

Regarding "Postresection Period-Specific Hazard of Recurrence as a Framework for Surveillance Strategy in Patients with Hepatocellular Carcinoma: A Multicenter Outcome Study"

Hiroshi Imamura^a Kiyoshi Hasegawa^b Yuji Soejima^c Akio Saiura^a

^aDepartment of Hepatobiliary-Pancreatic Surgery, Juntendo University School of Medicine, Tokyo, Japan;

^bHepato-Biliary-Pancreatic Surgery Division, Artificial Organ and Transplantation Division, Department of Surgery, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan;

^cDepartment of Surgery, Shinshu University School of Medicine, Matsumoto, Japan

Dear Editor,

We enjoyed the article by Kim et al. [1] assessing the hazard function of postoperative recurrence in patients with hepatocellular carcinoma (HCC) undergoing hepatectomy. The authors are to be commended for having estimated the recurrence hazard function of HCC over a period of up to 10 years in a very large cohort ($n = 1,918$).

A hazard function can be derived from a survival function using the following equation:

$$h(t) = \frac{-dS(t)}{dt} \times \frac{1}{S(t)}$$

where $h(t)$ denotes the hazard function and $S(t)$ signifies the survival function.

These two functions are mathematically equivalent, but they represent different, complementary clinical aspects. A recurrence-free survival function, which corresponds to $S(t)$, depicts the percentage of patients who remain recurrence-free at a given time after tumor removal and provides a quick reference for estimating the recurrence-free survival rate and the median recurrence-free survival. This approach focuses on the cumulative event-free time distribution, i.e., the cumulative incidence risk. On the other hand, a hazard function, that is, $h(t)$, delineates the risk of recurrence among patients who remain

recurrence-free over time and provides the event risk pattern through time. Therefore, this function enables us to obtain qualitative insight into the recurrence dynamics, viz., the timing of tumor recurrence [1].

The first notable finding of this article is that extrahepatic recurrence, which is definitely a recurrence by metastasis, occurred constantly at an annualized incidence of 0.4–1.0% until 6 postoperative years. Considering that the incidental ratio of liver to extrahepatic sites at the time of initial recurrence was reportedly 9:1, which was similar to the ratio reported in another study [2, 3], and that the majority of these recurrences were thought to be metastatic, recurrences by this mechanism were presumed to emerge at an annual incidence of 4–10% during the corresponding period, although this assumption may be too simplistic. Landmark analysis to investigate early and late phases of recurrences was first reported by Poon et al. [4] in 2000, followed by us in 2003 using a hazard function [5]. Since then, many have argued, citing our article, that metastatic recurrences rarely occur after 2 postoperative years. However, this conclusion cannot be drawn from our data. Our article provided epidemiological evidence that recurrence by metastasis occurred mainly during the earlier postoperative phase, while de novo secondary recurrences were chronologically distributed evenly

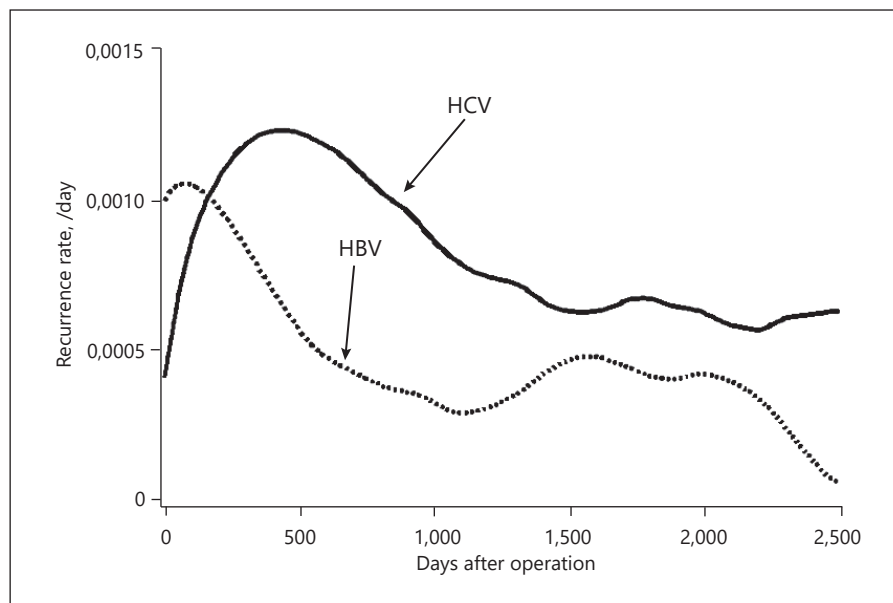


Fig. 1. Postoperative recurrence-survival functions stratified according to the associated viral infectious status. $n = 537$ ($n = 160$, Shinsyu University Hospital between 1991 and 1998; and $n = 377$, Tokyo University Hospital between 1998 and 2006).

throughout the postoperative period, leading to the majority of late-phase recurrences representing de novo carcinogenesis. It should be emphasized, however, that this temporal relationship holds true only in a relative context. Likewise, the division of the postoperative period into two phases (before or after 2 years) was arbitrary. Similar hold true for the work by Poon et al. [4] setting 1 year and the present study setting 5 years as the division between early and late phases. In other words, recurrence by metastasis continues to occur constantly even during the late postoperative phase at a significant rate. The present article clearly verified this contention.

