Antiviral Therapy Inhibits Viral Reactivation and Improves Survival after Repeat Hepatectomy for Hepatitis B Virus-Related Recurrent Hepatocellular Carcinoma

Shengyu Huang, MD, Yong Xia, MD, Zhengqing Lei, MD, Qifei Zou, MD, Jun Li, MD, Tian Yang, MD, Kui Wang, MD, Zhenlin Yan, MD, Xuying Wan, MD, Feng Shen, MD

BACKGROUND: The aim of this study was to explore the impact of antiviral therapy (AVT) on short- and long-term outcomes after rehepatectomy for patients with recurrent hepatitis B virus (HBV)-related hepatocellular carcinoma (HCC).

STUDY DESIGN: We analyzed data from 583 consecutive patients who underwent rehepatectomy for intrahepatic recurrence of HBV-related HCC after initial hepatectomy, between 2006 and 2011 at the Eastern Hepatobiliary Surgery Hospital. Tumor re-recurrence, recurrence to death survival (RTDS), and overall survival (OS) were compared using the Kaplan-Meier method and log-rank test. The independent risk factors of prognoses were analyzed using the Cox proportional hazards model. Postoperative viral reactivation, surgical morbidity, and mortality were also observed.

RESULTS: Preoperative AVT reduced viral reactivation rate after rehepatectomy (5.8% for AVT patients, 16.3% and 16.6% for non-AVT patients with viral level $\leq$ or $>$2,000 IU/mL, respectively; $p \leq 0.028$). Viral reactivation and non-AVT were independent risk factors of tumor re-recurrence (hazard ratios 1.446 and 1.778, respectively), RTDS (1.691 and 2.457, respectively), and OS (1.781 and 1.857, respectively). The AVT improved long-term outcomes as compared with non-AVT with a viral level of $\leq$ or $>$2,000 IU/mL (5-year re-recurrence rate: 69% vs 81% vs 96%, respectively; 5-year RTDS rate: 47% vs 27% vs 17%, respectively; all $p \leq 0.016$). Pre- plus postoperative AVT achieved a better 5-year OS rate than postoperative AVT alone (83% vs 60%; $p = 0.045$); there were insignificant differences in 5-year re-recurrence and RTDS rates (61% vs 77%, $p = 0.102$; 50% vs 44%, $p = 0.395$).

CONCLUSIONS: Preoperative AVT decreased viral reactivation rate, and AVT initiated either before or after rehepatectomy contributed to better long-term prognoses after rehepatectomy for recurrent HBV-related HCC. (J Am Coll Surg 2017;224:283−293. © 2016 Published by Elsevier Inc. on behalf of the American College of Surgeons.)

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Drs Huang, Xia, and Lei contributed equally to this work.

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From the Departments of Hepatic Surgery IV (Huang, Xia, Lei, Li, Yang, Yan, Shen), Hepatic Surgery II (Zou, Wang), and Clinical Database (Wan), the Eastern Hepatobiliary Surgery Hospital, Second Military Medical University, Shanghai, China.

Correspondence address: Feng Shen, MD, Department of Hepatic Surgery IV, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University, Shanghai, 200438, China. email: shenfengehbh@sina.com

Hepatocellular carcinoma (HCC) is the fifth most common malignancy and second leading cause of cancer-related death worldwide.[1] Hepatitis B virus (HBV) infection is an important causative factor of HCC, especially in the majority of Asian and African regions with higher incidence of this malignancy.[2] A high level of HBV DNA has been reported to be an important risk factor of HCC development.[2,3]

Although curative liver resection is one of the first-line treatments for patients with HCC, its effectiveness is still unsatisfactory due to a high incidence of tumor recurrence, which mainly occurs intrahepatically.[4-6] Multiple therapeutic options have been applied to patients with intrahepatic

