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EDITORIAL – HEPATOBILIARY TUMORS

Genomic Predictors of Recurrence Patterns After Complete Resection of Colorectal Liver Metastases and Adjuvant Hepatic Artery Infusion Chemotherapy by Narayan et al.

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Since the early description of the adenoma–carcinoma sequence by Fearon and Vogelstein,[1] the number of genes that have been implicated in colorectal tumorigenesis has markedly expanded. Specifically, the prognostic and predictive implications of various alterations, including *TP53*, *KRAS/NRAS*, *APC*, *SMAD4*, *BRAF*, *POLE*, *ERBB2*, and mismatch repair genes, have led to remarkable improvements in patient selection for targeted therapies, and ultimately clinical outcomes. Changes in *APC*, *KRAS*, and *TP53* have been the most extensively studied in the pathogenesis of colorectal carcinoma, and additional work has focused on the association between mutation status and outcomes. It has been reported that wild-type *APC* is associated with worse outcomes in localized and metastatic colorectal cancer.[2,3] Prior work by Conlin et al.[4] showed that mutant *KRAS* was associated with worse outcomes independent of tumor stage, using a retrospective database of 107 patients with colorectal cancer. Williams et al.[5] identified p53 overexpression, a result of *TP53* alterations, as being associated with a survival detriment in stage III colorectal cancer. However, this was observed only in patients who underwent adjuvant chemotherapy, but not in those who underwent surgery alone. These findings highlight the biologic heterogeneity of the primary tumors and the interaction it may have with systemic therapies. This area of research has expanded into the treatment of liver only metastatic disease with hepatic artery infusion (HAI) for colorectal liver metastases (CRLMs). Here, we have learned that patients with *KRAS* mutated CRLMs who undergo resection have worse outcomes compared with those with *KRAS* wild type, although adjuvant HAI therapy appears to improve survival in both genetic cohorts.[6] Clearly, a more detailed understanding of how these specific genetic alterations interact with HAI and systemic therapy is needed and will open new avenues for novel treatment strategies, including HAI therapy.

In this issue of *Annals of Surgical Oncology*, Narayan et al.[7] explore the relationship between tumor-specific mutations and outcomes in patients who underwent adjuvant HAI and systemic chemotherapy for CRLMs. With an extensive database of patients who underwent HAI over the last two decades, this group from the Memorial Sloan Kettering is well suited to ask such questions regarding biologic factors and patient selection variables for optimizing HAI therapy. Using targeted next-generation sequencing [Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT) assay] of matched tumor and normal tissue from these patients, the authors present a comprehensive analysis of the genetic differences that are associated with outcomes in patients who receive adjuvant HAI therapy. In total, 230 patients with CRLM were evaluated, of whom 172 underwent adjuvant HAI and systemic chemotherapy (HAI/SYS), and 58 with adjuvant systemic chemotherapy only (SYS). The authors examined the cohort of 172 patients who underwent HAI/SYS and identified some notable associations. Within the HAI/SYS cohort, extrahepatic recurrence was increased in patients with mutations in *FLT3*, *KRAS*, and *SMAD4* genes and alterations in the *RTK–RAS*, *RAS/RAF*, and cell cycle pathways. Co-alteration in *RAS/RAF–TP53* was associated

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with worse any recurrence, local recurrence, and extrahepatic recurrence. This supports the observation that these mutations are poor prognostic factors that even regional therapy cannot overcome. The association of a co-alteration in *RAS/RAF–TP53* with increased recurrence rate was not observed in the SYS group.

The authors should be lauded for their efforts in advancing the HAI field by analyzing the immense volume of clinical and molecular profiling data that have been generated over several years. These results add to the research community at large, and prospective collection of molecular sequencing data is a forward-thinking and creative method to address heretofore unanswered questions in tumor heterogeneity and patient selection. It is quite notable that this same correlation between specific genetic alterations and outcomes was not detected in the SYS only group, as the authors point out. Although the differences in how mutations impact outcomes in the SYS and HIA/SYS groups may represent a true observation on the interaction between therapies and the tumor, it is difficult to ignore the significant selection bias and potentially underpowered cohort present in this nonrandomized setting. Specifically, sequencing results showed that this small cohort of 58 patients who underwent adjuvant systemic therapy only (SYS) had a higher rate of *KRAS*, *BRAF*, and *SMAD4* mutations, compared with the HAI/SYS group. These biologic differences may underlie the selection bias in those patients who ultimately undergo HAI therapy. The authors even note that the HAI/SYS cohort, among other differences, was younger and had fewer positive margins after liver resection, supporting the notion that these may be biologically distinct groups from the outset. On the other hand, this work may give insight into how systemic and regional therapies differ in their interaction with tumor-intrinsic mutational alterations.

While the direct implications of this work have yet to be realized, future trials should include these—and likely additional—variables in all analyses to avoid selection bias. In particular, including specific details on adjuvant chemotherapy regimens is critical, as is primary tumor sidedness, a prognostic and predictive biomarker known to correlate with different genetic alterations and survival differences in the metastatic setting.[8] This will also support better identification of response biomarkers, including those in concert with circulating tumor DNA changes as a tool to detect minimal residual disease and stratify high-risk biology for further therapies. The authors of the present study are already spearheading trials within the HAI Consortium Research Network to answer some of these questions. More broadly, this study highlights the principle that CRLMs provides a platform for novel drug development, combination therapies, and biomarkers of response.

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