

Comments to the Author

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: A comprehensive retrospective study. The limitations mentioned are valid and it does confound the data interpretation. Nevertheless, it will require prospective data for recommendations. The following suggestions are offered for enhancing the manuscript: 1. Please add the following for enhancing the discussion: a) Portolani N, Coniglio A, Ghidoni S, Giovanelli M, Benetti A, Tiberio GA, Giulini SM. Early and late recurrence after liver resection for hepatocellular carcinoma: prognostic and therapeutic implications. *Ann Surg*. 2006 Feb;243(2):229-35. b) Yang SL, Luo YY, Chen M, Zhou YP, Lu FR, Deng DF, Wu YR. A systematic review and meta-analysis comparing the prognosis of multicentric occurrence and vs. intrahepatic metastasis in patients with recurrent hepatocellular carcinoma after hepatectomy. *HPB (Oxford)*. 2017 Oct;19(10):835-842. c) Yan WT, Li C, Yao LQ, Qiu HB et al. Predictors and long-term prognosis of early and late recurrence for patients undergoing hepatic resection of hepatocellular carcinoma: a large-scale multicenter study. *Hepatobiliary Surg Nutr* 2021. doi: 10.21037/hbsn-21-288 d) Byeon J, Cho EH, Kim SB, Choi DW. Extrahepatic recurrence of hepatocellular carcinoma after curative hepatic resection. *Korean J Hepatobiliary Pancreat Surg*. 2012 Aug;16(3):93-7.

→ We would like to thank the reviewer for evaluating our manuscript and for their valuable comment. Please note that we have cited the suggested references and added a new part to enhance our manuscript:

The added part is as follows:

“Since the proportion of IHR cases is higher than that of EHR cases after surgical resection of HCC, previous studies have analyzed various risk factors associated with IHR alone, previous studies have analyzed various risk factors associated with IHR. Portolani et al. examined the early and late recurrence of HCC after

liver resection and showed that the survival rates in the early recurrence group were significantly lower than those in the late recurrence group (25.7% vs. 4.5% at 5 years)^[1]. Moreover, similar results were demonstrated in a large-scale multicenter study conducted in China by Yan et al. comprising 1,426 patients, where patients in the early recurrence group showed poor post-recurrence survival (13.5 vs. 36.6 months, $p<0.001$).^[2] Furthermore, Yang et al. stated that recurrent HCC cases with multicentric recurrence may have had greater survival than intrahepatic metastasis cases ^[3]. In contrast, Byeon et al. compared the outcomes of 111 patients with IHR and 41 patients with EHR who had undergone surgical resection for HCC and found that patients in the EHR group showed significantly lower 5-year survival rates than those in the IHR group (21.5% vs. 36.3%, $p<0.001$)^[4]."

Reviewer #2:

Scientific Quality: Grade C (Good)

→ We would like to thank the reviewer for the positive evaluation.

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: Overall the article is well written. The title reflects the main subject of the manuscript. The abstract summarizes and reflects the work described in the manuscript. Please, if possible, avoid the use of abbreviations in the abstract. The key words reflect the focus of the manuscript. The manuscript adequately describes the background, present status and significance of the study. The manuscript describes methods in adequate detail. The research objectives are achieved. The manuscript interpretes the findings adequately and appropriately, highlighting the key points concisely, clearly and logically. The findings and their relevance to the literature are stated in a clear and definite manner. The discussion is accurate and outlines the paper's scientific significance to clinical practice. I did not detect self-cite or plagiarism. The manuscript is coherently organized and presented. Style, language and grammar are appropriate. The STROBE statement - checklist of items has been applied. Ethics documents reviewed and approved by the local ethical review committee are present. This manuscript is about extrahepatic disease recurrence after HCC surgery. Authors propose that there are clinical and laboratory findings which are associated to early extrahepatic HCC recurrence. Authors found that various laboratory findings are associated with early extrahepatic recurrence. The conclusions appropriately summarize the findings.

- The "p" of p-value should be always written in lowercase italics; please change this throughout the text.

