Annals of Surgical Oncology, **7**(10):764–770
Published by Lippincott Williams & Wilkins

Comparison of Surgical Outcomes for Hepatocellular Carcinoma in Patients With Hepatitis B Versus Hepatitis C: A Western Experience

Sasan Roayaie, MD, Menahem Ben Haim, MD, Sukru Emre, MD, Thomas M. Fishbein, MD, Patricia A. Sheiner, MD, Charles M. Miller, MD, and Myron E. Schwartz, MD

Background: We reviewed our experience in patients with hepatocellular carcinoma (HCC) and chronic hepatitis to determine if differences exist in preoperative status and postoperative survival between those with hepatitis B virus (HBV) and hepatitis C virus (HCV) infections.

Methods: We reviewed the records of 240 consecutive patients with HCC who underwent hepatic resection or liver transplantation at Mount Sinai Hospital between February 1990 and February 1998. Patients who tested negative for hepatitis B antigen and hepatitis C antibody (74 patients) as well as those who tested positive for both (2 patients) were excluded. Age as well as preoperative platelet count, prothrombin time (PT), albumin, and total bilirubin were measured in all patients. The presence of encephalopathy or ascites also was noted. Explanted livers and resection specimens were examined for size, number, and differentiation of tumors as well as the presence of vascular invasion and cirrhosis in the surrounding parenchyma.

Results: One hundred twenty-one patients with HCC tested positive for HCV, and 43 tested positive for HBV. A significantly higher proportion of patients with HCV required transplant for the treatment of their HCC when compared to those with HBV. In the resection group, patients with HCV were significantly older that those with HBV. They also had significantly lower mean preoperative platelet counts and albumin levels and higher mean PT and total bilirubin levels. Resected patients with HCV had significantly less-differentiated tumors and a higher incidence of vascular invasion and cirrhosis when compared to those with HBV. There was no statistical difference in the multicentricity and size of tumors between the two groups. The 5-year disease-free survival was significantly higher for HBV patients treated with resection when compared to those with HCV (49% vs. 7%, $P = .0480$). Patients with HCC and HCV had significantly longer 5-year disease-free survival with transplant when compared to resection (48% vs. 7%, $P = .0001$).Transplanted patients with HBV and HCC had preoperative status, pathological findings, and survival similar to those of patients with HCV.

Conclusions: Based on preoperative liver function and tumor location, a much higher proportion of HCC patients with HBV were candidates for resection. Significant differences in preoperative status, tumor characteristics and disease-free survival exist between HCC patients with chronic HBV and HCV infection who have not yet reached end-stage liver disease. Serious consideration should be given to transplanting resectable HCC with concomitant HCV, especially in cases with small tumors.

Key Words: Hepatitis B—Hepatitis C—Hepatocellular carcinoma—Liver transplantation.

Abundant epidemiological and molecular studies have linked chronic infection with the hepatitis B virus (HBV) to the development of hepatocellular carcinoma (HCC).[1–6] Since the hepatitis C virus (HCV) was first characterized in 1989, it also has been implicated in the pathogenesis of HCC.[7–17] There is considerable evidence to suggest that the integration of HBV DNA into the host

Received June 21, 1999; accepted August 8, 2000.

From The Recanati-Miller Transplantation Institute, Mount Sinai Medical Center, New York, New York.

Presented at the 52nd Annual Meeting of the Society of Surgical Oncology, Orlando, Florida, March 4-7, 1999.

Address correspondence and reprint requests to: Dr. Myron E. Schwartz, 19 East 98th Street, Suite 6F, New York, NY 10029; Fax: 212-289-0875; E-mail: myron_schwartz@smtplink.mssm.edu

genome leads to the development of HCC.[18–23] In contrast, HCV is an RNA virus that is not integrated ,and its role in hepatocarcinogenesis is not completely clear.

