Impact of Diabetes Mellitus on the Prognosis of Patients with Hepatocellular Carcinoma

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Received July 3, 2000; accepted November 8, 2000.

BACKGROUND. The majority of patients with hepatocellular carcinoma (HCC) have coexisting cirrhosis or chronic hepatitis, often complicated by diabetes mellitus. In the current study, the authors evaluated the impact of diabetes mellitus on the prognosis of patients with HCC.

METHODS. Among 581 patients with HCC who had been diagnosed and treated between 1990 and 1999, survival was compared between those patients with and those patients without diabetes mellitus. The rate of disease recurrence after treatment also was analyzed.

RESULTS. Ninety-two patients (15.8%) had diabetes mellitus. There was no significant difference with regard to patient characteristics (i.e., age, gender, or alcohol intake) or liver function between those patients with and those patients without diabetes mellitus. No differences were observed in survival between patients with diabetes mellitus and patients without it. Among the 195 patients with a solitary HCC lesion measuring ≤ 3 cm in greatest dimension, the survival of the 32 patients with diabetes mellitus was significantly poorer than that of the 163 patients without diabetes mellitus (P = 0.0273), despite no apparent difference in liver function between the 2 groups. On multivariate analysis, diabetes mellitus was found to be an independent factor predicting lower survival after treatment (P = 0.0077) among patients with a solitary HCC lesion measuring ≤ 3 cm in greatest dimension. No difference in the rate of recurrence was observed between the two groups in all the patients and in those patients with a solitary HCC lesion measuring ≤ 3 cm in greatest dimension.

CONCLUSION. The results of the current study indicated that the presence of diabetes mellitus worsens the prognosis of patients with a solitary HCC lesion measuring ≤ 3 cm in greatest dimension; it appears to impact prognosis in patients with HCC when HCC is treatable, based on the size and the number of lesions. However, diabetes mellitus did not appear to affect the prognosis in the general population of patients with HCC. Based on the current study data, diabetes mellitus does not appear to modify the progression of HCC and its recurrence after treatment, but it does appear to worsen the prognosis of patients with HCC by means of a rapid decline in remnant liver function caused by repeated treatment of HCC. Cancer 2001;91:957–63. © 2001 American Cancer Society.

KEYWORDS: hepatocellular carcinoma, diabetes mellitus, survival, recurrence.

Hepatocellular carcinoma (HCC) is one of the most common malignancies, and is particularly prevalent in Southeast Asia. In Japan, the incidence of HCC has been increasing over the last 30 years, and has increased > 2-fold over the last 10 years. HCC is the third leading cause of death from cancer among Japanese individuals. Epidemiologic surveys have shown the hepatitis B virus (HBV) and hepatitis C virus (HCV) to be causative agents. The majority of HCC develops in the presence of cirrhosis, which in Japan often occurs as
a complication of HBV or HCV. The incidence of HCC has been shown to be higher in patients with chronic hepatitis C than in those with chronic hepatitis B.

Alterations in carbohydrate metabolism are frequent in patients with cirrhosis. In addition, previous reports have suggested an association between diabetes and HCV infection, although to our knowledge this remains controversial. According to the criteria of National Diabetes Data Group, the prevalence of diabetes mellitus is higher in patients with cirrhosis than in those with chronic hepatitis, and in patients with cirrhosis the risk of diabetes depends on the stage of the disease. These data suggest that decreased liver function and/or portal-systemic shunting may contribute to the development of diabetes in these patients.

Therefore, diabetes mellitus is one of the most common complications observed in patients with HCC. In addition, a higher risk of primary liver carcinoma has been reported in patients with diabetes mellitus. However, to our knowledge few data exist regarding the impact of diabetes mellitus on the survival of patients with HCC. A previous study analyzed the effect of diabetes mellitus on the prognosis of HCC patients who underwent hepatic resection. However, patients with HCC who can be considered candidates for hepatic resection are only a small proportion of the total number of patients with HCC, and the majority of patients are treated nonsurgically. To our knowledge, no studies to date have analyzed the impact of diabetes mellitus on the prognosis of patients with HCC. In the current study, we evaluated the impact of diabetes mellitus on the long-term outcome of patients with HCC.

