Genomic Subtypes of Appendiceal Adenocarcinoma: Enough to Guide Clinical Decision Making?

TO THE EDITOR:

Foote et al[1] have reported on the molecular classification of 273 patients with appendiceal adenocarcinoma (AC) who had next-generation sequencing through the MSK-IMPACT study. We applaud the authors of this study for investigating the outcomes of these patients with such a rare and aggressive disease where so little is understood regarding the biology of the tumor and its microenvironment. The investigators have classified AC into four molecular subtypes: (1) RAS-mutant (mut) predominant, (2) GNAS-mut predominant, (3) TP53-predominant, and (4) triple-negative (*RAS*/*GNAS*/*TP53* wildtype). The first RAS-mut predominant group demonstrated improved overall survival (OS) compared with the other subtypes with median OS not reached. This group also demonstrated signals of chemoresistance with the investigators suggesting implications on clinical decision making regarding recommendations for cytoreductive surgery (CRS) and use of systemic chemotherapy.

We would like to raise some additional discussion points not included in this manuscript that are important for readers interpretation of the data provided. Although the investigators have documented the surgical status of the patient cohort studied (whether CRS was performed or palliative debulking) and described the burden of disease on the basis of the standard scoring according to the Peritoneal Cancer Index, there has not been presentation of outcomes according to the completeness of cytoreduction (CC) for those patients, where CC0 is no residual disease (RD), CC1 <0.25 cm RD, CC2 0.25-2.5 cm RD, and CC3 >2.5 cm RD.[2] Interestingly, 180 (66%) patients did not receive intraperitoneal chemotherapy, potentially indicating a significant cohort of patients who received suboptimal debulking operations rather than complete cytoreduction. This suggests a group of patients with either high burden of disease or with unfavorable location of the disease (eg, implants affecting the small bowel). This is also supported by the fact that only 15 samples had <10% tumor purity. Given that CRS can be curative, especially when complete cytoreduction is achieved (CC0), we feel this would be an important confounder to include in any analysis of prognostic variables. Additionally, nodal staging has not been included as a covariate, with previous data demonstrating prognostic value.[3] It is, therefore, important to take these factors into consideration before any conclusions regarding guidance for current clinical decision making are drawn.

To conclude, this study provides important insights to this neglected disease; we congratulate the investigators on their in-depth analysis and eagerly await external validation in other cohorts before any change in clinical decision making. In addition, although understanding the genomic classification of AC in different populations is important, we need more dedicated study of the tumor and the peritoneal microenvironment to gain further understanding of the mechanisms of chemotherapy response and resistance to ultimately drive rational development of novel drug and treatment strategies.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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