Several recent Japanese studies have examined the differences among HCC patients infected with HBV versus those with HCV infection.[24–28] Most of these series have shown that whereas HCC arising in patients with HCV occurs in older patients with more severe liver disease than those with HBV, there is no difference between the two groups in long-term disease-free or overall survival.[24–27] The Japanese, however, have been limited to resection as their only means for the treatment of HCC; as a result, their patients and operative results are not necessarily comparable with those of Western countries where liver transplantation is an option. In addition to the Japanese reports, studies from Toronto and London have shown poor outcome after liver transplantation for the treatment of HCC patients with HBV.[29,30] We reviewed our own experience in patients with HCC and chronic hepatitis to determine if differences exist in preoperative status, pathological findings, and postoperative outcome between those with HBV and HCV infections treated in a setting where both resection and liver transplantation are considered.

MATERIALS AND METHODS

We reviewed the records of 240 consecutive patients with HCC who underwent hepatic resection or liver transplantation at Mount Sinai Hospital between February 1990 and February 1998. All patients were tested for the presence of hepatitis B surface antigen and hepatitis C antibody. Patients who tested negative for HBV and HCV (n = 74) as well as those who tested positive for both (n = 2) were excluded from the study. One patient who was resected and subsequently transplanted was excluded. Age as well as preoperative platelet count, prothrombin time (PT), albumin, total bilirubin, alanine aminotransferase (ALT), and alpha-fetoprotein (AFP) were measured in all patients. The presence of encephalopathy or ascites was noted in transplanted patients. Given the scarcity of donor organs, resection was the preferred treatment modality for all patients. Hepatic resection was performed in noncirrhotic patients as well as those with Child's A cirrhosis when the location of their tumors did not necessitate resection of a significant amount of functioning parenchyma. Patients with either encephalopathy or ascites were not considered for resection. Patients with platelet counts below 100,000 also were excluded from resection, because we use thrombocytopenia as an indicator for the presence of portal hypertension.

Patients with HBV transplanted after 1993 received hepatitis B immune globulin (Abbot, Chicago, IL) intraoperatively and postoperatively to maintain antibody titers above 500 SRU/ml. Posttransplant immunosuppression consisted of cyclosporine or tacrolimus in combination with steroids and azathioprine. Patients with tumors larger than 5 cm who presented after 1992 were entered into a multimodality protocol. These patients underwent subselective arterial chemoembolization before transplant. They then received a single systemic dose of adriamycin intraoperatively and six cycles beginning 4 weeks after liver transplantation. Patients in this protocol did not receive azathioprine while on adriamycin. None of the patients undergoing resection received adjuvant therapy. Informed consent was obtained from each patient, and all procedures were in accord with the ethical standards of the Committee on Human Experimentation at Mount Sinai Hospital.

Resection specimens and explanted livers were examined for the number, size, and differentiation of tumors. The presence of microscopic and gross vascular invasion by tumor and cirrhosis in the surrounding parenchyma were noted.

All patients were followed postoperatively at Mount Sinai Hospital. Resection and transplant patients were monitored for recurrence by CT scans of the chest and abdomen. Patients with tumors larger than 5 cm were scanned every 3 months for the first year and every 6 months thereafter, whereas those with tumors smaller than 5 cm were scanned annually. Alpha-fetoprotein was measured every 6 weeks for the first year and every 3 months thereafter.

Statistical analysis was carried out using Student's *t*-test and the χ^2 test. Actuarial survival was calculated using the Kaplan-Meier method. Differences in survival were examined using the log-rank test. Cox proportional hazards regression analysis was used for multivariate analysis of variables found to be significant with univariate analysis. A P value of less than < 0.05 was considered significant.