The second important finding was that the annualized recurrence rates between the 5th and 10th postoperative years were approximately 5% in their overall cohort and between 3% and 10% in cirrhotic patients. The latter figure was comparable to or even lower than the reported annual incidence of HCC in cirrhotic patients with HBV infection in Asia (3.2–4.3%) and that in cirrhotic patients with HCV infection in Japan (7.1%) [6], especially considering that recurrences by metastases comprised at least some proportion of their cohort. These findings were markedly different from those reported by Cucchetti et al. [7], who reported that the annual incidences of late (>2 years)-phase postoperative HCC recurrence in cirrhotic patients versus HCC emergence in surveilled cirrhotic patients were 18.4% versus 5.8%, respectively, of whom 80% were with HCV infection. The results by Cucchetti et al. [7] can be more naturally interpreted because de novo secondary HCC is supposed to emerge at a higher

rate in patients with HCC than in initial HCC emergence in surveilled patients, even though the extent of liver cirrhosis was similar, because patients in whom HCC had occurred once were thought to be under a stronger carcinogenic influence than surveilled HCC-naïve patients, whatever the calculated sum of known risk factors. Patients with HCV-derived HCC comprised nearly 80% of the cohort in the study reported by Cucchetti et al. [7] whereas they comprised 5.6% in the present study; thus, a simple comparison is difficult. Nevertheless, the differences between these two reports should be kept in mind.

On the other hand, several issues in interpreting the present results should be pointed out, particularly with regard to the annualized incidence of and factors affecting late (>5 years)-phase recurrence. First, although HBV infection and HCV infection were present in 84.5% and 5.4% of the total population ($n = 1,918$), the authors amalgamated these two groups together when calculating the hazard function. Patients with HCV-related HCC reportedly had a higher incidence of multinodular tumors [8], poorer postoperative recurrence-free survival [9], and an increasingly higher incidence of intrahepatic recurrence in a person-year-based analysis [10], compared with patients with HBV-related HCC. All these findings lend support to the hypothesis that the background liver of HCV-related HCC has a higher carcinogenic activity than that of HBV-related HCC, at least during the era before the advent of direct-acting antivirals. We plotted the recurrence hazard functions of patients with HBV- and HCV-related HCC, respectively, who underwent liver re-

section in two institutions where the first author (H.I.) previously worked (Fig. 1). Patients with HCV-related HCC had a consistently higher recurrence hazard than those with HBV-related HCC beginning 1 year after surgery. These results are in accordance with the above hypothesis and provide the real-world landscape before the advent of direct-acting antivirals.

Second, the authors assessed risk factors for recurrence simply that they were common to different etiologies of HCC, despite the large number of patients with HBV-related HCC ($n = 1,623$; 84.6%). Long-term liver damage arising from the immune response to virus infection and/or other stimuli is considered to trigger chronic inflammation, oxidative DNA damage, and continuous cell death; these processes are thought to promote HCC progression through accelerated hepatocyte turnover rates and the resulting accumulation of mutations [11]. This holds true for HCV-related HCC because HCV is known to be an RNA virus with a restricted incorporation of its genetic information into the host gene. Consequently, the carcinogenic prospect of HCV is linked to an indirect mechanism, and HCC usually emerges from a cirrhotic liver background. In contrast, HBV, which is a DNA virus and can integrate into the host genome, executes direct carcinogenic activity in addition to the above-mentioned indirect mechanism [12]. In fact, cirrhosis is absent in up to one-third of patients with HBV-related HCC [6]. Furthermore, several risk factors specifically linked to the development of HBV-related HCC have been reported, including a high serum HBV DNA level, HBeAg positivity, a higher HBsAg level, HBV genotype C, etc. [13]. The authors would have obtained interesting results had they evaluated the risk factors for late-phase recurrence exclusively in patients with HBV infection, including these covariates into the analysis.