→ We appreciate the reviewer's insightful comment. Please note that we have used lowercase italics when describing the *p*-values throughout the entire manuscript, as per the reviewer's suggestion.

- Discussion: please change "was the first recurrence of HCC after surgical resection (Supplementary Table 3), and the both of the interval" to "was the first recurrence of HCC after surgical resection (Supplementary Table 3), and both interval" -

→ Please note that we have revised this sentence as follows:

"In 52.7% of the patients with early EHR, EHR was the first recurrence of HCC after surgical resection (Supplementary Table 3), and both interval to first recurrence and EHR were significantly shorter in the early EHR group compared with that in the non-early EHR group (5.2 *vs.* 21.6 months, $p<0.001$; and 8.81 *vs.* 58.57 months, $p<0.001$)."

Discussion: after talking about limitations, authors should briefly speak about future perspectives and unanswered questions on this topic, proposing how to better expand knowledge on this topic (e.g. how to correctly treat early extrahepatic recurrence, use of radiomics features for recurrence prediction: see below).

→ We would like to thank the reviewer for the recommendation. Please note that we have added the potential role of radiomic features and the future perspective in prediction of early EHR. The added part is as follows:

"Especially, the use of radiomic tumor features for the prediction of recurrence after HCC treatment can be considered as an additional tool for prompt detection of early EHR [5, 6]. Using an accurate tool for the prediction of early EHR, the prognosis of patients with a high risk of early EHR may be improved with the utilization of adjunctive post-operative therapy."

- Please add a reference to the updated BCLC guidelines (2022) in the first paragraph of the introduction, and also change it in materials and methods (ref 14): doi: 10.1016/j.jhep.2021.11.018.

→ As per the reviewer's insightful suggestion, we have revised the BCLC guideline reference to the updated (2022) guideline reference and added it at the first paragraph of the Introduction section.

- Please add a reference to the use of radiomics in the prediction of poor responders after treatments; studies have been performed on surgical and locoregional patients. Please cite: doi: 10.2147/JHC.S362772, doi: 10.26355/eurrev_202204_28620.

→ As requested, we have cited the suggested references in the revised manuscript (References #34, 35).

Moreover, we have added the following part to enhance our discussion:

“Especially, the use of radiomic tumor features for the prediction of recurrence after HCC treatment can be considered as an additional tool for prompt detection of early EHR [5, 6]. Using an accurate tool for the prediction of early EHR, the prognosis of patients with a high risk of early EHR may be improved with the utilization of adjunctive post-operative therapy.”

Reviewer #3:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: The article focused on "Early extrahepatic recurrence (Early EHR)" and the survival in patients with hepatocellular carcinoma resected. Those published literatures nearly mainly described the difference between the EHR and IHR recurrence in cases with hepatocellular carcinoma. Thus, the article is of its novelty. However, the basis for this risk subgroup ? Please explain it in the discussion part.

→ We would like to thank the reviewer for evaluating our manuscript and for his/her comment. Please note that we have described the two different types of HCC recurrence (intrahepatic recurrence [IHR] and extrahepatic recurrence [EHR]) and enhanced our discussion concerning the consequences of poor prognosis. The added parts is as follows:

"We have reported simple parameters for predicting EHR after hepatectomy [7], and in that study, approximately 49.2% of the patients with EHR (31 of 63 patients) showed early EHR and demonstrated poorer recurrence-free survival (RFS) and overall survival rates. There have been many reports regarding the risk factors and predictive models for early recurrence mostly concerning IHR of HCC after surgery [8-10]; however, there are limited data regarding the risk factors and survival outcomes related to early EHR after surgical resection of HCC. Moreover, the clinical characteristics and survival outcomes of patients with early EHR in comparison with those with a later onset of EHR have not been examined. Hence, we aimed to investigate the characteristics and potential risk factors of early EHR after curative surgical resection for HCC and explore the relationship between early EHR and survival outcomes."

