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Unmasking High-Grade (HG) Neuroendocrine Carcinoma (NEC) biology through transcriptomic profiling in lung and bladder cancer

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BACKGROUND

High grade neuroendocrine carcinomas (HGNECs), including small-cell (SC) and large-cell (LCNEC), are aggressive malignancies frequently misclassified due to subtle morphology and inconsistent use of neuroendocrine (NE) immunohistochemistry in routine pathology workflows. Whether transcriptomically defined tumors with HGNEC-like biology have inferior outcomes when treated conventionally is unknown. Leveraging a large real-world dataset, this study aims to identify biologically equivalent HGNEC to improve upon morphology-based classification.

METHODS

49,144 lung cancer and 13,087 bladder cancer specimens underwent DNA and RNA sequencing at Caris Life Sciences. Using a previously reported framework, we developed a weighted, z-scored based HGNEC activity score (HAS) from 10,137 pathologically defined HG- and LG- NEC specimens and applied it to characterize NSCLC and bladder cancer samples (lacking pathologist assigned HGNEC diagnosis) further stratified by histology. Overall survival (OS) was obtained from insurance claims data and calculated from specimen biopsy to last contact using Kaplan-Meier and Cox proportional hazards estimates. Where applicable, P values were adjusted for multiple hypothesis testing using the Benjamini–Hochberg method, with $q < 0.05$ considered statistically significant.

RESULTS

To identify a high-confidence HGNEC-like subpopulation, a HAS threshold (z-score>=3) was applied for NSCLC, classifying 0.2% squamous (sq) and 2.3% non-squamous (nsq) as HGNEC-like, consequently our analysis is focused in nsq. Patient demographics including age, gender, race, ethnicity and smoking history, were similarly matched between the HGNEC-like and non-HGNEC-like nsq-NSCLC. HGNEC-like neoplasms were associated

with poor OS (HR:1.18, 95% CI:1.07–1.31, p<0.001). In bladder cancers, applying a HAS cutoff of **1.5** identified 4.0% of papillary variant urothelial carcinomas (PUC) as HGNEC-like and were associated with significantly poorer overall survival (HR, 1.39; 95% CI, 1.01–1.92; p=0.045).For nsq-NSCLC, HGNEC-like neoplasms were enriched for mutations in *TP53*, *PTEN*, *RUNX1*, *MTOR* and *RB1* (OR: 1.7-14.1), as well as amplifications in *MYC* and *CCNE* (OR: 2.2–3.5). These neoplasms were also predominantly PDL1 negative (64 vs 47%) with significantly lower odds of *KRAS* and *EGFR* mutations (OR: 0.4–0.5, all p-adj<0.05). Consistent with a highly proliferative phenotype, nsq-NSCLC HGNEC-like neoplasms were enriched for replication rates (3.0-fold) and cell-cycle scores (1.5-fold, all p-adj<0.05). Similar molecular features were observed in HGNEC-like PUC, including increased odds of *TP53* and *RB1* mutations (OR: 1.7–10.0), *MYC* amplification (OR: 2.5), elevated replication rates (1.3-fold), and higher cell-cycle scores (1.5-fold, all adjusted p<0.05.Finally, HGNEC-like neoplasms demonstrated significantly increased transcriptomic expression of clinically actionable NE targets, including *DLL3* (10-fold), *SEZ6* (3.7-fold), *SEZ6L* (10-fold), and *SSTR2* (10-fold) in nsq-NSCLC, as well as *DLL3* (5-fold) and *SEZ6* (2.6-fold) in PUC (all p-adj<0.05).

CONCLUSIONS

We identify a transcriptomically defined subset of NSCLC and PUC with HGNEC-like biology, inferior survival and potential therapeutic targets. These observations support using transcriptomics to complement morphology-based classification in a multimodal approach to inform clinical trial design and identify NEC-targeted therapies in lung and bladder cancer.

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