RESULTS

Of the 240 patients with HCC, 121 tested positive for HCV and 43 for HBV. A much higher proportion of those with HCV were treated with liver transplantation (odds ratio [OR] = 3.858, $P = .0005$) (Table 1). Among those treated with resection, patients with HCV were significantly older than those with HBV (Table 1). They also had significantly lower mean platelet counts and albumin levels and significantly higher mean PT, total bilirubin, and ALT (Table 1). Mean AFP levels did not

TABLE 1. *Preoperative demographics and laboratory values*

	HBV Rsxn	HCV Rsxn	*P*	HBV Tx	HCV Tx	*P*
n	21	24		22	97	
Age (y)[a]	54.3 ± 15.3	63.4 ± 8.5	.01	54.8 ± 10.7	56.4 ± 8.1	NS
Sex			NS			NS
Male	10	17		14	74	
Female	11	7		8	23	
Platelets (×1000)[a]	218 ± 121	147 ± 86	.04	88 ± 57	81 ± 54	NS
PT (sec)[a]	12.4 ± 0.79	13.2 ± 1.2	.01	16.1 ± 3.0	15.0 ± 2.3	.05
Albumin (g/dl)[a]	4.2 ± 0.36	3.4 ± 0.6	.0001	2.7 ± 0.7	2.8 ± 0.4	NS
Total bilirubin (mg/dl)[a]	0.94 ± 0.40	2.2 ± 2.1	.02	6.1 ± 11.5	4.0 ± 5.6	NS
ALT (U/L)[a]	50.6 ± 28.4	85.7 ± 54.8	.02	64.5 ± 48.9	84.3 ± 98.2	NS
AFP (ng/ml)[a]	14015 ± 49341	6739 ± 22158	NS	4928 ± 14076	1963 ± 10442	
Ascites						NS
Present				11	59	
Absent				11	38	
Encephalopathy						NS
Present				8	37	
Absent				14	60	

AFP, alpha fetoprotein; ALT, alanine aminotransferase; PT, prothrombin time; HBV Tx, hepatis B virus positive patients treated with transplant; HBV Rsxn, hepatitis B virus positive patients treated with resection; HCV Rsxn, hepatitis C positive patients treated with resection; HCV Tx, hepatitis C virus positive patients treated with transplant; NS, not significant.

[a] Data expressed as mean ± SD.

differ significantly between the two groups (Table 1). There was no significant difference between HBV and HCV patients in the magnitude of resections performed (Table 2).

Pathological examination of resected specimens showed a trend toward larger tumors in those with HBV, whereas those with HCV had a higher number and more advanced stage of tumors (Tables 3 and 4), although these differences did not reach significance. Resected patients with HCV were much more likely to have cirrhosis in the surrounding parenchyma (OR 12.5, $P = .0006$). They also were more likely to have less differentiated tumors ($P = .005$) and had a higher incidence of vascular invasion (OR 6.0, $P = .007$) than those with HBV.

Mean follow-up of resected patients was 22.6 ± 18.6 months (median, 20.3 months; range, 0.2–77.1 months), and perioperative mortality was 11.1%. Actuarial disease-free survival was significantly better for HCC patients with HBV after resection when compared to those with HCV ($P = .0480$)(Fig. 1). Overall survival was similar in both groups ($P = .535$)(Fig. 2). Two patients (8.3%) with HCV and one patient (4.8%) with HBV undergoing resection died of early postoperative liver failure. Multivariate analysis revealed preoperative albumin levels ($P = .0178$) and platelet counts ($P = .0307$) as independent predictors of overall survival after resection. Multicentricity ($P = .0214$) was the only independent predictor of disease-free survival among resection patients by multivariate analysis.

TABLE 2. *Type of resections performed for treatment of hepatocellular carcinoma*

	HBV Rsxn	HCV Rsxn	*P*
Resection type			NS
Nonanatomic	6	14	
Segmentectomy	4	2	
Lobectomy	8	7	
Trisegmentectomy	3	1	
Units PRBCs[a]	2.3 ± 4.4	1.8 ± 2.5	NS
Weight of specimen (g)[a]	743 ± 604	372 ± 438	.07

HBV Rsxn, hepatitis B virus positive patients treated with resection; HCV Rsxn, hepatitis C positive patients treated with resection; PRBCs, packed red blood cells transfused; NS, not significant.

