ORIGINAL ARTICLE

Clinical Significance of Hepatic Resection in Hepatocellular Carcinoma

Analysis by Disease-Free Survival Curves

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Hypothesis: The clinical significance of hepatectomy for hepatocellular carcinoma (HCC) is still controversial because of frequent intrahepatic recurrence, which results from either recurrence due to residual intrahepatic metastasis (Rim) or recurrence due to metachronous, multicentric liver carcinogenesis (Rmc).

Design: Retrospective review. Disease-free survival curves were obtained by the Kaplan-Meier method and the rates of Rim and Rmc were analyzed using 2 regression lines, based on the evidence that Rmc occurs at a constant rate throughout follow-up, whereas Rim occurs only in the early postoperative period.

Setting: University hospital.

Patients: From 1980 to 1996, 241 patients with HCC who underwent curative hepatic resection.

Main Outcome Measure: Intrahepatic recurrence.

Results: Disease-free survival curves for all patients in the early (within 2 years) and late (4 years after surgery) follow-up were approximated by 2 regression lines, which represent both Rim and Rmc ($Y_1 = -3.4X + 48$) and only Rmc ($Y_2 = -23.1X + 98$). Using this approximation, the annual incidence of Rim within 2 years ($a_1 - a_2$) was calculated as 19.7% and that of Rmc (a_2) was 3.4%. The ratio of Rim in tumor recurrence ($b_1 - b_2$) was 50%, and that of Rmc (b_1) was 48%. The ratios of Rmc in patients with stages I and II HCC were 60% and 64%, respectively. In contrast, the values could not be calculated in patients with stages III and IVA because all but 2 patients showed recurrence within 4 years after surgery.

Conclusion: Tumor recurrence is estimated to result from metachronous liver carcinogenesis in 48% of hepatectomized patients with HCC.

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POSTOPERATIVE tumor recurrence in hepatocellular carcinoma (HCC) results from 2 different processes—the growth of undetectable, intrahepatic metastasis and metachronous, multicentric carcinogenesis. Several studies have examined the possible histologic[1,2] and genetic[3-7] differential diagnoses of these lesions, but this is still impossible at present. Recent studies of the incidence of HCC in patients with viral hepatitis suggest that the involvement of multicentric carcinogenesis in tumor recurrence may be more frequent than previously thought, particularly in those associated with liver cirrhosis.[8-12] In addition, the postoperative recurrence is frequent and the 5-year survival rate ranges from 31% to 53%.[13-17] Because of these patterns, the clinical significance of hepatic resection for HCC is still controversial,[18,19] although it has been the mainstay of treatment.[20,21] Theoretically, recurrence due to residual intrahepatic metastasis (Rim) is likely to appear soon after surgery and its risk decreases with prolongation of the postoperative period. In contrast, recurrence due to multicentric liver carcinogenesis (Rmc) is considered to occur at a constant rate throughout the observation period, which varies with the severity of liver disease and type of hepatitis viruses.[8-12]

Based on these different patterns of tumor recurrence, we estimated in the present study the incidence of both events in patients with resectable HCC, by analyzing the postoperative disease-free survival.

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RESULTS

Disease-free survival curves for all patients appeared to consist of 2 phases (**Figure 1**). The late phase (>4 years after surgery) was almost linear and could be approximated by the regression line Y_2 (%) = $-a_2X$ (year) + b_2, where $a_2 = 3.4$ and $b_2 = 48$. This regression line is considered to reflect Rmc because of its con-

PATIENTS AND METHODS

We studied 241 patients who underwent curative hepatic resection for HCC between 1980 and 1996. Forty-nine patients had stage I, 117 had stage II, 52 had stage III, and 23 had stage IVA disease according to the Union Internationale Contre le Cancer (UICC) classification.[22] Histopathologic examination revealed that there were 157 cirrhotic and 84 noncirrhotic patients. Moderate to severe hepatitis was noted in 55 patients and mild or no hepatitis was seen in 186 patients. With respect to hepatitis viral infection, 56 patients were positive for hepatitis B surface antigen and 185 were negative. Eighty-one patients were positive for hepatitis C virus (HCV) antibody and 41 were negative. As the assay kit was unavailable before 1991, the HCV antibody status could not be determined in the remaining 119 patients. Patients were followed up for tumor recurrence in the liver at our outpatient clinic or associated hospitals at least every 3 months by identification of tumor markers (α-fetoprotein or des-γ carboxy prothrombin) or by imaging modalities such as ultrasonography, abdominal computed tomography, and magnetic resonance imaging. The onset of tumor recurrence was designated as the time when the tumor was detected by one of these imaging techniques. Tumor recurrence was confirmed by surgical resection or hepatic angiography. Disease-free survival rate was calculated by the Kaplan-Meier method[23] and the regression lines for tumor recurrence were illustrated with the SAS statistical program (SAS Institute, Cary, NC).