Moreover, we have highlighted the significance of detection of early EHR in the Discussion section as follows:

“Since the proportion of IHR cases is higher than that of EHR cases after surgical resection of HCC, previous studies have analyzed various risk factors associated with IHR alone, previous studies have analyzed various risk factors associated with IHR. Portolani et al. examined the early and late recurrence of HCC after liver resection and showed that the survival rates in the early recurrence group were significantly lower than those in the late recurrence group (25.7% vs. 4.5% at 5 years) [1]. Moreover, similar results were demonstrated in a large-scale multicenter study conducted in China by Yan et al. comprising 1,426 patients, where patients in the early recurrence group showed poor post-recurrence survival (13.5 vs. 36.6 months, $p<0.001$). Furthermore, Yang et al. stated that recurrent HCC cases with multicentric recurrence may have had greater survival than intrahepatic metastasis cases [3]. In contrast, Byeon et al. compared the outcomes of 111 patients with IHR and 41 patients with EHR who had undergone surgical resection for HCC and EHR group showed significantly lower 5-year survival rates compared to IHR (21.5% vs. 36.3%, $p<0.001$) [4]. Considering the non-negligible rates of EHR after surgical resection of HCC and the dismal prognosis of patients with EHR, risk stratification and prediction of early EHR may have been of great importance in improving the clinical outcome.”

References

- 1 Portolani N, Coniglio A, Ghidoni S, Giovanelli M, Benetti A, Tiberio GA, Giulini SM. Early and late recurrence after liver resection for hepatocellular carcinoma: prognostic and therapeutic implications. *Annals of surgery* 2006; **243**(2): 229-235 [PMID: 16432356 PMCID: PMC1448919 DOI: 10.1097/01.sla.0000197706.21803.a1]
- 2 Yan W-T, Li C, Yao L-Q, Qiu H-B, Wang M-D, Xu X-F, Zhou Y-H, Wang H, Chen T-H, Gu W-M. Predictors and long-term prognosis of early and late recurrence for patients undergoing hepatic resection of hepatocellular carcinoma: a large-scale multicenter study. *Hepatobiliary surgery and nutrition* 2021
- 3 Yang SL, Luo YY, Chen M, Zhou YP, Lu FR, Deng DF, Wu YR. A systematic review and meta-analysis comparing the prognosis of multicentric occurrence and vs. intrahepatic metastasis in patients with recurrent hepatocellular carcinoma after hepatectomy. *HPB : the official journal of the International Hepato Pancreato Biliary Association* 2017; **19**(10): 835-842 [PMID: 28734693 DOI: 10.1016/j.hpb.2017.06.002]
- 4 Byeon J, Cho EH, Kim SB, Choi DW. Extrahepatic recurrence of hepatocellular carcinoma after curative hepatic resection. *Korean journal of hepatobiliary-pancreatic surgery* 2012; **16**(3): 93-97 [PMID: 26388915 PMCID: PMC4575006 DOI: 10.14701/kjhbps.2012.16.3.93]
- 5 Wang F, Chen Q, Zhang Y, Chen Y, Zhu Y, Zhou W, Liang X, Yang Y, Hu H. CT-Based Radiomics for the Recurrence Prediction of Hepatocellular Carcinoma After Surgical Resection. *J Hepatocell Carcinoma* 2022; **9**: 453-465 [PMID: 35646748 PMCID: PMC9139347 DOI: 10.2147/JHC.S362772]
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- 8 Li WF, Yen YH, Liu YW, Wang CC, Yong CC, Lin CC, Cheng YF, Wang JH, Lu SN. Preoperative predictors of early recurrence after resection for hepatocellular carcinoma. *American journal of surgery* 2021 [PMID: 34399978 DOI: 10.1016/j.amjsurg.2021.08.012]
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Kaneoka Y, Hazama S, Nagano H, Mirza AH, Graf HP, Cosatto E, Murakami Y, Kuroda M. Prediction of early recurrence of hepatocellular carcinoma after resection using digital pathology images assessed by machine learning. *Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc* 2021; **34**(2): 417-425 [PMID: 32948835 PMCID: PMC7817520 DOI: 10.1038/s41379-020-00671-z]