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Abbreviations and Acronyms

ALT = alanine transaminase
AVT = antiviral therapy
HBV = hepatitis B virus
HCC = hepatocellular carcinoma
OS = overall survival
RTDS = recurrence to death survival
TACE = transarterial chemoembolization
ULN = upper limit of normal

recurrent HCC, including repeat hepatectomy (rehepatectomy), salvage liver transplantation, percutaneous radiofrequency ablation, and transarterial chemoembolization (TACE), all of which have been proven effective in selected patients.[7-11] Although salvage liver transplantation might achieve better outcomes, its application has been limited by a lack of liver donors.[12-14] Percutaneous radiofrequency ablation is suitable for patients with earlier intrahepatic recurrent HCC, and TACE is frequently used in patients with more advanced diseases, but the overall prognoses of these patients after treatments with these procedures have been reported to be worse than those of patients subjected to rehepatectomy.[15-18] Currently, rehepatectomy is still an effective and extensively applied option for intrahepatic recurrent HCC.[19-21] Reportedly, it could obtain a similar result as initial liver resection for primary HCC.[22] However, compared with initial HCC, recurrent HCC has more complicated mechanisms of carcinogenesis and development processes, and the recurrent patients usually have a decreased tolerance for further antirecurrence treatments.[23-25]

Previous studies showed that a high serum level of HBV DNA was associated with an increased recurrence rate and a shortened survival after liver resection for HBV-related HCC at the initial stage.[26-28] Early antiviral therapy (AVT) could increase survival outcomes of these patients through decreasing viral level and viral reactivation rate.[29-32] However, all previous studies were focused on the initial HCC,[26-28,33] and the effects of AVT on the prognosis of patients with recurrent HCC have not been reported. In this study, we analyzed the prognostic impacts of viral level and AVT on short- and long-term surgical outcomes of patients who underwent rehepatectomy for recurrent HBV-related HCC.

METHODS

Patients and study design

The study protocol was approved by the Institutional Review Board of the Eastern Hepatobiliary Surgery Hospital. The informed consent was obtained from all patients before surgery for use of their data in the research.

Data of 731 patients, who consecutively underwent rehepatectomy for intrahepatic recurrent HCC at the Eastern Hepatobiliary Surgery Hospital between October 2006 and October 2011, were prospectively collected and retrospectively reviewed. All of these patients underwent initial partial hepatectomy for histopathologically proven HCC. Patients who met the following inclusion criteria were identified: seropositive for hepatitis B surface antigen and/or hepatitis B core antibody, but negative for hepatitis C virus antibody; no history of other malignancies; no history of anticancer treatment including TACE, percutaneous ablation, percutaneous ethanol injection, chemo- and radiotherapy, or sorafineb before rehepatectomy; and histopathologically confirmed HCC after rehepatectomy. Based on these, 583 patients were included in this study (Fig. 1).

Routine serologic examination before rehepatectomy included hepatitis B surface antigen, hepatitis B core antibody, hepatitis B e antigen, hepatitis C virus antibody, alpha fetoprotein, albumin, total bilirubin, alanine transaminase (ALT), aspartate aminotransferase, and prothrombin time. Reverse transcription-polymerase chain reaction was used to quantitatively examine serum HBV DNA level (ABI 7300, Applied Biosystems). An abdominal ultrasound, contrast-enhanced CT scan, and/or MRI of the abdomen, and chest radiography or noncontrast CT scan were routinely carried out. Hepatic arteriography or positron emission tomography was used for patients with uncertainty of diagnosis of recurrence or with suspected distant metastasis. The clinical diagnosis of HCC was based on the criteria of the American Association for the Study of Liver Diseases (AASLD).[34]

Patients with good general performance, Child-Pugh grade A of liver function, technically resectable, intrahepatic recurrent HCC, sufficient estimated volume of future liver remnant after a second liver resection, and without any evidences of distant metastasis or major vascular invasion on imaging, were recommended for rehepatectomy. Rehepatectomy was performed generally through the original operation incision, which was extended if necessary. The adherent tissue left from the previous operation was carefully separated for good liver dissociation, with a full attention to protect the porta hepatis and the gastrointestinal tracts. The operation was carried out with an intention to completely remove macroscopic tumor nodule(s), and the type of rehepatectomy was determined by surgeons based on the location of recurrent tumors, degree of cirrhosis, width of resection margin, and the estimated volume of future liver remnant. After rehepatectomy, all patients received similar postoperative care by the same team of