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Time to recurrence, but not recurrence-free survival, should be the endpoint used to predict early recurrence after HCC resection

To the Editor:
We read with great interest the article by Dr. Chan *et al.*[1] In this study, gender, preoperative albumin-bilirubin (ALBI) grade, preoperative alpha-fetoprotein (AFP) level, tumor size, tumor number, and microvascular invasion were revealed as independent predictors associated with early recurrence after resection of hepatocellular carcinoma (HCC). Using these independent predictors, the authors developed and validated 2 models for predicting early recurrence, *i.e.,* the preoperative model (ERASL-pre) and the postoperative model (ERASL-post). Based on these 2 models, the authors conducted risk stratification to better determine the risk of early recurrence for patients undergoing HCC resection. However, for both model establishment and risk stratification, the authors adopted recurrence-free survival (RFS) as the study endpoint. In terms of the optimal study endpoint and the enrolled clinical variables in this study, we have the following comments:

In the 'Patients and methods' section, the authors defined RFS as "the time from date of curative surgery to the time of recurrence", and "patients with no recurrent disease were censored at the last time at which they were known to be recurrence free". However, the description mentioned above is not the generally-recognized definition of RFS, but always regarded as the definition of time to recurrence (TTR). Actually, in most previous studies, RFS is generally defined as "the time from date of curative surgery to the time of recurrence or death". In other words, if a patient died without recurrence in the follow-up after surgery, it should be considered as an endpoint for RFS but not a censored event. For example, 1 male patient died of decompensated cirrhosis at the 10th month after resection of HCC, but recurrence did not occur at the time of death. For this patient, the RFS should be considered as having an endpoint event (defined as "1"), while the TTR should be considered as a censored event (defined as "0"). Although the time of RFS and TTR is the same (10 months), it was totally different between the 2 final events. We believe that TTR, rather than RFS, may be the optimal study endpoint for predicting early recurrence after HCC resection.

Additionally, what puzzled us was that in this study, ALBI grade, an indicator of hepatic function, was an independent predictor of early recurrence after HCC resection. It is commonly known that early recurrence is most likely the consequence of occult metastasis from the initial tumor, and those aggressive tumor characteristics, including large tumor size, multi-nodularity, poor tumor differentiation, microvascular and macrovascular invasion, and satellite nodules, have been demonstrated to be associated with early recurrence after HCC resection in numerous previous studies.[2–7] Furthermore, in these studies, those characteristics reflecting preoperative hepatic function, such as the Child-Pugh grade, the ALBI grade, and the model for end-stage liver disease score, were always proven to be associated with worse survival rate after HCC resection, instead of early recurrence. Therefore, we wonder if Chan *et al.* used RFS (considering recurrence and death as an end event), but not TTR (only considering recurrence as an end event) as the study endpoint for multivariate Cox-regression analyses in their study.

Last but not least, the authors adopted many clinical variables to set up preoperative and postoperative models for predicting early recurrence before and after surgery, respectively. In most cases, some clinical variables for developing the preoperative model are usually based on preoperative imaging findings, while some clinical variables for developing the postoperative model are often derived from postoperative pathological examinations of specimens.[8–10] The determinations of some clinical variables, including tumor size, tumor number, and gross/macroscopic vascular invasion, would overlap but lead to different results between preoperative imaging findings and postoperative pathological examinations. However, in Chan *et al.*'s study, the analyses of tumor size and tumor number used the same data both before and after surgery. The authors should explain clearly which results the predictive variables, used to develop their 2 models, were based on – the preoperative imaging findings or the postoperative pathological examinations.

In summary, clarification regarding these issues would greatly solidify the conclusions of Chan *et al.*'s study.

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Conflict of interest

All authors have declared no conflict of interest.

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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-