[a] Data given as mean ± SD.

Average age and preoperative laboratory values were similar in those with HBV and HCV treated with liver transplantation, with the only significant difference being a higher mean PT in those with HBV (Table 1). There also was no difference in the incidence of preoperative ascites or encephalopathy between the two groups (Table 1). Pathological examination of explanted livers showed similar size, number, differentiation of tumor, and incidence of vascular invasion in those with HCV and HBV (Table 3). Tumor stage also was similar in both groups (Table 4). All but 4 transplanted patients had cirrhosis, all of whom had HBV. Nineteen of the 97 HCV patients (19%) and 7 of the 22 HBV patients (32%) transplanted were entered into the multimodality protocol ($P = .276$).

Mean follow-up of transplanted patients was 31.8 ± 18.6 months (median, 28.1 months; range, 0.1–86.3 months) and perioperative mortality was 6.7%. Overall and disease-free survivals were better for those with HBV treated with transplant than for those with HCV but

TABLE 3. *Pathological findings of resected and explanted livers*

	HBV Rsxn	HCV Rsxn	*P*	HBV Tx	HCV Tx	*P*
Multicentric			NS			NS
Yes	14	18		12	63	
No	7	6		10	34	
Size (cm)[a]	7.9 ± 4.2	5.9 ± 3.7	NS	3.7 ± 3.1	3.3 ± 2.0	NS
Differentiation[b]			.005			NS
Well	11	2		11	46	
Moderate	7	15		6	27	
Poor	3	7		3	9	
Vascular invasion			.01			NS
Present	7	18		10	48	
Absent	14	6		12	49	
Cirrhosis			.0006			
Present	6	20				
Absent	15	4				

HBV Rsxn, hepatitis B virus positive patients treated with resection; HCV Rsxn, hepatitis C positive patients treated with resection; HBV Tx, hepatitis B virus positive patients treated with transplant; HCV Tx, hepatitis C virus positive patients treated with transplant.

[a] Data expressed as mean ± SD.

[b] Differentiation was not available on all transplanted specimens.

not significantly so ($P = .636$ and .445, respectively) (Figs. 1 and 2). Multivariate analysis showed that preoperative PT ($P = .0492$) and total bilirubin levels ($P = .0007$) correlated with overall survival in transplant patients. Tumor size greater than 5 cm ($P = .01$) and vascular invasion ($P = 0.0310$) were the only variables found to correlate significantly with disease- free survival by multivariate analysis. Patients with HCC and chronic HCV had significantly longer disease-free survival when treated with liver transplant than with resection ($P = .0001$). This did not hold true when resection and transplant were compared for HCC patients with HBV ($P = .3255$).

DISCUSSION

Studies have shown that integration of HBV DNA into the host genome results in enhanced expression of C-myc and N-myc oncogenes as well as inactivation of the p53 gene by HBV X protein, leading to development of HCC.[31–33] In contrast, HCV is a positive-strand RNA virus that is not integrated. Therefore, insertional mutation is unlikely to be the mechanism responsible for HCV-related HCC. Instead, it has been proposed that HCV leads to carcinogenesis by first causing cirrhosis.[34] Whether these distinct viral mechanisms will result in clinically relevant differences in the preoperative status of patients, tumor size and number, and surgical outcome is the focus of this study.

Given the respective viral mechanisms, it is not surprising to find that a significantly higher number of resected patients with HCV had cirrhosis in the surrounding parenchyma when compared to those with HBV. Also, a substantially higher proportion of HCV patients required liver transplantation for treatment of their HCC. Japanese studies examining the same topic have failed to show any significant difference in the incidence of cirrhosis between resected HCC patients infected with HCV and HBV.[24–26] However, Shiratori et al.[24] did demonstrate significantly more severe grades of cirrhosis in their HCC patients infected with HCV. The disparity between our results and those of the Japanese

TABLE 4. *Tumor stage according to American Joint Committee on Cancer (n =)*

	HBV Rsxn	HCV Rsxn	*P*	HBV Tx	HCV Tx	*P*
Tumor stage			.061			NS
I	0	0		6	14	
II	11	5		3	33	
III	7	10		7	21	
IVA	3	9		6	29	

HBV Rsxn, hepatitis B virus positive patients treated with resection; HCV Rsxn, hepatitis C positive patients treated with resection; HBV Tx, hepatitis B virus positive patients treated with transplant; HCV Tx, hepatitis C virus positive patients treated with transplant.