MATERIALS AND METHODS
Between January 1990 and June 1999, a total of 670 patients were diagnosed with HCC at Ogaki Municipal Hospital. Of these, we studied 581 patients who had been followed for > 6 months. They were comprised of 425 males and 156 females with a mean age of 64.0 ± 8.6 years. One hundred three patients were infected with HBV and 422 were infected with HCV. Of the remaining 56 patients, 40 had evidence of alcoholic cirrhosis and 16 had cryptogenic hepatitis. No patient had primary biliary cirrhosis, autoimmune hepatitis, Wilson disease, or α1-antitrypsin deficiency. Five hundred twenty patients had cirrhosis at the time of diagnosis of HCC. According to the Child-Pugh classification, 313 patients were classified as Grade A, 204 were classified as Grade B, and 64 were classified as Grade C. Four hundred thirty-seven patients had been followed regularly at our hospital before the detection of HCC, and the remaining 144 patients were found to have HCC at the time of first admission to our hospital. At the time of diagnosis of HCC, esophageal and/or gastric varices were observed in 266 patients (45.8%), ascites was observed in 194 patients (33.4%), and hepatic encephalopathy was observed in 44 patients (7.6%).

Diabetes mellitus was diagnosed based on the presence of hyperglycemia (> 8 mmol/L) in at least 2 postabsorptive samples, overt glycosuria, or both; or active treatment with insulin, oral hypoglycemic agents, or both. No consideration was given to minor alterations in glucose metabolism, such as impaired glucose tolerance based on an oral glucose tolerance test (World Health Organization criteria).

As treatment for HCC, 122 patients underwent hepatic resection, 189 patients received percutaneous ethanol injection therapy (PEIT) or percutaneous microwave thermocoagulation therapy (PMCT), and 204 patients received transcatheter arterial embolization (TAE). Because of extreme progression of HCC or severely decreased liver function, 36 patients were treated only with systemic or local arterial-infusion chemotherapy, and 30 patients were not treated. No patient underwent liver transplantation. All patients were followed regularly for > 6 months. Follow-up ranged from 6–157 months (median, 32 months). Patients usually were evaluated every 4 weeks by biochemical tests including tumor markers such as α-fetoprotein and des-γ-carboxy prothrombin, and by ultrasonography or computed tomography every 2–4 months. Retreatment usually was performed when disease recurrence was detected.

Statistical Analysis
In the analysis of patient characteristics, data were expressed as the mean ± the standard deviation. Differences in proportions were tested by the chi-square test. Mean quantitative values were compared by the Student t test. Nonparametric data were compared using the Mann–Whitney U test.

For analyses of patient survival and recurrence, the date of the HCC diagnosis was defined as time zero for calculations. Surviving patients and patients who died of causes other than liver disease or diabetic disease were defined as censored cases. Patients who died of HCC-related causes, liver failure, metastasis from HCC, rupture of varices, or diabetes-related causes were defined as noncensored cases. The date of recurrence was defined as the date of the detection of recurrent tumor. The Kaplan–Meier method was used to calculate survival rates and the log-rank test was used to analyze differences.

For multivariate analysis, the Cox proportional hazards model was used. The variables analyzed...
were age at HCC diagnosis (≥ 65 years vs. > 65 years), gender, viral hepatitis infection (HBV infection vs. HCV infection), Child–Pugh grade (A vs. B and C), alcohol abuse (intake of 86 g of ethanol daily for at least 10 years, according to the criteria of the Liver Cancer Study Group of Japan), diabetes mellitus, tumor size (≤ 20 mm vs. > 20 mm), and therapy (surgery vs. PEIT, PMCT, or TAE).

Data analyses were performed with the SAS statistical package (SAS Institute, Cary, NC). All P values were derived from two-tailed tests, and a level of < 0.05 was considered to be statistically significant. The entire protocol was approved by the hospital ethics committee and was performed in compliance with the Helsinki declaration.