Third, the description that cirrhosis was the only risk factor contributing to late-phase recurrence is misleading in two aspects. First, it is too simplistic to conclude that the cirrhosis was the only contributor to the late phase of recurrence because HCC develops via a multistep process in which many factors are thought to be involved. Second and most importantly, although recent studies shed light on fibrosis-dependent hepatocarcinogenesis through integrin signaling, paracrine stellate cell signaling, reduced NK cell function, etc. [14], the main mechanism of HCC development from cirrhotic livers is inflammation-caused indirect carcinogenesis. In this situation, a long latency period from viral infection and/or long-lasting exposure to exogenous carcinogenic stimuli, such as aflatoxins and alcohol, are thought to underlie the develop-

ment of HCC. Concurrently, inflammation caused by the host immune response promotes liver fibrosis, culminating in cirrhosis. In other words, liver fibrosis is an epiphenomenon caused by long-lasting inflammation. Therefore, the stage of liver fibrosis, i.e., cirrhosis, is thought to be a surrogate marker of the accumulated amounts of carcinogenic stimuli each subject has been exposed to or a marker indicating how much distance a patient has advanced in the multistep process of carcinogenesis. As a whole, it could be said in a figurative sense that the stage of liver fibrosis indicates a position each patient stands at in a metaphorical boardgame of “parcheesi,” ending in HCC occurrence, while the degree of hepatitis activity and/or the strength of additive/synergistic effects of several carcinogens are thought to represent the speed at which each subject proceeds in the parcheesi game. If we understand correctly, many investigators may confuse a pathogenic factor with its surrogate marker when interpreting the significance of fibrosis in studies investigating risk factors leading to HCC development.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare. Dr. Kiyoshi Hasegawa is an Editorial Board Member of *Liver Cancer*.

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Author Contributions

Hiroshi Imamura contributed mainly to the conception of the work and interpretation of the data and wrote the manuscript. Kiyoshi Hasegawa and Yuji Soejima contributed to the acquisition of the data presented in Figure 1. Kiyoshi Hasegawa, Yuji Soejima, and Akio Saiura contributed to the conception of the work and analysis of the data. They revised the manuscript for important

intellectual content. Hiroshi Imamura, Kiyoshi Hasegawa, Yuji Soejima, and Akio Saiura did the final approval of the version to be published and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data Availability Statement

The data used to create Figure 1 are available from Hiroshi Imamura.

References

- 1 Kim HI, An J, Kim JY, Shin HP, Park SY, Song GW, et al. Postresection period-specific hazard of recurrence as a framework for surveillance strategy in patients with hepatocellular carcinoma: a Multicenter Outcome Study. *Liver Cancer* 2022;11:141-51.
- 2 Simes RJ, Zelen M. Exploratory data analysis and the use of the hazard function for interpreting survival data: an investigator's primer. *J Clin Oncol*. 1985;3:1418-31.
- 3 Cha C, Fong Y, Jarnagin WR, Blumgart LH, DeMatteo RP. Predictors and patterns of recurrence after resection of hepatocellular carcinoma. *J Am Coll Surg*. 2003;197:753-8.
- 4 Poon RT, Fan ST, Ng IO, Lo CM, Liu CL, Wong J. Different risk factors and prognosis for early and late intrahepatic recurrence after resection of hepatocellular carcinoma. *Cancer*. 2000;89:500-7.
- 5 Imamura H, Matsuyama Y, Tanaka E, Ohkubo T, Hasegawa K, Miyagawa S, et al. Risk factors contributing to early and late phase intrahepatic recurrence of hepatocellular carcinoma after hepatectomy. *J Hepatol*. 2003;38:200-7.
- 6 Fattovich G, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. *Gastroenterology*. 2004;127:S35-50.
- 7 Cucchetti A, Piscaglia F, Caturelli E, Benvenuto L, Vivarelli M, Ercolani G, et al. Comparison of recurrence of hepatocellular carcinoma after resection in patients with cirrhosis to its occurrence in a surveilled cirrhotic population. *Ann Surg Oncol*. 2009;16:413-22.
- 8 Miyagawa S, Kawasaki S, Makuuchi M. Comparison of the characteristics of hepatocellular carcinoma between hepatitis B and C viral infection: tumor multicentricity in cirrhotic liver with hepatitis C. *Hepatology*. 1996;24:307-10.
- 9 Sasaki Y, Yamada T, Tanaka H, Ohigashi H, Eguchi H, Yano M, et al. Risk of recurrence in a long-term follow-up after surgery in 417 patients with hepatitis B- or hepatitis C-related hepatocellular carcinoma. *Ann Surg*. 2006;244:771-80.
- 10 Naito S, Imamura H, Tukada A, Matsuyama Y, Yoshimoto J, Sugo H, et al. Postoperative 1 the hepatitis viral infection status. *Liver Int*. 2014;34:802-13.
- 11 Refolo MG, Messa C, Guerra V, Carr BI, D'Alessandro R. Inflammatory mechanisms of HCC development. *Cancers*. 2020;12:641.
- 12 Levrero M, Zucman-Rossi J. Mechanisms of HBV-induced hepatocellular carcinoma. *J Hepatol*. 2016;64:S84-S101.
- 13 Kanda T, Goto T, Hirotsu Y, Moriyama M, Omata M. Molecular mechanisms driving progression of liver cirrhosis towards hepatocellular carcinoma in chronic hepatitis B and C infections: a review. *Int J Mol Sci*. 2019;20:1358.
- 14 Zhang DY, Friedman SL. Fibrosis-dependent mechanisms of hepatocarcinogenesis. *Hepatology*. 2012;56:769-75.