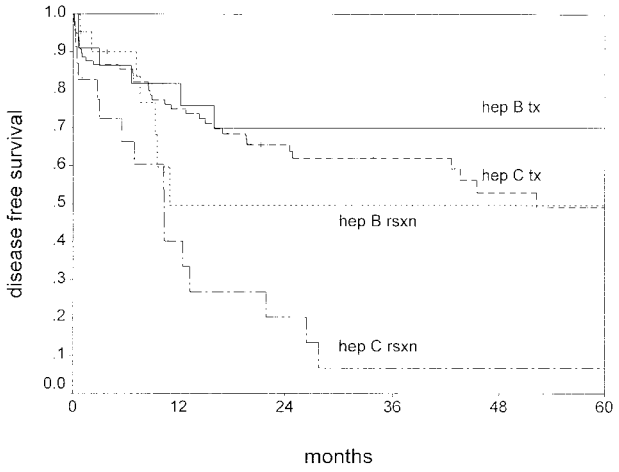

FIG. 1. Disease-free actuarial survival for HCC patients undergoing resection and liver transplant according to serologies. hep B, hepatitis B; hep C, hepatitis C; rsxn, resection; tx, transplant.

likely stems from the fact that, until very recently, the Japanese have been prohibited from performing cadaveric transplants. As a result, their resection population is skewed by inclusion of patients with advanced liver disease who would have been treated with liver transplantation in other countries.

Among the resection patients, those with HCV had significantly lower albumin levels and higher total bilirubin levels and PT. These figures are not surprising, given that they are all measures of hepatic function and that resection patients with HCV had a significantly higher incidence of cirrhosis. Platelet counts, a reflection of the degree of portal hypertension, also were lower in those with HCV. These findings are consistent with the decreased indocyanine green retention and lower preoperative cholesterol and albumin levels in HCC patients with HCV reported by Takenaka et al.[25] and Yamanaka et al.[28] Significantly higher mean preoperative ALT levels in resection patients with HCV also have been demonstrated by Japanese series and are consistent with the higher incidence of active hepatitis reported in these patients.[25,28] These differences in preoperative laboratory values did not exist among those treated with liver transplantation. All patients in this group had reached end-stage liver disease and, as a result, they were more homogeneous in their preoperative status.

There was a trend toward larger tumors in those with HBV in resected as well as transplanted patients. Takenaka et al.[25] and Yamanaka et al.[28] have also reported similar findings in their patients. Contrary to Japanese reports, however, we found no significant increase in the incidence of multicentricity between HBV and HCV infected patients in either the transplanted or resected groups. We also observed that resected HCC patients with HCV had less-differentiated tumors and a higher incidence of vascular invasion. Again, Takenaka et al.[25] did not demonstrate similar results in their patient population, whereas Tanizaki et al.[27] found significantly less-differentiated tumors among those with HBV.

Given their less favorable preoperative status and more advanced tumors, it is not surprising that resected HCV patients had substantially shorter disease-free survival when compared to those with HBV. The majority of Japanese series have not shown a significant difference in overall and disease-free survival between the two groups, in spite of a higher incidence of multicentricity and diminished preoperative hepatic function in those with HCV.[24–26] However, Yamanaka et al.[28] were able to demonstrate substantially lower survival in patients with HCC and chronic HCV after hepatic resection. Again, the disparity between our results and those of the Japanese can be attributed to the availability of transplant to treat patients with advanced liver disease at our institution.