RESULTS

Of the 581 patients with HCC, 92 had diabetes mellitus whereas the remaining 489 did not. Diabetes was either untreated or was treated by simple dietary modifications in 16 patients, by oral hypoglycemic agents in 44 patients, and by long-acting insulin in 32 patients. Eighty of 92 patients had been followed for diabetes mellitus at our hospital or another institution, and the remaining 12 patients were diagnosed with diabetes mellitus after the diagnosis of HCC.

Comparison of Clinical Characteristics, Survival, and Recurrence between Patients with and Patients without Diabetes Mellitus

Table 1 shows the clinical characteristics at the time of diagnosis of HCC for patients with and without diabetes mellitus. There were no differences between the two groups, including patient characteristics (i.e., age, gender, or alcohol intake), liver function, complications other than HCC (i.e., esophageal/gastric varices, ascites, or hepatic encephalopathy), size and number of HCC lesions, and treatment. At the time of last follow-up (the end of 1999), 39 patients (42.4%) with diabetes mellitus and 209 patients (42.7%) without diabetes mellitus had died. All patients died of liver-related causes and no patients died of diabetes-related complications such as cardiovascular diseases and nephropathy. The survival and recurrence rates of patients with and without diabetes mellitus after the diagnosis of HCC are compared in Figures 1 and 2. There was no significant difference in survival or the recurrence rate between patients with and patients without diabetes mellitus (survival rate, P = 0.5516; recurrence rate, P = 0.2699). Child–Pugh grade, size of the largest tumor, and therapy were found to be significant factors affecting survival on both univariate and multivariate analyses, and the type of viral hepatitis infection was found to be an additional significant factor in the multivariate analysis (Table 2). Extrahepatic HCC metastases were observed in 12 of 92 patients (13.0%) with diabetes mellitus and in 55 of 489 patients (11.2%) without diabetes mellitus.

Comparison of Characteristics, Survival, and Recurrence between Patients with and Patients Without Diabetes Mellitus in Those Patients with a Solitary HCC Lesion Measuring ≤ 3 cm in Greatest Dimension

Among patients with a solitary HCC lesion measuring ≤ 3 cm in greatest dimension, there were no differences in the clinical characteristics between 32 patients with diabetes mellitus and 163 patients without diabetes mellitus (Table 3). HCC was treated in all patients with a solitary lesion measuring ≤ 3 cm in greatest dimension. The survival rate after treatment in patients with diabetes mellitus was significantly lower than that of patients without diabetes mellitus (Fig. 3) (P = 0.0273). The Child–Pugh grade and diabetes mellitus were found to be significant factors affecting survival on the univariate analysis. The presence of diabetes mellitus was found to be an indepen-

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**Table 1**

| Patients with diabetes | Patients without diabetes | P value |
|------------------------|---------------------------|---------|
| No.                     | 92                        | 489     | NS      |
| Gender (male/female)    | 70/22                     | 355/134 | NS      |
| Age (yrs) (mean ± SD)   | 63.5 ± 7.6                | 64.1 ± 8.8 | NS      |
| History of transfusion (+/-) | 28/64                  | 106/383 | NS      |
| Etiology (HBV/HCV/other) | 17/65/10                | 86/357/46 | NS      |
| Alcohol abuse (+/-)     | 40/52                     | 163/326 | NS      |
| Cirrhosis (+/-)         | 82/10                    | 438/51  | NS      |
| Esophageal/gastric varices (+/-) | 41/51               | 225/264 | NS      |
| Ascites (+/-)           | 28/64                    | 166/323 | NS      |
| Hepatic encephalopathy (+/-) | 11/81               | 33/456  | NS      |
| Laboratory data (mean ± SD) |                        |         |         |
| Total bilirubin (g/dL)  | 1.05 ± 0.77              | 1.13 ± 0.92 | NS      |
| Albumin (g/dL)          | 3.17 ± 0.61              | 3.36 ± 0.60 | NS      |
| Platelet count (1/uL)   | 11.1 ± 7.1               | 11.6 ± 8.5 | NS      |
| Prothrombin time (%)    | 83.9 ± 19.6              | 82.3 ± 19.2 | NS      |
| ICG R15 (%) (mean ± SD) | 25.0 ± 16.8              | 22.8 ± 14.9 | NS      |
| Child-Pugh grade (A/B/C) | 48/29/15                | 263/175/49 | NS      |
| Size of largest tumor (cm) (mean ± SD) | 3.76 ± 0.68 | 4.23 ± 6.50 | NS      |
| No. of tumors (solitary/multiple) | 48/46                  | 261/228 | NS      |
| Initial treatment (surgery/PEIT or PMCT/TAE)a | 21/31/29             | 101/150/175 | NS      |