stant recurrence rate in the late observation period (from 4 to 10 years). Since Rmc is considered to occur at any time during the observation period, this regression line was extended to the ordinate and b_2, which represents the intercept of the regression line of Rmc. On the other hand, the disease-free survival curve in the early phase (within 4 years after surgery) reflects both Rim and Rmc. Therefore, the area between the disease-free survival curve and Y_2 is considered to correspond to Rim, which decreased in a time-related manner and became almost negligible at 4 years. In particular, the initial observation period (within 2 years after surgery) was almost linear, and could be approximated by another regression line ($Y_1 = -a_1X + b_1$, where a_1 = 23.1, and b_1 = 98). Based on these data, the annual rate of Rim ($a_1 - a_2$, within 2 years) was estimated to be 19.7% and that of Rmc (a_2) was 3.4%. The ratios of Rim ($b_1 - b_2$) and Rmc (b_2) were 50% and 48%, respectively.

When patients were stratified into 4 groups according to UICC staging criteria, regression lines similar to those of Y_1 and Y_2 were obtained in patients with stages I and II HCC (**Figure 2**). The annual rates of Rim in stages I and II were 19.0% and 15.7%, and those of Rmc were 3.4% and 5.3%, respectively. The ratios of Rmc in these stages were 60% and 64%. For patients in stages III and IVA, the regression line of Y_2 (Rmc) was not obtained because only 2 patients survived without recurrence for more than 4 years after surgery, and thereby the values of Rmc (a_2, b_2) could not be obtained. The annual recurrence rates of the initial phase (Y_1: Rim + Rmc) in stages III and IVA were 38% and 24%, respectively (Figure 2). Since the annual rate of Rmc in patients with stage I or II HCC was not less than that of all patients, that of stages III and IVA was considered less than 3.4%. Furthermore, since almost all patients with stages III and IVA HCC showed recurrence within 4 years, the ratio of Rmc in these patients was estimated to be at most 13.6% (3.4% per year × 4 years), and that of Rim was at least 86.4%.

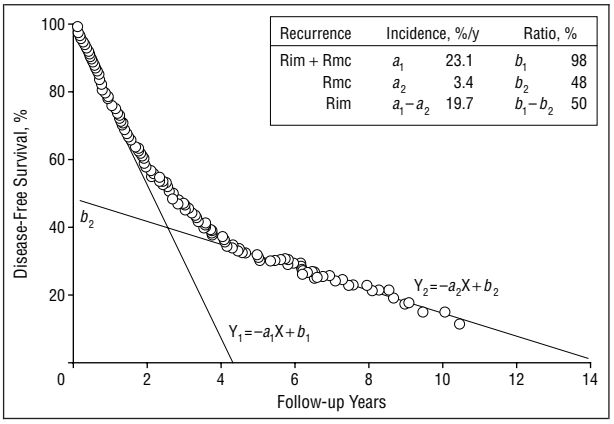

Figure 1. *Determination of incidence of recurrence due to residual intrahepatic metastasis (Rim) and recurrence due to multicentric liver carcinogenesis (Rmc) by analyzing disease-free survival in all patients who underwent curative hepatic resection (n=241). Disease-free survival curve in the early (within 2 years after surgery) and late (>4 years) phases was almost linear and could be approximated by the regression lines (Y_1 and Y_2). Y_1 represents Rim and Rmc; Y_2 reflects Rmc only.*

The activity of hepatitis appeared to influence the risk of Rmc, as shown in **Figure 3**. The annual incidence of Rmc in patients with moderate to severe hepatitis (a_2 = 5.2%) was about 2-fold greater than that in patients with no or mild hepatitis (a_2 = 2.7%). The ratio of Rmc in patients with active hepatitis was 54%, and 11 percentage points higher than that in those with no or mild hepatitis (Figure 3). In contrast, the presence of liver cirrhosis did not appear to affect the annual incidence of Rmc (3.7%), although the ratio of Rim in patients with liver cirrhosis (55%) was 10 percentage points higher than that in patients without cirrhosis (45%), as shown in **Figure 4**.

