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Molecular landscape of extra-pulmonary small cell neuroendocrine carcinomas based on site of origin

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BACKGROUND

Extrapulmonary small cell neuroendocrine carcinomas (EP-SC-NECs) are uncommon but aggressive malignancies. Although they are treated with similar chemotherapy regimens, their distinct genomic profiles have not been fully explored. We aimed to investigate the genomic profile of these tumors to characterize distinct molecular subgroups of EP-SC-NECs and to identify mutations that could enable more personalized therapy.

METHODS

Patients with a diagnosis of SC-NEC that originated outside the lung were selected from the de-identified Tempus real-world multimodal database. Patients were further stratified by primary tumor site into gastrointestinal (GI), genitourinary (GU), head and neck (H&N), and gynecological origin (GYN). Patient demographic/clinical characteristics and genomic/transcriptomic data were described as N (%) or median (IQR), min, and max and compared between primary tumor site groups by Chi-squared/Fisher's Exact tests or Kruskal-Wallis rank-sum test, 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

186 patient samples (61 GI, 95 GU, 23 GYN, and 7 H&N) were identified. Age at diagnosis significantly differed between the subtypes, with GYN having the youngest age at diagnosis. There was no difference in race and ethnicity between groups. GI and GU SC-NECs have higher median TMB, and results were significant when comparing GI to GYN SC-NECs (3.8 vs 2.1 mut/MB, p=0.026). MSI-H was rare in all groups, with no significant differences. There were differences in CNVs among the four groups, with H&N having the highest frequency of *PAX8, RET*, and *SLC3F5* deletions, while GYN and H&N SC-NECs had higher rates of *CDKN1B* amplification. However, these were not significant after correction for multiple testing. There were also significant differences in SNVs between the four groups, in which *TP53* and *RB1* mutations were more common in GI and GU compared to GYN and H&N SC-NECs (q<0.001 and 0.087, respectively). GI SC-NECs had more frequent *KRAS* and *APC* mutations

(q<0.001 and 0.002, respectively), while GU SC-NECs had more *TERT* mutations compared to other groups (q<0.001).

CONCLUSIONS

Our results demonstrated that EP-SC-NEC possess distinct heterogeneous genomic profiles associated with different primary origins despite their histological and morphological similarities. These distinct molecular signatures could impact precision therapeutic decisions for EP-SC-NEC according to their primary site of origin.

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