC were identified from the de-identified Tempus real-world multimodal database and stratified by primary tumor site and categorized as SCLC or EP-SC-NEC. Patient demographic/clinical characteristics and genomic/transcriptomic data were described as N (%) or median (IQR), min, and max and compared between groups by Chi-squared/Fisher's Exact tests or Wilcoxon rank-sum tests, as applicable. The prevalence of somatic mutations (SNVs, CNVs, and Fusions) was compared similarly, with a false-discovery rate correction for multiple comparisons. Analyses were two-sided, with statistical significance evaluated at the 0.05 alpha level.

RESULTS

228 SCLC vs 186 EP-SC-NEC were compared. The two groups did not differ in age, race, or ethnicity when diagnosed. SCLC samples had significantly higher median TMB than EP-SC-NEC samples (5.0 vs 3.4 mut/MB, $p<0.001$). MSI-H was rare in both groups (SCLC 0.4% vs EP-SC-NEC 2.7%, $p=0.10$). There were significant differences in SNVs with *TP53, RB1, EGFR*, and *NOTCH1* mutations more common and *TERT, ARID1A, APC, FOXA1*, and *CTNNB1* mutations less common in SCLC ($q<0.05$). SCLC also had significantly fewer *CCNE1* amplifications than EP-SC-NEC. Pathogenic fusions were also more frequent in EP-SC-NEC vs SCLC ($q<0.001$), with 24% of EP-SC-NEC fusions being TMPRSS2-ERG.

CONCLUSIONS

Despite the histological and morphological overlap between SCLC and EP-SC-NECs, our data revealed heterogeneous molecular characteristics between both groups. These distinct molecular signatures could impact therapeutic decisions for SC-NEC according to their site of origin.

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