NS: not significant; SD: standard deviation; +: positive; -: negative; HBV: hepatitis B virus; HCV: hepatitis C virus; ICG R15: 15-minute indocyanine green retention; PEIT: percutaneous ethanol injection therapy; PMCT: percutaneous microwave thermocoagulation therapy; TAE: transcatheter arterial embolization.

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*a Among those patients with diabetes, 4 received chemotherapy and 7 did not receive treatment; among patients without diabetes, 32 received chemotherapy and 23 did not receive treatment.*
dent factor impacting prognosis after the treatment of HCC on multivariate analysis (Table 4) \((P = 0.0077)\). The Child–Pugh classification prior to treatment \((P = 0.0006)\) and the therapy performed \((P = 0.0137)\) also were found to be factors affecting prognosis on multivariate analysis. No difference in the recurrence rate was observed between patients with and patients without diabetes mellitus (Fig. 4) \((P = 0.8686)\).

**DISCUSSION**

In the current study, we compared the long-term prognosis of patients with HCC between patients with and patients without diabetes mellitus at the time of diagnosis. We observed no difference in survival between these two groups. However, among patients whose HCC was solitary and was no more than 3 cm in greatest dimension, patients with diabetes mellitus were found to have poorer survival than those without

### Table 2

| Factor                        | Univariate | Multivariate |
|-------------------------------|------------|--------------|
| Age (yrs) \(\leq 65\) vs. > 65 | 0.5999     | 0.1315       |
| Gender Male vs. female        | 0.2186     | 0.2118       |
| Viral infection* HBV vs. HCV  | 0.1210     | 0.0067       |
| Child–Pugh grade A vs. B and C| < 0.0001   | < 0.0001     |
| Alcohol abuse No vs. yes      | 0.9451     | 0.9601       |
| Diabetes mellitus No vs. yes  | 0.5516     | 0.3984       |
| Size of largest tumor (mm) \(\leq 20\) vs. > 20 | < 0.0001 | < 0.0001 |
| Therapy* Surgery vs. PEIT, PMCT, or TAE | < 0.0001 | 0.0043 |

* Fifty-six patients were not infected with the hepatitis B virus or the hepatitis C virus.
* Thirty-six patients received chemotherapy and 30 did not receive treatment.

