

Conference Abstracts

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Genomic Profiling defines Molecular Drivers of Colorectal Neuroendocrine Carcinoma

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Abstract

Background

Neuroendocrine carcinoma (NEC) is a rare and aggressive subtype of colorectal cancer (CRC). Two histologic subtypes, small cell NEC (SCNEC), and large cell NEC (LCNEC), have been described. However, how these subtypes differ, and what genomic drivers underlie their development, are poorly understood. Better characterization of NEC genomic alterations is needed to clarify disease biology and improve outcomes.

Methods

We identified 123 patients with NEC of the colon and rectum treated at Memorial Sloan Kettering Cancer Center. All tumors were profiled using the targeted sequencing platform MSK-IMPACT. In 11 patients with mixed adenocarcinoma and neuroendocrine carcinoma (MANEC), the adenocarcinoma and NEC components were sequenced separately.

Results

Among the cohort, 32 patients had SCNEC, 51 had LCNEC, and 40 had histologic features intermediate between the two. 62% of patients presented with stage IV disease, and the NEC

component was enriched at metastatic sites in MANEC cases. Clinical outcomes were poor across all groups, with a median survival of 11 months among stage IV patients (SCNEC: 9m, LCNEC: 11m). SCNEC arose more frequently in the rectum and was genomically characterized by frequent RB1 loss (68%), with a smaller subset harboring PTEN loss (16%). TP53 mutations were identified in only 58% of cases, a lower frequency than reported in sporadic advanced CRC. In contrast, LCNEC was more often right sided, commonly associated with an adenocarcinoma component, and enriched for MYC amplification (29%) and BRAF mutations (37%). MYCamp frequently occurred on extrachromosomal DNA, confirmed by both FISH and shallow whole genome sequencing. In 11 MANEC cases with separately sequenced components, RB1 loss and MYCamp were restricted to the NEC component, supporting their necessary role in neuroendocrine transformation and clonal evolution from an adenocarcinoma precursor. PIK3CA (6%) and SMAD4 (9%) mutations were less frequent than expected across the cohort and were often absent in the NEC component of MANEC cases. DLL3 expression, evaluated in a subset of cases, was positive in most SCNEC but rarely in LCNEC.

Conclusion

SCNEC and LCNEC represent clinically and genomically distinct subtypes of colorectal NEC. For intermediate cases that cannot be classified

based on histology alone, genomic profiling may aid classification. Ongoing studies aim to validate our genomic findings and to model the biology of NEC to identify more effective therapeutic strategies.

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