Our study found that HCC patients with HBV treated with liver transplant had similar long-term survival when compared to those with HCV. Although other Western series have reported poor outcomes after transplant in HCC patients with HBV, deaths in these studies have not been due to recurrence of tumor but rather to recurrence of HBV.[29,30] Several centers have reported improved survival after transplantation for HBV with the use of hepatitis B immune globulin.[35–37] Currently, transplant for HBV at our institution carries a prognosis that is better than the mean when all indications are considered.

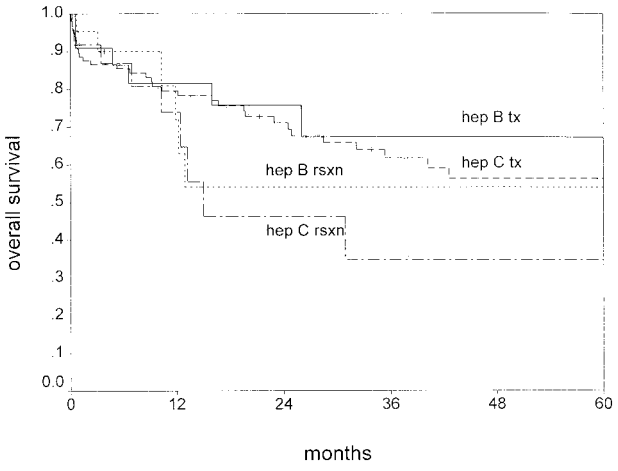

FIG. 2. Overall actuarial survival for HCC patients undergoing resection and liver transplant according to serologies. hep B, hepatitis B; hep C, hepatitis C; rsxn, resection; tx, transplant.

Mazzaferro et al.[38] have established liver transplant as an effective treatment for small, unresectable HCC in cirrhotic patients. The role of liver transplant for resectable HCC, however, remains a controversial topic. Whereas some authors have been able to demonstrate a clear survival advantage with transplant, others have shown no clear benefit over resection.[39–43] We were able to demonstrate a significantly longer disease-free survival in HCC patients with HCV who were treated with liver transplant when compared to resection. The same was not true for those with HBV. Given that cirrhosis places individuals at risk for HCC and that HCC patients with HCV were much more likely to have cirrhosis, it is not surprising that transplant would result in fewer recurrences, because it involves removal of the recipient liver, which is predisposed to tumorigenesis.

In conclusion, a much higher proportion of patients with HCC and chronic hepatitis B will be candidates for resection at presentation. We have demonstrated that significant differences in preoperative status, tumor characteristics, and disease-free survival exist between HCC patients with chronic HBV and HCV infection who have not yet reached end-stage liver disease. A 3-year disease-free survival of less than 10% after resection makes a compelling argument for transplanting resectable cases of HCC with concomitant HCV, especially in light of the substantially higher disease-free survival rates achieved in these patients after transplant.