### Table 3

| Patients with diabetes | Patients without diabetes | P value |
|------------------------|---------------------------|---------|
| No. 32                 | 163                       |         |
| Gender (male/female)   | 24/8                      | 98/65   | NS      |
| Age (years) \(\text{mean} \pm \text{SD}\) | 63.5 ± 6.5 | 64.2 ± 9.3 | NS      |
| History of transfusion (+/−) | 11/21 | 56/107 | NS      |
| Etiology (HBV/HCV/others) | 2/26/4 | 16/131/16 | NS      |
| Alcohol abuse (+/−)    | 15/17                     | 56/107  | NS      |
| Cirrhosis (+/−)        | 27/5                      | 137/26  | NS      |
| Esophageal/gastric varices (+/−) | 13/19 | 68/95 | NS      |
| Ascites (+/−)          | 10/22                     | 58/105  | NS      |
| Laboratory data \(\text{mean} \pm \text{SD}\) | | |
| Total bilirubin \((g/dL)\) | 1.10 ± 0.73 | 1.14 ± 1.08 | NS |
| Albumin \((g/dL)\)     | 3.28 ± 0.62               | 3.38 ± 0.59 | NS |
| Platelet count \((\mu L)\) | 11.0 ± 7.3 | 10.6 ± 5.8 | NS |
| Prothrombin time (%)   | 81.9 ± 18.4               | 83.0 ± 20.9 | NS |
| ICG R15 (%) \(\text{mean} \pm \text{SD}\) | 23.9 ± 16.9 | 22.3 ± 14.6 | NS |
| Child–Pugh grade (A/B/C) | 18/10/4 | 91/53/19 | NS      |
| Tumor size \((cm)\) \(\text{mean} \pm \text{SD}\) | 1.63 ± 0.55 | 1.77 ± 0.38 | NS |
| Initial treatment (surgery/PEIT or PMCT/TAE) | 10/17/5 | 45/85/33 | NS      |

*NS: not significant; SD: standard deviation; +: positive; −: negative; HBV: hepatitis B virus; HCV: hepatitis C virus; ICG R15: 15-minute indocyanine green retention; PEIT: percutaneous ethanol injection therapy; PMCT: percutaneous microwave thermocoagulation therapy; TAE: transcatheter arterial embolization.
diabetes mellitus. In the case of patients with larger HCC lesions, survival depended on the state of progression of the tumor itself, including the size and/or the number of lesions. However, in patients with a solitary, small HCC lesion, a decrease in liver function may affect prognosis because such tumors usually are treatable.

Ikeda et al. investigated the prognosis of HCC patients with diabetes mellitus, and reported a lower survival rate in patients with diabetes mellitus compared with patients without it among those HCC patients who underwent hepatic resection.15 In the patients in their study, the tumor was operable and the liver function was not so impaired (approximately 50% of their patients did not have cirrhosis). In the current study, the majority of patients (520 of 581 patients [89.5%]) had cirrhosis and hepatic resection was possible in only 21% (122 of 581 patients). The current study data showed a poorer prognosis in patients with diabetes mellitus compared with patients who did not have diabetes mellitus, even when patients who could not be considered candidates for hepatic resection were included, among those patients with a solitary HCC lesion measuring \( \leq 3 \) cm in greatest dimension, a lesion that usually is treatable.

It is difficult to distinguish clearly death from HCC from death from liver failure; it is difficult to clarify whether patients with HCC in the current study died of HCC progression or from a decrease in liver function. However, although we observed an adverse effect of diabetes mellitus on prognosis among patients with treatable HCC with regard to the size and number of the lesions, no difference in survival was observed between patients with diabetes mellitus and patients without it when all patients with HCC were analyzed. In addition, there were no differences noted in the recurrence rate (both overall and in patients with a solitary HCC measuring \( \leq 3 \) cm in greatest dimension) or in the incidence of extrahepatic metastasis. Based on these results, diabetes mellitus may not affect the progression or recurrence of HCC, but it may worsen the prognosis of patients with HCC by decreasing liver function and causing rapid progression to liver failure.

Although a previous study suggested that the presence of diabetes mellitus was not a significant risk factor for mortality using a Cox regression model in a
large series of patients with cirrhosis, a more recent series including 106 patients with cirrhosis and clinically detectable diabetes showed that diabetes is a negative prognostic factor for long-term survival in patients with cirrhosis. In addition, it has been reported that the cause of death in these patients mainly was related to liver failure and not to diabetes-associated cardiovascular complications.

The prevalence of diabetes among patients with cirrhosis is associated with the severity of cirrhosis. Therefore, it might be suspected that the grade of cirrhosis at the time of HCC diagnosis in patients with diabetes mellitus was more severe than that of patients without diabetes mellitus. However, there was no difference in either the Child–Pugh grade or the 15-minute indocyanine green retention between patients with and without diabetes mellitus in the current study. In addition, a recent study reported that cirrhosis was diagnosed first in 25% of patients and diabetes mellitus was diagnosed first in 44% of patients, whereas 31% of patients were diagnosed with both conditions simultaneously. Thus, the presence of diabetes mellitus does not necessarily correlate with the severity of cirrhosis at the time of HCC diagnosis.

