

Conflict of interest

All authors have declared no conflict of interest.
Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Conception: Wen-Tao Yan, Hao Xing, Tian Yang; Manuscript preparation: Wen-Tao Yan, Bing Quan, Hao Xing; Critical revision: Meng-Chao Wu, Tian Yang. All the authors reviewed the paper and approved the final version. Wen-Tao Yan, Bing Quan, and Hao Xing contribute equally to this work.

Supplementary data

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Factors predicting early recurrence after surgical resection of hepatocellular carcinoma

To the Editor:

We read with great interest the study by Dr. Chan *et al.*¹ in which male gender, large tumor size, multinodular tumor, high albumin-bilirubin (ALBI) grade, high preoperative alpha-fetoprotein (AFP) level, and microvascular invasion were identified as independent risk factors of early recurrence (<2 years) after curative surgical resection for hepatocellular carcinoma (HCC). Using these variables, the authors proposed a preoperative model (ERASL-pre) and a postoperative model (ERASL-post) for predicting early recurrence. These 2 statistical models achieved ideal performance in external cohorts from different countries. Herein, we would like to raise the following comments:

It is generally recognized that early recurrence represents pre-existing intrahepatic occult metastasis, whereas late recurrence is most likely a *de novo* tumor, which is different from the original tumor.² Numerous previous studies showed that early recurrence was often associated with aggressive tumor characteristics, including poor differentiation, large tumor size, multiple tumors, macrovascular and microvascular invasion, and

satellite lesions.^{3,4} Apart from these risk factors, to our surprise, Chan *et al.* revealed in their study that being male was an independent risk factor of early recurrence after HCC resection. Furthermore, in the Cox-regression analyses of this study, being male had the highest hazard ratios (HRs) among all independent risk factors, both in the preoperative model (HR 2.265) and postoperative model (HR 1.969). To the best of our knowledge, this is the first study to point out the independent relationship between gender and early HCC recurrence.

There happened to be a multicenter study from China which exactly investigated the relationship between gender and recurrence after HCC resection.⁵ The results of this study showed that the rates of early recurrence (<2 years after surgery) between males and females were similar (43.3% vs. 42.0%; *p* = 0.728), while the rate of late recurrence (>2 years) in male patients was higher than female patients (17.2% vs. 11.2%; *p* = 0.044). The authors explained that the gender difference in late recurrence actually mirrored the fact that the incidence of HCC is higher in males than in females. Actually, it is hard to under-

stand if there was really an independent relationship between gender and early recurrence. Unfortunately, we did not find out the related explanation on this issue in Chan *et al.*'s study.

In addition, we are surprised to discover that the proportion of microvascular invasion varied widely among the derivation cohort (Hong Kong) and the 5 validation cohorts (Japan, the US, Wenzhou of China, Nanning of China, and Italy). Especially, 73.1% of patients with HCC from the US cohort had microvascular invasion, which was much higher than the other cohorts (26.8%~49.3%). Are there different criteria for microvascular invasion in pathological examination among these hospitals or a big difference in the baseline characteristics of these patients enrolled in each hospital? Previous studies reported that the incidence of microvascular invasion in patients undergoing liver resection for HCC ranged from 15% to 57.1%.⁶ We really think that 73.1% in the US cohort is too high. Is this the result of a typographical error?

Our confusion about the disproportionate proportion of microvascular invasion also exists for macrovascular invasion in Chan *et al.*'s study. We note that in this study, the proportion of macrovascular invasion in the 6 cohorts was from 0% (Italy), 7.4% (Japan), 8.1% (Hong Kong), 9.0% (Wenzhou of China), 17.0% (Nanning of China) to 28.6% (the US). In other words, the proportion of macrovascular invasion in patients undergoing liver resection of HCC in Western countries (the US) was higher than those in Eastern countries and regions (Japan, Hongkong, and China), which seems inconsistent with the real world.⁷⁻¹⁰ Furthermore, macrovascular invasion has been regarded as the most important risk factor associated with HCC recurrence in almost all previous studies. However, the authors did not confirm the independent relationship between macrovascular invasion and early recurrence, although the proportion of patients with macrovascular invasion was considerable in this study.

In conclusion, the study by Chan *et al.* performed reasonable statistical approaches to predict early HCC recurrence after resection, which has potentially important value in our clinical practice. However, the independent factors predicting early recurrence after HCC resection in this study contradict our usual understanding. Besides, there are large differences in the proportions of macrovascular and microvascular invasion among the 6 cohorts in this study. The authors need to provide further verification and rational explanation to enhance the reliability and rationality of the research.

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Authors' contributions

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Supplementary data

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