COMMENT

Differential diagnosis between intrahepatic metastasis and multicentric carcinogenesis has been one of the major concerns in the treatment of HCC.[1-8] It is particularly important from the surgical point of view because Rmc suggests that tumor(s) was completely resected and therefore surgery was successful. In contrast, Rim implies unsuccessful surgery because undetectable metastatic tumors remained unresected. In addition to the histologic criteria,[1,2] several genetic approaches such as hepatitis B virus (HBV) DNA integration pattern,[5,24-26] loss of heterozygosity of chromosome 16,[3] the p53 mutation pattern,[4,6,7,27] and DNA fingerprint analysis[28] have been used for this purpose. These methods are considered to be more precise and sensitive than the conventional histologic method. However, a definite differential diagnosis is still

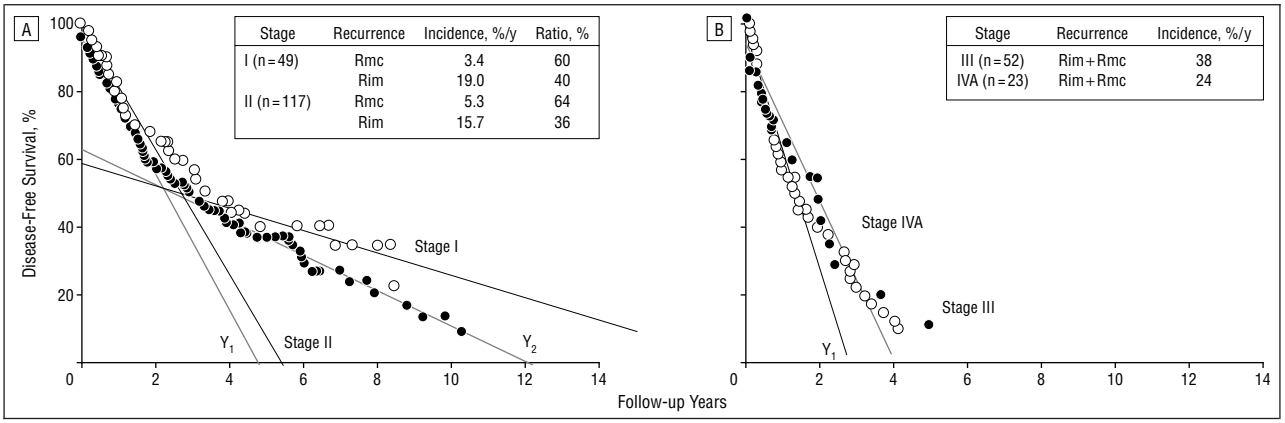

Figure 2. *Incidence of recurrence due to residual intrahepatic metastasis (Rim) and recurrence due to multicentric liver carcinogenesis (Rmc) in patients with stages I and II (A) and stages III and IVA (B) hepatocellular carcinoma. Y_1 represents Rim and Rmc; Y_2 reflects Rmc only.*

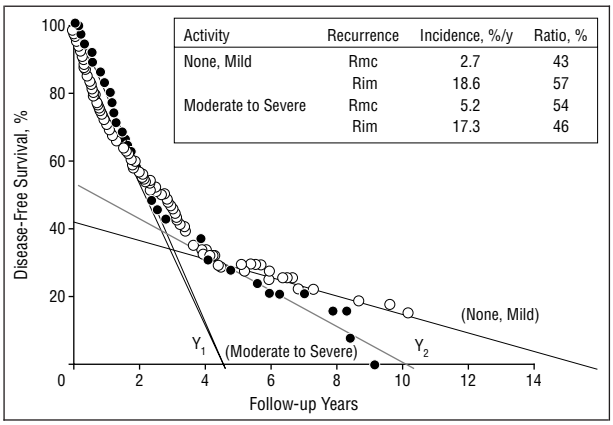

Figure 3. *Incidence of recurrence due to residual intrahepatic metastasis (Rim) and recurrence due to multicentric liver carcinogenesis (Rmc) in patients with active (moderate to severe; n=55) or inactive (none or mild; n=186) hepatitis. Y_1 represents Rim and Rmc; Y_2 reflects Rmc only.*

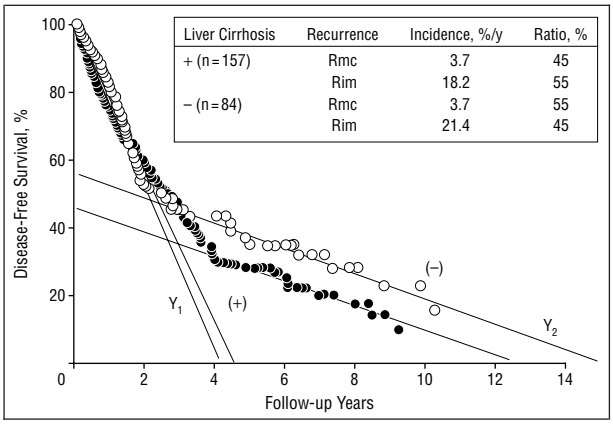

Figure 4. *Incidence of recurrence due to residual intrahepatic metastasis (Rim) and recurrence due to multicentric liver carcinogenesis (Rmc) in patients with (+) or without (–) liver cirrhosis. Y_1 represents Rim and Rmc; Y_2 reflects Rmc only.*