Insulin deficiency has been reported to impair the regenerative response of the liver after hepatectomy. In diabetic rats that had undergone partial hepatectomy, it was reported that diabetes mellitus impaired hepatic regeneration because of decreased hepatic intracellular energy reserve. In addition, diabetes mellitus has been reported to be the only independent risk factor for liver failure after major hepatic resection for HCC in patients with a low remnant liver volume. Impaired liver regeneration after treatment of HCC, induced by diabetes mellitus, may accelerate the decline in liver function associated with the repeated treatment of both primary and recurrent HCC. This may hasten the development of liver failure, resulting in poorer survival.

The data from the current study indicate that diabetes mellitus worsens the long-term prognosis in patients with early-stage, treatable HCC, not by enhancing the progression of HCC or its recurrence but by inducing the rapid decline of remnant liver function accompanying repeated treatment of HCC, resulting in liver failure. These findings should be taken into consideration when treating HCC patients. Further prospective studies will be required to evaluate the impact of diabetes mellitus in patients with HCC. In addition, the effect of diabetes mellitus on patients with HCC treated by liver transplantation also should be studied further, because transplantation is one of the main options for the treatment of HCC in the West.

REFERENCES

1. Di Bisceglie AM, Goodman ZD, Ishak KG, Hoofnagle JH, Melpolder JJ, Alter HJ. Long-term clinical and histological follow-up of posttransfusion hepatitis. Hepatology 1991;14:969–74.
2. Kiyosawa K, Sodeyama T, Tanaka E, Gibo Y, Yoshizawa K, Nagano Y, et al. Interrelationship of blood transfusion, non-A, non-B hepatitis and hepatocellular carcinoma. Analysis by detection of antibody to hepatitis C virus. Hepatology 1990;12:671–5.
3. Takano S, Yokosuka O, lmazeki F, Tagawa M, Omata M. Incidence of hepatocellular carcinoma in chronic hepatitis B and C. A prospective study of 251 patients. Hepatology 1995;21:550–5.
4. Conn HO, Schreiber W, Elkington SG. Cirrhosis and diabetes. II. Association of impaired glucose tolerance with portal-systemic shunting in Laennec’s cirrhosis. Am J Dig Dis 1971;6:227–39.
5. Kingston ME, Ali MA, Atiyeh M, Donnelly RJ. Diabetes mellitus in chronic active hepatitis and cirrhosis. Gastroenterology 1984;87:688–94.
6. Allison ME, Wreghtt T, Palmer CR, Alexander GM. Evidence for a link between hepatitis C virus infection and diabetes mellitus in a cirrhotic population. J Hepatol 1994;21:1135–9.
7. Simo R, Hernandez C, Genesca J, Jardi R, Mesa J. High prevalence of hepatitis C virus infection in diabetic patients. Diabetes Care 1996;19:998–1000.
8. Mason AL, Lau JYN, Hong N, Qian K, Alexander GM, Xu L, et al. Association of diabetes mellitus and chronic hepatitis C virus infection. Hepatology 1999;29:328–33.
9. Caronia S, Taylor K, Pagliaro L, Carr C, Palazzo U, Petrik J, et al. Further evidence for an association between non-insulin-dependent diabetes mellitus and chronic hepatitis C virus infection. Hepatology 1999;30:1059–63.
10. Hadziyannis S, Karamanou B. Diabetes mellitus and chronic hepatitis C virus infection. Hepatology 1999;29:604–5.
11. Balik I, Yilmaz N, Turkcapar N, Yasa H. Association of diabetes mellitus and chronic hepatitis C virus infection. Hepatology 1999;30:584.
12. National Diabetes Data Group. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. Diabetes 1979;28:1039–57.
13. Buzzelli G, Chiariantini E, Cotrozzi G, Relli P, Matassi L, Romanelli R, et al. Estimate of prevalence of glucose intolerance in chronic liver disease. Degree of agreement among some diagnostic criteria. Liver 1988;8:354–9.
14. Adami H-O, Chow W-H, Nyren O, Berne C, Linet MS, Ekborn A, et al. Excess risk of primary liver cancer in patients with diabetes mellitus. J Natl Cancer Inst 1996;88:1472–7.
15. Ikeda Y, Shimada M, Hasegawa H, Gion T, Kajiyama K, Shirabe K, et al. Prognosis of hepatocellular carcinoma with diabetes mellitus after hepatic resection. Hepatology 1998;27:1567–71.
16. Pugh RNH, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973;60:646–9.
17. Kaplan EL, Meier P. Non parametric estimation for incomplete observation. J Am Stat Assoc 1958;53:457–81.
18. Cox DR. Regression models and life tables. J R Stat Soc B 1972;34:187–220.
19. Liver Cancer Study Group of Japan. Primary liver cancer in Japan. Clinicopathological features and results of surgical treatment. *Ann Surg* 1990;211:277–87.

