Letter to the Editor

Clinical Cancer Research

# Postoperative Recurrence of Hepatocellular Carcinoma: The Importance of Distinguishing between Intrahepatic Metastasis and Multicentric Occurrence—Response

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We thank Bai and Liang for their interest in our work and the valuable comments they have provided (1).

Intrahepatic recurrence of hepatocellular carcinoma (HCC) may be caused by intrahepatic metastasis (IM) of the primary carcinoma or by *de novo* multicentric occurrence (MO). Although genetic or molecular studies can be used to definitively distinguish between the two, these techniques are not part of the standard evaluation process owing to their technical complexity. Several recent studies have reported that aggressive characteristics in primary tumors are associated with early recurrence within 2 years after surgery, whereas late recurrence (>2 years) is associated with underlying liver conditions, such as liver cirrhosis (2). In our study, we identified that radiomics with border extensions predicted both early (using 3-mm border extension) and late recurrence (using 3- and 5-mm border extensions) to a comparable level with the postoperative clinicopathologic model. Aggressive peritumoral morphologic characteristics, such as microvascular invasion for early recurrence and peritumoral cirrhotic parenchyma for late recurrence, could confer prognostic power to radiomics in these conditions. Interestingly, the prognostic power of radiomics for predicting late recurrence tended to increase with the widening of the border extension. In the absence of the border extension, the prognostic power of radiomics tended to be inferior to that of the clinicopathologic model. This suggests that the presence of cirrhosis in the peritumoral hepatic parenchyma included in the border extension may have affected the efficacy of radiomics for predicting late recurrence.

In addition, the only known predictor of late recurrence of HCC is cirrhosis, and there may be morphologic differences between HCC arising in cirrhotic and noncirrhotic livers. HCC in noncirrhotic livers often presents at an advanced stage as a large-sized solitary or dominant mass with satellite nodules, unlike HCC in cirrhotic livers (3, 4). This tendency can be explained by either the inherent biological aggressiveness of noncirrhotic HCC or the typically delayed diagnosis (5). Radiomics may distinguish morphologic differences in primary HCCs depending on the presence of cirrhosis, which may be reflected in the prediction of late recurrence.

However, the accuracy for distinguishing between IM and MO based on a 2-year cut-off value is limited, and an overlap is expected when using this cut-off value. Further research on radiomics for molecularly or genetically confirmed IM and MO are required. We believe that a radiomics study on the differential diagnosis between molecularly or genetically confirmed IM and MO is also needed.

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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