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EDITORIAL – TRANSLATIONAL RESEARCH

Exploring the Relationship: Low-Grade Appendiceal Mucinous Neoplasms (LAMN) and Mucinous Adenocarcinoma as Phases of the Same Disease Spectrum

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Interpreting the genetic information in appendiceal cancer poses several challenges due to limited availability of data, presence of tumor heterogeneity, a lack of standardized testing methods, uncertainty regarding the clinical relevance of driver and passenger mutations, and limited integration of genetic information with clinical data.

While high-grade appendiceal cancer is typically treated similarly to colon cancer, it is important to recognize that these two cancer types are distinct entities with different oncogenic drivers and somatic mutation profiles.[1,2] Furthermore, it is not uncommon to observe patients that exhibit coexisting high- and low-grade components within the same tumor or who underwent repeat cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) procedures for low-grade tumors, only to discover biphasic disease with both low- and high-grade components upon final pathology examination.[3] Similar heterogeneity has been observed in the development and testing of organoids derived from spatially distinct lesions within the same patient.[4]

In the current issue of *Annals of Surgical Oncology* (*ASO*), Wald et al. present sequencing data from 183 patients with pseudomyxoma. Their findings elegantly provide further support for the clinical observation mentioned above, indicating that low-grade appendiceal mucinous neoplasm (LAMN) and mucinous adenocarcinoma are possibly phases of the same disease spectrum, similar to the evolution seen in pancreatic intraductal papillary mucinous neoplasm (IPMN) progressing to adenocarcinoma.

The authors of this study employed a targeted exome sequencing approach to investigate the mutational spectrum of 28 genes known to be involved in gastrointestinal malignancies. Among these genes, *KRAS* and *GNAS* were found to be the most frequently mutated, with a tendency for mutational cooccurrence. This finding is consistent with previous reports.[1,5] Other genes, including *TP53*, *SMAD4*, *ATM*, *CDKN2A*, *PIK3CA*, and *PTEN*, were also observed to be recurrently mutated, although at lower frequencies.

The authors proposed a genetic progression model based on their findings. According to this model, early genomic events in the development of the disease involve mutations in mitogen-activated protein kinase (MAPK) genes and/or *GNAS*. These mutations were detected in both LAMNs and mucinous adenocarcinomas. Late genomic events, on the other hand, were characterized by mutations in *TP53*, *SMAD4*, *ATM*, *CDKN2A*, and mTOR genes, which were predominantly observed in mucinous adenocarcinomas.

The presence of mutations in *GNAS* or MAPK-associated genes (*KRAS*, *NRAS*, and *BRAF*) was significantly associated with younger age, lower histologic grade, and decreased levels of invasion. Conversely, the collective mutations in *TP53*, *SMAD4*, *ATM*, *CDKN2A*, *PIK3CA*, or *PTEN* were associated with older age, higher grade, nodal metastasis, and a lower mean peritoneal cancer index (PCI).

Survival analysis revealed a substantial difference in overall survival between two groups of patients based on their mutational status. Patients with at least one mutation in *TP53*, *SMAD4*, *ATM*, *CDKN2A*, *PIK3CA*, or *PTEN* had a significantly shorter survival interval (55% survival at

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5 years) compared with those without mutations in these genes (88% survival at 5 years). Importantly, in multivariable analysis, the presence or absence of these mutations remained a significant predictor of poor survival after adjusting for histologic grade, peritoneal cancer index (PCI), and completeness of cytoreduction (CC) score, indicating that these late genomic mutations may hold clinical value in the management of this disease.

The findings of Wald et al. parallel those of a recent publication by Foote et al. in which the authors similarly observed a poor survival-associated subgroup of mucinous adenocarcinoma cases defined by *TP53* mutations.[6] This subgroup, termed the "*TP53*-mutation predominant" subtype by the authors, experienced a significantly worse overall survival than a clinically indolent, "*RAS*-mutation predominant" subtype lacking mutations in *TP53* and *GNAS*. The authors also identified poor survival associations for "*GNAS*-mutation predominant" and "triple negative" subgroups in mucinous adenocarcinoma, and further demonstrated the prognostic relevance of these subtypes in colonic-type and goblet cell carcinoma histologies. In the Wald et al. study, only 4% of *GNAS*-mutant tumors in their cohort lacked concurrent mutations in *RAS* (or *BRAF*) genes, thus potentially obscuring the detection of a survival difference between the *GNAS* and *RAS* mutation predominant subtypes.

Moving forward, the therapeutic relevance of these mutational subtypes must also be investigated. For instance, do one or more of these mutations, or their combinations, impact drug sensitivity or resistance, and if so, how can this information be incorporated into the treatment selection process?

Is it time to offer universal somatic and germline mutational analysis for all appendiceal cancer patients given that sequencing cost is dramatically decreasing, one out of three appendiceal cancer patients are diagnosed below the age of 50, and 17% of all cancer patients harbor a germline pathogenic or probably pathogenic variant? [7,8]

For how long is it prudent to observe a recurrent LAMN within a landscape of genetically evolving lesions? Is it logical to assume that the more residual disease, the greater the chance for a critical mutational event that can impact outcomes? Is this in reality what is captured in the literature as the impact of PCI on survival? Furthermore, how early does a genetic alteration precede its phenotypic effects and how can we leverage this knowledge in patient care?

In conclusion, the absence of an identifiable genetic signature for determining eligibility for a CRS/HIPEC procedure or predicting treatment response in appendiceal cancer patients underscores the need for further research and correlation with clinical findings. Before we can effectively utilize the genetic underpinnings of appendiceal cancer in a clinical setting, additional advancements are required. Nevertheless, the presented work represents a meaningful step in the direction of achieving this goal.

DISCLOSURES The authors declare no conflict of interest.

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