ORIGINAL ARTICLE

Survival Outcomes in Liver Transplantation for Hepatocellular Carcinoma, Comparing Impact of Hepatitis C Versus Other Etiology of Cirrhosis

Adel Bozorgzadeh,[1] Mark Orloff,[1] Peter Abt,[1] Georgios Tsoulfas,[1] Durald Younan,[1] Randeep Kashyap,[1] Ashok Jain,[1] Parvez Mantry,[2] Benedict Maliakkal,[2] Alok Khorana,[2] and Seymour Schwartz[1]
[1]Departments of [1]Surgery and [2]Medicine, [3]University of Rochester Medical Center, Rochester, NY

The incidence of hepatocellular carcinoma (HCC) is on the rise worldwide as the most common primary hepatic malignancy. In the US approximately one half of all HCC is related to Hepatitis C virus (HCV) infection. The relationship between the primary disease and HCC recurrence after liver transplantation is unknown. We hypothesized that the primary hepatic disease underlying the development of cirrhosis and HCC would be associated with the risk of recurrent HCC after transplantation. A retrospective review was conducted of all primary liver transplants performed at the University of Rochester Medical Center from May 1995 through June 2004. The pathology reports from the native livers of 727 recipients were examined for the presence of HCC. There were 71 liver transplant recipients with histopathological evidence of HCC. These patients were divided in two groups on the basis of HCV status. Group 1 consisted of 37 patients that were both HCV and HCC positive, and Group 2 consisted of 34 patients that were HCC positive but HCV negative. Patient characteristics were analyzed, as well as number of tumors, tumor size, presence of vascular invasion, lobe involvement, recipient demographics, donor factors, pretransplantation HCC therapy, rejection episodes, and documented HCC recurrence and treatment. There were no statistically significant differences between the 2 groups, with the exception of recipient age and the presence of hepatitis B coinfection. The tumor characteristics of both groups were similar in numbers of tumors, Milan criteria status, vascular invasion, incidental HCC differentiation, and largest tumor size. The HCV positive population had a far lower patient survival rate with patient survival in Group 1 at 1, 3, and 5 years being 81.1%, 57.4%, and 49.3% respectively, compared with 94.1%, 82.8%, and 76.4% in Group 2 ($p = 0.049$). Tumor-free survival in Group 1 at 1, 3, and 5 years was 70.3%, 43%, and 36.8% respectively, vs. 88.1%, 73%, and 60.8% in Group 2. In a subgroup analysis, tumor-free survival was further examined by stratifying the patients on the basis of Milan criteria. Group 1 patients outside of Milan criteria had a statistically lower tumor-free survival. By contrast, there was no statistical difference in tumor-free survival in Group 2 patients stratified according to Milan criteria. Cox regression analysis identified HCV and vascular invasion as significant independent predictors of tumor-free survival. Our results suggest that Milan selection criteria may be too limiting and lose their predictive power when applied to patients without HCV infection. ***Liver Transpl 13:807-813, 2007.*** © **2007 AASLD.**

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Worldwide, hepatocellular carcinoma (HCC) is the most common primary hepatic malignancy, with an annual incidence of over half a million cases.[1] The single most important risk factor for the development of HCC is cirrhosis; however, the risk of developing HCC varies with the etiology of cirrhosis.[2,3] If cirrhosis develops as a consequence of genetic hemochromatosis and iron overload, the risk for developing HCC is high (7-9% per year).[4] Primary biliary cirrhosis, alcoholic cirrhosis, α1-antitrypsin deficiency, and Wilson disease are all implicated as risk factors for the development of HCC. Cirrhosis as a result of chronic viral hepatitis, however, accounts for most primary liver cancer worldwide.[5,6]

Abbreviations: HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HBV, hepatitis B virus; IFN, interferon; UNOS, United Network for Organ Sharing.

Address reprint requests to Adel Bozorgzadeh, MD, Director, Solid Organ Transplantation and Hepatobiliary Surgery, 601 Elmwood Avenue, Box SURG, Rochester, NY 14642-8410. Telephone: (585) 275-7986; FAX: (585) 276-0054; E-mail: adel_bozorgzadeh@urmc.rochester.edu

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TABLE 1. Patient and Tumor Characteristics

