



Letter to the Editor

How long should physicians follow up with patients after curative treatment for hepatocellular carcinoma?

Bo Hyun Kim

Division of Gastroenterology, Department of Internal Medicine, Center for Liver and Pancreatobiliary Cancer, National Cancer Center, Goyang, Korea

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Dear Editor,

We have read the article entitled "Substantial risk of recurrence even after 5 recurrence-free years in early-stage hepatocellular carcinoma patients" by Kim et al.¹ with great interest. The article describes the evaluation of the recurrence risk after 5 disease-free years in patients with hepatocellular carcinoma (HCC) undergoing curative treatment, such as surgical resection or radiofrequency ablation.

HCC is well-known for its high recurrence rate even after curative surgical resection.² Overall, the 5-year recurrence rate of HCC after curative resection is reported to be 60–70%,³ compared with 1–2% for early gastric cancer and about 30% for non-metastatic colorectal cancer.^{4,5} Even for single nodular HCC sized less than 3 cm, the 5-year recurrence rate after surgical resection is 44%.⁶ Typically, recurrence within 2 years after resection is classified as early recurrence, recurrence after 2 years is classified as late recurrence, and late recurrence of more than 2 years after resection is considered to be *de novo* HCC.⁷ Tumor-related factors contribute to early recurrence. In contrast, underlying disease-re-

lated factors influence late recurrence.^{2,7,8} Most patients with HCC have underlying chronic liver disease, which contributes to the *de novo* development of liver cancer, even though the patients have favorable tumor-related factors.

In this issue of *Clinical and Molecular Hepatology*, Kim et al.¹ highlight a high recurrence rate for HCC even after 5 recurrence-free years. The cumulative recurrence rates at 5 and 10 years were 60.3% and 71.0%, respectively, for 1,451 patients with HCC receiving radiofrequency ablation or surgical resection.¹ The next 5-year cumulative recurrence rate was 27.0% among 487 patients who had not experienced recurrence for at least 5 years after the initial diagnosis. This result is strikingly high compared with non-metastatic colon cancer for which recurrence rates are <1.5% per year after 5 years.⁵ Due to this low recurrence rate, no further specified surveillance for non-metastatic colon cancer is recommended 5 years after the initial diagnosis.⁵

For HCC, periodic surveillance is recommended for patients with risk factors such as hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, or liver cirrhosis.² In South Korea, biannual surveillance with ultrasonography and serum alpha-fetoprotein

Abbreviations:

HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; NAFLD, nonalcoholic fatty liver disease

Corresponding author : Bo Hyun Kim

Division of Gastroenterology, Department of Internal Medicine, Center for Liver and Pancreatobiliary Cancer, National Cancer Center, 323 Ilsandong-gu, Goyang 10408, Korea
Tel: +82-31-920-1758, Fax: +82-31-920-2798
E-mail: bohkim@ncc.re.kr
<https://orcid.org/0000-0001-8355-3126>

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have been adopted as a national cancer screening program for patients aged 40 years or older with HBV, HCV, or cirrhosis. Even if patients have survived 5 years or more after curative surgical resection, patients with HBV, HCV, or cirrhosis should undergo bi-annual surveillance for HCC.

But what if patients do not have any established risk factors such as HBV, HCV, or cirrhosis? Recently, the number of HCC patients without established risk factors have been increasing, and the proportions of nonalcoholic fatty liver disease (NAFLD)-associated HCC have also been gradually growing.⁹⁻¹¹ NAFLD is a major risk factor for HCC in Western countries, and 10–20% of HCC cases are attributed to NAFLD in the USA.¹² Retrospective studies of the South Korean population have indicated that the proportions of NAFLD-associated HCC are 7–8%.^{9,10} About 60–70% patients with NAFLD-associated HCC do not have underlying cirrhosis.^{10,11} Kim et al.¹ also reported that only a minority of patients (6.9%) did not have HBV, HCV, or cirrhosis. Among 37 patients without HBV, HCV, or cirrhosis who did not develop recurrence for more than 5 years, six patients experienced recurrence 5.7 to 8.0 years after the initial diagnosis, with a 5-year cumulative recurrence rate of 20%. Although these patients previously have not been regarded as high-risk population for developing HCC, their recurrence rate was as high as those with established risk factors. Given that NAFLD-associated HCC patients have shown similar recurrence-free survival as other etiology-related HCC, it is conceivable that the recurrence rate is quite high.^{13,14}

If the recurrence rate is so high, how long and how often should we follow up on HCC patients without established risk factors? To date, there has been a lack of guidelines on the follow-up strategies for HCC cases from any etiology. The latest guideline by the American Association for the Study of Liver Disease recommends that patients should undergo surveillance after resection with imaging and alpha-fetoprotein at an interval of least every 3–6 months, without mentioning the follow-up period.¹⁵ The latest National Comprehensive Cancer Network guideline for surveillance after curative treatment recommends imaging and alpha-fetoprotein every 3–6 months for 2 years, then every 6–12 months thereafter.¹⁶ Given that the greatest risk of recurrence is observed during the first 2–3 years after curative treatment, intensive surveillance is required for the first 2–3 years.⁷ Surveillance should be continued even after the first 2–3 years, and probably indefinitely. The surveillance interval may depend on the tumor doubling time, as in patients with high risk of developing HCC. Consequently, a 6-month interval seems to be reasonable. Another question of “Which imaging modalities would be better” remains a debatable

issue. One consideration in this debate is that patients with NAFLD are more prone to obesity, which may hamper ultrasonography-based surveillance.

Since the results of the present study were based on a small number of patients in a retrospective study, we need to be very careful to avoid drawing a hasty conclusion. However, the results of this study still provide a glimpse as to whether physicians should follow up on HCC patients with or without established risk factors after 5 disease-free years. Further studies using detailed follow-up strategies are warranted.

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Conflicts of Interest

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