Letter to the Editor

Confounders in developing a machine learning model for colorectal liver metastasis post-hepatectomy prognostications

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We extend our gratitude to Dr. Liu and colleagues for their valuable feedback and comments on our article (1). We developed a machine learning model which predicted the outcomes of surgical treatment for colorectal liver metastasis (CRLM) with good discriminative ability. While analyzing the data, we found that patients who underwent neoadjuvant chemotherapy before resection had lower rates of overall survival and disease-free survival. We agree that the negative impact of neoadjuvant chemotherapy on survival is probably a confounding factor due to a more advanced disease status at the time of presentation. This is supported by our data, which show that patients who received neoadjuvant therapy were more likely to have had bilobar liver metastasis (45.2% *vs.* 23.3%, P<0.001) and multiple liver lesions (64.9% *vs.* 42.3%, P<0.001) when compared to those who underwent upfront hepatectomy.

Our prognostic model effectively predicted the inferior survival in patients with more advanced diseases who underwent neoadjuvant chemotherapy. However, we agree that when developing a clinical model to predict outcomes of surgical treatment for CRLM, only baseline parameters at the time of presentation should be incorporated. Treatment parameters, particularly those with confounding effects, should be excluded from the analysis as they may lead to misguided treatment decisions. Furthermore, to enhance clinical applicability, the prognostic model should be simple, like the scoring system proposed by Fong *et al.* (2). The simplicity means that it can be easily used for prognostication and to guide patient selection for surgery. Nevertheless, Fong's model was derived from data more than 2 decades ago. Recent advances in surgical techniques, such as laparoscopic hepatectomy and ALPPS (associating liver partition and portal vein ligation for staged hepatectomy), along with improvements in systemic therapy, are likely to have enhanced the outcomes of surgical treatment for CRLM. In addition, molecular prognosticators, e.g., KRAS mutant status, have been widely used clinically. Patients with KRAS mutant status typically have poorer prognostic outcomes, as they are associated with resistance to EGFR-targeted therapies and more aggressive tumor behavior (3). We support the idea of developing an updated yet simple-to-use clinical prognostic score for CRLM, and incorporation of KRAS should improve its prognostic ability.

Finally, we would like to clarify that the histological grading of metastatic adenocarcinoma in our study was made based on the parameters of mitotic activity and degree of differentiation. The tumors were graded into well, moderately, and poorly differentiated adenocarcinoma based on the percentage of the tumor exhibiting the formation of glandular structures. The Edmonson grading should be reserved for grading hepatocellular carcinoma. We highly appreciate the insightful comments and suggestions by Dr. Liu and colleagues.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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