20. SAS Institute Inc. SAS/STAT user’s guide. Version 6. 4th edition. Cary, NC: SAS Institute Inc., 1989.

21. Schlichting P, Christensen E, Andersen PK, Fauerholdt L, Juhl E, Poulsen H, et al. Prognostic factors in cirrhosis identified by Cox’s regression model. *Hepatology* 1983;3:889–95.

22. Bianchi G, Marchesini G, Zoli M, Bugianesi E, Fabbri A, Pisi E. Prognostic significance of diabetes in patients with cirrhosis. *Hepatology* 1994;20:119–25.

23. Marchesini G, Ronchi M, Forlani G, Bugianesi E, Bianchi G, Fabbri A, et al. Cardiovascular disease in cirrhosis—a point-prevalence study in relation to glucose tolerance. *Am J Gastroenterol* 1999;94:655–62.

24. Johnston DG, Johnson GA, Alberti KG, Millward-Sadler GH, Mitchell J, Wright R. Hepatic regeneration and metabolism after partial hepatectomy in diabetic rats: effects of insulin therapy. *Eur J Clin Invest* 1986;16:384–90.

25. Chin S, Ramirez S, Greenbaum LE, Naji A, Taub R. Blunting of the immediate-early gene and mitogenic response in hepatetomized type 1 diabetic animals. *Am J Physiol* 1995; 269:E691–700.

26. Barra R, Hall JC. Liver regeneration in normal and alloxan-induced diabetic rats. *J Exp Zool* 1977;201:93–100.

27. Bucher NLR, Swaffield MN. Regulation of hepatic regeneration in rats by synergistic action of insulin and glucagon. *Proc Natl Acad Sci USA* 1975;72:1157–60.

28. Mori K, Ozawa K, Yamamoto Y, Maki A, Shimahara Y, Kobayashi N, et al. Response of hepatic mitochondrial redox state to oral load; redox tolerance test as a new predictor of surgical risk in hepatectomy. *Ann Surg* 1990; 211:438–46.

29. Shirabe K, Shimada M, Gion T, Hasegawa H, Takenaka K, Utsunomiya T, et al. Postoperative liver failure after major hepatic resection for hepatocellular carcinoma in the modern era with special reference to remnant liver volume. *J Am Coll Surg* 1999;188:304–9.

30. Zein NN, Abdulkarim AS, Wiesner RH, Egan KS, Persing DH. Prevalence of diabetes mellitus in patients with end-stage liver cirrhosis due to hepatitis C, alcohol, or cholestatic disease. *J Hepatol* 2000;32:209–17.

31. Mazaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996;334:693–9.

32. Yamamoto J, Iwatsuki S, Kosuge T, Dvorchik I, Shimada K, Marsh JW, et al. Should hepatomas be treated with hepatic resection or transplantation? *Cancer* 1999;86: 1151–8.