Variable	Group 1	Group 2	*P* value
Recipient age (yr)	53.8 ± 8.0	60.5 ± 8.2	**0.001**
Gender (male/female)	28/9	26/8	0.938
Donor type (deceased/living)	32/5	27/7	0.427
Donor age (yr)	45.8 ± 19	47.9 ± 20.5	0.644
Follow-up time (months)	37.1 ± 23	43.8 ± 30	0.299
Rejection episodes	12 (32.4%)	12 (35.3)	0.799
Pretransplant HCC treatment	8 (21.6%)	7 (20.6%)	0.915
Hepatitis B coinfection	20 (54.1%)	7 (20.6%)	**0.004**
No. of tumors	1.84 ± 1.1	1.91 ± 1.2	0.786
Exceeds Milan criteria	14 (37.8%)	12 (35.3%)	0.824
Vascular invasion	6 (16.2%)	6 (17.6%)	0.872
Lobe involvement (single/multiple)	30/7	20/14	**0.040**
Incidental HCC	13 (35.1%)	15 (44.1%)	0.952
Differentiation (well/moderate/poor)	22/11/4	20/11/3	0.946
Tumor stage (I/II/III/IV)	5/17/8/7	8/11/7/8	0.575
Largest tumor size (cm)	3.8 ± 2.2	3.4 ± 3.0	0.552

NOTE: Bold means $p < 0.05$.
Data after ± symbol are standard deviation.
Abbreviation: HCC, hepatocellular carcinoma.

Numerous epidemiological studies have established a clear association between chronic viral infection and development of HCC.[7-10]

Liver transplantation is conceptually an attractive therapy for HCC in a cirrhotic liver because it incorporates the radical resection of a total hepatectomy combined with liver replacement.[11,12] Although initial results were disappointing,[13-17] better outcomes have been consistently achieved by refining the selection criteria, with a focus on tumor characteristics, including in particular size, number, lobar distribution, and vascular invasion.[18-22] A landmark study by Mazzaferro et al.[23] published in 1996 set the stage for the current guidelines and policies, which are currently in use to allocate hepatic allografts to those patients with HCC.[24]

Although the natural history of cirrhosis progressing to HCC has been extensively studied and characterized in the general population,[2,5,7,9,10,25] the relationship between HCC recurrences and the primary liver disease is unknown after liver transplantation. We hypothesized that the primary hepatic disease underlying the development of cirrhosis and subsequent HCC would be associated with the risk of recurrent HCC after transplantation. To our knowledge, this is the first report to directly examine the impact of hepatitis C virus (HCV) on the recurrence of HCC after liver transplantation.

METHODS

Patient Population

A retrospective review was conducted of all primary liver transplants performed at our center from May 1995 through June 2004. The pathology reports from the native livers of 727 recipients were examined for the presence of HCC. There were 71 liver transplant recipients with histopathological evidence of HCC. These patients were then divided into 2 groups on the basis of HCV status, which was determined by anti-HCV with at least one positive HCV RNA before transplantation. Group 1 (n = 37) consisted of 28 men and 9 women with a mean age of 53.8 ± 8 years, that were both HCV positive and HCC positive. Group 2 (n = 34) comprised 26 men and 8 women with a mean age of 60.5 ± 8.2 years, all of whom were HCV negative and HCC positive. The data points coded for analysis included number of tumors, tumor size, presence of vascular invasion, lobe involvement, recipient demographics, donor factors, pretransplantation HCC therapy, rejection episodes, and documented HCC recurrence. All recipients received a triple-based immunosuppression regimen consisting of tacrolimus, mycophenolate mofetil, and corticosteroid taper after the same dosing protocols, regardless of HCV status.

Data Analysis

SPSS 13.0 for Windows statistical software package was used for data analysis (SPSS, Chicago, IL). χ^2 test was performed to compare groups in terms of gender, donor type (dead vs. living), Milan criteria status, vascular invasion, tumor differentiation, and tumor stage (Table 1). The Milan criteria subgroups were based on actual pathology from the liver after removal. There were only 7 (2 HCV positive, 5 HCV negative) patients (9.9%) with tumors outside of the Milan criteria on the basis of preoperative imaging. None of these patients had evidence of vascular invasion or extrahepatic metastasis. Patients that were outside of Milan criteria were transplanted at their Model for End-Stage Liver Disease (MELD) score without the benefit of exceptional MELD.