REFERENCES

1. Szmuness W. Hepatocellular carcinoma and the hepatitis B virus: evidence for a causal relationship. *Prog Med Virol* 1978;24:40–69.
2. Beasley RP, Hwang LY. Overview on the epidemiology of hepatocellular carcinoma. In: Hollinger FB, Lemon SM, Margolis HS, eds. *Viral hepatitis and liver disease.* Baltimore: Williams & Wilkins, 1990:532–35.
3. Lu SN, Lin TM, Chen CJ, et al. A case-control study of primary hepatocellular carcinoma in Taiwan. *Cancer* 1988;62:2051–5.
4. Sallie R, DiBisceglie AM. Viral hepatitis and hepatocellular carcinoma. *Gastroenterol Clin North Am* 1994;23:567–79.
5. Beasley RP, Hwang LY, Lin CC, Chien CS. Hepatocellular carcinoma and hepatitis B virus: a prospective study of 27707 men in Taiwan. *Lancet* 1981;2:1129–33.
6. Liaw YF, Tai DI, Chu CM, et al. Early detection of hepatocellular carcinoma in patients with chronic type B hepatitis: A prospective study. *Gastroenterology* 1986;90:263–7.
7. Choo QL, Kuo G, Weiner AJ, et al. Isolation of cDNA clone derived from blood-borne non-A, non-B virus hepatitis genome. *Science* 1989;244:359–62.
8. Kuo G, Choo QL, Alter HJ, et al. An assay for circulating antibodies to a major etiologic virus of human non-A, non-B hepatitis. *Science* 1989;244:362–64.
9. Tsukuma H, Hiyama T, Tanaka S, et al. Risk factors for hepatocellular carcinoma among patients with chronic liver disease. *N Engl J Med* 1993;328:1797–1801.
10. Saito I, Miyamura T, Ohbayashi A, et al. Hepatitis C virus infection is associated with the development of hepatocellular carcinoma. *Proc Natl Acad Sci U S A* 1990;87:6547–9.
11. Nishioka K, Wantanabe J, Furuta S, et al. A high prevalence of antibody to hepatitis C virus in patients with hepatocellular carcinoma in Japan. *Cancer* 1991;67:429–33.
12. Ohkoshi S, Kato N, Kinoshita T, et al. Detection of hepatitis C virus RNA in sera and liver tissue of non-A, non-B hepatitis patients using the polymerase chain reaction. *Jpn J Cancer Res* 1990;81:862–5.
13. Bruix J, Barrera JM, Calvet X, et al. Prevalence of antibodies to hepatitis C virus in Spanish patients with hepatocellular carcinoma and hepatic cirrhosis. *Lancet* 1989;2:1004–6.
14. Ruiz J, Sangro B, Cuenda JI, et al. Hepatitis B and C viral infections in patients with hepatocellular carcinoma. *Hepatology* 1992;16:637–41.
15. Colombo M, Kuo G, Choo QL, et al. Prevalence of antibodies to hepatitis C virus in Italian patients with hepatocellular carcinoma. *Lancet* 1989;2:1006–8.
16. Hasan F, Jeffers LJ, De Medina M, et al. Hepatitis C associated hepatocellular carcinoma. *Hepatology* 1990;12:589–91.
17. Liang TJ, Jeffers L, Reddy KR, et al. Viral pathogenesis of hepatocellular carcinoma in the United States. *Hepatology* 1993; 18:1326–33.
18. Diamantis ID, McGandy CE, Chen TJ, et al. The integration state of hepatitis B virus in hepatocellular carcinoma. *J Virol Dis* 1993; 1:9–15.
19. Yaginuma K, Kobayashi H, Kobayashi M, et al. Multiple integration sites of hepatitis B virus DNA in hepatocellular carcinoma and chronic active hepatitis tissues from children. *J Virol* 1987;61: 1808–13.
20. Rogler CE, Sherman M, Su CY, et al. Deletion in chromosome 11p associated with a hepatitis B integration site in hepatocellular carcinoma. *Science* 1985;230:319–22.
21. Hino H, Shows TB, Rogler CB. Hepatitis B virus integration site in hepatocellular carcinoma at chromosome 17;18 translocation. *Proc Natl Acad Sci U S A* 1986;83:8338–42.
22. Rogler CE. Cellular and molecular mechanisms of hepatocarcinogenesis associated with hepadenavirus infection. *Curr Top Microb Immunol* 1991;168:103–40.
23. Robinson WS. The role of hepatitis B virus in the development of primary hepatocellular carcinoma. *J Gastroenterol Hepatol* 1992; 7:622–38 and 1993;8:95–106.
24. Shiratori Y, Shiina S, Imamura M, et al. Characteristic differences of hepatocellular carcinoma between hepatitis B- and C- viral infections in Japan. *Hepatology* 1995;22:1027–33.
25. Takenaka K, Yamamoto K, Taketomi A, et al. A comparison of surgical results in patients with hepatitis B versus hepatitis C-related hepatocellular carcinoma. *Hepatology* 1995;22:20–24.
26. Miyagawa S, Kawasaki S, Makuuchi M. Comparison of the characteristics of hepatocellular carcinoma between hepatitis B and hepatitis C viral infections: tumor multicentricity in cirrhotic liver with hepatitis C. *Hepatology* 1996;24:307–10.
27. Tanizaki H, Ryu M, Kinoshita T, et al. Comparison of clinical features and survival in patients with hepatitis B and C virus-related hepatocellular carcinoma. *Jpn J Clin Oncol* 1997;27:67–70.
28. Yamanaka N, Tanaka T, Tanaka W, et al. Correlation of hepatitis virus serologic status with clinicopathologic features in patients undergoing hepatectomy for hepatocellular carcinoma. *Cancer* 1997;79:1509–15.
29. Chung SW, Toth JL, Rezieg M, et al. Liver transplantation for hepatocellular carcinoma. *Am J Surg* 1994;167:317–21.
30. Wong PY, McPeake JR, Portmann B, et al. Clinical course and survival after liver transplantation for hepatitis B virus infection complicated by hepatocellular carcinoma. *Am J Gastroenterol* 1995;90:29–34.
31. Tiollais P, Hsu TY, Moroy T, et al. Hepadenavirus as an insertional mutagen in hepatocellular carcinoma. In: Hollinger FB, Lemon SM, Margolis HS, eds. *Viral hepatitis and liver disease*. Baltimore: Williams & Wilkins, 1990:541–6.