impossible because of clonal divergence during the progression of tumors.[29,30] In this study, we took a different approach, ie, analysis of disease-free survival curves by approximation of 2 regression lines (Y_1, Rim and Rmc; Y_2, Rmc), and determined the incidence of these events in patients who had hepatectomy. The analysis is based on the evidence that Rim is an early postoperative event, the risk of which decreases exponentially with prolongation of the postoperative period, whereas Rmc, the development of HCC from chronic hepatitis or liver cirrhosis, occurs at a constant rate even in the late observation period. This constant decrease of disease-free survival in the second phase (Y_2, Rmc) is not usually observed in hepatectomized patients with liver metastasis.[31-34]

Postoperative tumor recurrence was theoretically estimated to result from multicentric liver carcinogenesis in 48% of all the hepatectomized patients with HCC (Figure 1). This indicates that complete resection of the tumor, ie, "true" curative surgery, was performed in about half of the patients. On the other hand, Rim was considered to occur within 4 years in the remaining half of patients. In patients with stages I and II HCC, Rmc was more frequent than Rim in contrast to the general idea of postoperative tumor recurrence in HCC. However, the annual rate of Rim in the first 2 postoperative years (19.0% and 15.7%) was marked and was about 3 to 6 times higher than that of Rmc (3.4% and 5.3%). Therefore, not only prevention of liver carcinogenesis but also adjuvant therapy such as arterial infusion chemotherapy[35] may be indicated during this period. In contrast, for patients surviving without tumor recurrence for more than 4 years, care should be taken only for the underlying viral hepatitis to prevent multicentric liver carcinogenesis. On the other hand, in patients with stages III and IVA HCC, almost all tumor recurrences developed within 4 years irrespective of recurrence type. Therefore, postoperative adjuvant therapy and close follow-up are mandatory in these patients.

The present study also provides information about the risk of liver carcinogenesis in surgical patients with HCC. As described above, the annual incidence of Rmc was 3.4% in all patients. It was about 2-fold more frequent in patients with moderate to severe hepatitis (5.2%) than in those with no or mild hepatitis (2.7%) (Figure 3). Various follow-up studies on patients with chronic hepatitis or liver cirrhosis also showed similar annual incidence rates of HCC (1.4%-7.0%),[8-12,36] depending on the severity of hepatitis and the presence of liver cirrhosis. In contrast to these studies, the presence of liver cirrhosis did not influence the occurrence of Rmc in this study (Figure 4). This is partly because liver cirrhosis is gener-

ally mild (mostly Child class A) in these hepatectomized patients. Recent studies by Kasahara et al[36] also demonstrated that portal inflammation or response to interferon treatment, but not liver cirrhosis, correlated significantly to HCC development. Therefore, if associated hepatitis is considered to be active, interferon therapy may be indicated even in hepatectomized patients to prevent the postoperative liver carcinogenesis. Based on these findings, the following approaches perhaps should be followed for the prevention of postoperative recurrence of HCC, taking tumor staging and the underlining liver disease into account: (1) complete resection of tumor(s) (in all surgical patients), (2) postoperative treatment of viral hepatitis to prevent metachronous liver carcinogenesis (particularly in patients with stage I or II HCC with active hepatitis), and (3) the use of anticancer therapy for undetectable residual tumors (in patients with stage III or IVA HCC).

The effectiveness of treatment modalities (eg, surgical methods) or prognostic factors for HCC has usually been evaluated by the postoperative disease-free survival. However, this study demonstrated that the involvement of liver carcinogenesis in tumor recurrence was frequent. It was particularly evident in patients with stage I and II HCC because the incidence of Rmc was more than that of Rim (60% and 64%). These findings imply that all evidence of the curability of surgical methods obtained by the disease-free survival might be incorrect and thereby needs to be strictly reevaluated in the future.

Development of HCC is generally more frequent in patients with HCV infection than in those with HBV infection. Ikeda et al[8] demonstrated that the incidence of HCC did not increase after the late follow-up period (more than 8.5 years after surgery) in patients with HBV infection, while it continuously increased in those with HCV infection. Therefore, the present results may reflect the predominance of HCV infection in our patient population. In addition, the ratios of Rim and Rmc may differ between patients with HBV infection and those with HCV infection. However, we could not investigate these issues due to the insufficient number of patients since the determination of HCV antibody started in late 1991 in our hospital. This is an interesting subject and is now under investigation.

In conclusion, postoperative recurrence of HCC resulted from metachronous, multicentric liver carcinogenesis in about half of hepatectomized patients. To prevent tumor recurrence, treatment of the underlying hepatitis and adjuvant therapy should be considered in individual cases, taking into account tumor staging and activity of hepatitis.

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