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Conflicts of interest

The authors declare that they have no conflict of interest regarding the content of this manuscript.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Fredrik Åberg: conceptualization, writing - original draft, visualization, project administration; Panu Luukkonen: conceptualization, writing - review & editing, visualization; Martti Färkkilä: conceptualization, writing - review & editing, supervision.

Supplementary data

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The association of microvascular invasion with satellite nodule, tumor multiplicity, tumor encapsulation and resection margin of hepatocellular carcinoma

To the Editor:

We read with great interest the article by Beaufrère *et al.*[1] Microvascular invasion (MVI) is known to be a major risk associated with worse prognosis after resection of hepatocellular carcinoma (HCC), but it can only be detected by microscopic examination of the surgical specimen. By using their routine formalin-fixed paraffin-embedded (FFPE) biopsies and RNA-sequencing analysis, Beaufrère *et al.* developed and validated a 6-gene signature panel which can accurately predict MVI preoperatively. Meanwhile, this biogenetical panel was also demonstrated to be independently associated with overall survival after HCC resection. Although inspiring, we would like to raise a discussion on the association between MVI and other clinicopathological features in this study.

First, MVI and satellite nodules. Generally, satellite nodules are derived from MVI.[2,3] Similar to MVI, satellite nodules are only detectable by microscopy in the peritumoral liver of the surgical specimen.[2] While difficult to distinguish MVI and satellite nodule histologically, a diagnosis of satellite nodules is appropriate.[3] Not surprisingly, Beaufrère *et al.* also revealed an independently high correlation between MVI and satellite nodules in their study, with adjusted odds ratios (ORs) of 158.41 by univariate and multivariate analysis. However, what puzzles us is why the authors used satellite nodules as a variable in the multivariate analysis to predict MVI, given that their purpose was actually to preoperatively predict MVI, while the presence of satellite nodules also needs to be identified postoperatively like MVI. This approach appears to be incorrect and will likely change the adjusted OR value of the 6-gene signature when predicting MVI.

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Second, MVI and tumor multiplicity. Among the 178 patients in the whole cohort of this study by Dr Beaufrère *et al.*, 24 (13.5%) patients had multiple tumors (tumor number ≥2). Considering the high heterogeneity of HCC, whether these multiple tumor lesions are of monoclonal origin or polyclonal origin will be very different in their gene signature spectrum through tissue biopsy.[4,5] In this study, however, the authors did not mention whether both FFPE biopsy and transcriptome sequencing were performed for each tumor lesion of patients with multiple tumors, whether the MVI status of each tumor lesion was respectively examined and marked, and whether the RNA-sequencing result had a one-to-one correspondence with the MVI status of each tumor lesion. In our opinion, ambiguity of important information or possible labeling errors will inevitably affect the interpretability and credibility of the results.

Third, MVI and tumor encapsulation. Previous studies have shown that there is a negative correlation between tumor encapsulation and MVI, suggesting that once cancer cells of HCC break through the tumor capsule, the probability of forming MVI is greatly increased.[3,6] In the literature, most prognostic studies on HCC resection did not overlook the potential effect of tumor capsulation.[7,8] Unfortunately, we did not find this important pathological feature which may be related to both MVI and overall survival after HCC resection in this study by Beaufrère *et al.*

Fourth, MVI and resection margin. Another pity in this study is that the status of resection margin was not mentioned.[1] Actually, given that the status of resection margin (narrow or wide) and MVI (positive or negative) both involve the chance of residual cancer cells being left in the liver remnant after HCC resection, they are likely to have a synergic effect on postoperative recurrence and survival.[9] Our team has reported that concomitant narrow resection margin (<1.0 cm) and positive MVI increases the risks of postoperative recurrence and death by about 2-fold in patients with solitary HCC.[10]

In conclusion, clarification of the aforementioned issues would greatly solidify the conclusions of this study.

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Authors' contributions

Conception: Chao Li, Tian Yang; Manuscript preparation: Chao Li, Wei Ouyang; Critical revision: Tian Yang. All the authors reviewed the paper and approved the final version. Chao Li and Wei Ouyang contributed equally to this work.

Supplementary data

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