32. Wang XW, Forrester K, Yeh H, et al. Hepatitis B virus X protein inhibits p53 sequence-specific DNA binding, transcriptional activity and association with transcription factor ERCC3. *Proc Natl Acad Sci U S A* 1994;91:2230–4.
33. Truant R, Antunovic J, Greenblatt J, et al. Direct interaction of the hepatitis B virus HBX protein with p53 leads to inhibition by HBX of p53 response element-directed transactivation. *J Virol* 1995;69: 1107–14.
34. Castells L, Vargas V, Gonzalez A, et al. Long interval between HCV infection and development of hepatocellular carcinoma. *Liver* 1995;15:159–63.
35. Tchervenkov JI, Tector AJ, Barkun JS, et al. Recurrence-free long-term survival after liver transplantation for hepatitis B using interferon-alpha pretransplant and hepatitis B immune globulin posttransplant. *Ann Surg* 1997;226:356–8.
36. Gugenheim J, Baldini E, Ouzan D, Mouiel J. Absence of initial viral replication and long-term high dose immunoglobulin administration improve results of hepatitis B virus recurrence prophylaxis after liver transplantation. *Transplant Proc* 1997;29:517–18.
37. Nyman T, Shokouh-Amir MH, Vera SR, et al. Prevention of hepatitis B recurrence with indefinite hepatitis B immune globulin (HBIG) prophylaxis after liver transplantation. *Clin Transplant* 1996;10:663–7.
38. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996;334:693–9.
39. Pichlmayr R, Weimann A, Oldhafer KJ, et al. Appraisal of transplantation for malignant tumors of the liver with special reference to early stage hepatocellular carcinoma. *Eur J Surg Onc* 1998;24:60–7.
40. Tan KC, Rela M, Ryder SD, et al. Experience of orthotopic liver transplantation and hepatic resection for hepatocellular carcinoma of less than 8 cm in patients with cirrhosis. *Br J Surg* 1995;82: 253–6.
41. Bismuth H, Chiche L, Adam R, et al. Liver resection versus transplantation for hepatocellular carcinoma in cirrhotic patients. *Ann Surg* 1993;218:145–51.
42. Iwatsuki S, Starzl TE, Sheahan DG, et al. Hepatic resection versus transplantation for hepatocellular carcinoma. *Ann Surg* 1991;214: 221–9.
43. Otto G, Heuschen U, Hofmann WJ, et al. Survival and recurrence after liver transplantation versus liver resection for hepatocellular carcinoma: a retrospective analysis. *Ann Surg* 1998;227:424–32.