TABLE 2. Subgroup Tumor Characteristics

	Within Milan criteria			Outside Milan criteria		
Characteristic	Group 1 (n = 23)	Group 2 (n = 22)	*P* value	Group 1 (n = 14)	Group 2 (n = 12)	*P* value
Largest tumor size (cm)	2.4 ± 1.0	2.1 ± 1.1	0.324	5.2 ± 2.0	6.3 ± 4.0	0.395
Vascular invasion	2 (8.7%)	1 (4.5%)	0.577	4 (28.6%)	5 (41.7%)	0.484
Lobe involvement (single/multiple)	21/2	18/4	0.349	9/5	2/10	**0.014**
No. of tumors	1.4 ± 0.7	1.3 ± 0.6	0.723	2.6 ± 1.3	3.0 ± 1.1	0.379

NOTE: Bold means *P* value is significant ($P < 0.05$).
Data after ± symbols are standard deviation.

Tumor size, recipient age, donor age, MELD score, and number of tumors were compared with Student's *t* test. MELD score was calculated from actual laboratory values on the day of transplantation. Kaplan-Meier analysis was used to compute overall patient and tumor-free survival. Cox regression analysis was performed to identify the independent predictors associated with tumor recurrence. All potentially confounding variables were examined individually in a regression model along with HCV status. All variables that resulted in a ±10% change in the adjusted hazard ratio from the crude hazard ratio, for tumor-free survival when associated with HCV, were included in the final model. HCC recurrence was defined by irrefutable computed tomographic or magnetic resonance imaging, radiographic presence, histopathological evidence, or a combination of these. Incidental HCC, for our purposes here, occurred in patients without a confirmed diagnosis of HCC before transplantation. However, all but 10 (3 HCV positive, 7 HCV negative) patients (14.1%) had increases in alfa-fetoprotein levels, suspicious lesions on preoperative imaging, or both. Rejection episodes were calculated from biopsy-confirmed pathology reports.

RESULTS

Patient Characteristics

There were no statistically significant differences between the 2 groups, with the exception of recipient age and the presence of hepatitis B (HBV) coinfection (Table 1). The patients in group 2 were significantly older than those in group 1. There was a significantly larger number of patients with HBV coinfection in group 1. However, infection with HBV was not a significant predictor for HCC recurrence. There were no statistically significant differences in the types of HCC treatment before transplantation between the 2 groups. Resection was performed in 1 patient in group 1 and 2 patients in group 2. Other forms of treatment included radiofrequency ablation (n = 6 in group 1, n = 2 in group 2), chemoembolization (n = 0 in group 1, n = 2 in group 2), alcohol ablation (n = 0 in group 1, n = 1 in group 2), and radiation (n = 1 in group 1, n = 1 in group 2). The causes of cirrhosis in the HCV-negative group were as follows: autoimmune, 1 (2.9%); cryptogenic, 9 (26.5%); hemochromatosis, 1 (2.9%); hepatitis B, 3 (8.8%); Laennec, 13 (38.2%); nonalcoholic steatohepatitis, 4 (11.8%); and nonresectable HCC without cirrhosis, 3 (8.8%).

Treatment of HCV with interferon (IFN) did not have an impact on tumor recurrence in this study population. A total of 16 patients (43.2%) received IFN before transplantation; 21 patients (56.8%) did not. HCC recurrence occurred in 7 of 16 patients treated with IFN-α, compared with 5 of 21 patients without IFN treatment ($P = 0.176$). After transplantation, 26 patients experienced HCV recurrence as determined by histological criteria. The mean maximum histological activity index score was 5.67 ± 2.4, and the mean maximum fibrosis score was 1.5 ± 1.3. IFN treatment was offered to 13 patients after transplantation. HCC recurrence was present in 5 of 13 of those who were treated and in 7 of 24 of those who were not treated ($P = 0.413$). More importantly, tumor-free survival ($P = 0.420$) and patient survival ($P = 0.409$) did not differ between those who received IFN and those who did not.

Tumor Characteristics

The tumor characteristics of both groups were similar in terms of number of tumors, Milan criteria status, vascular invasion, incidental HCC, differentiation, and largest tumor size (Table 1). There were a statistically significant greater number of patients with multilobar tumor involvement in the HCV-negative group. In the subgroup analysis, based on the Milan criteria, the 2 groups were similar with the exception of lobe involvement. The patients outside of the Milan criteria who were HCV negative had a far greater number of multilobar tumors (Table 2).

Patient Survival

The HCV-positive population had a far lower patient survival rate by Kaplan-Meier analysis (Fig. 1). Patient survival in group 1 at 1, 3, and 5 years was 81.1%, 57.4%, and 49.3%, respectively, compared with the 94.1%, 82.8%, and 76.4% in group 2 ($P = 0.049$). There were a total of 15 deaths in group 1 from myocardial infarction (n = 2), sepsis (n = 3), intracranial bleeding

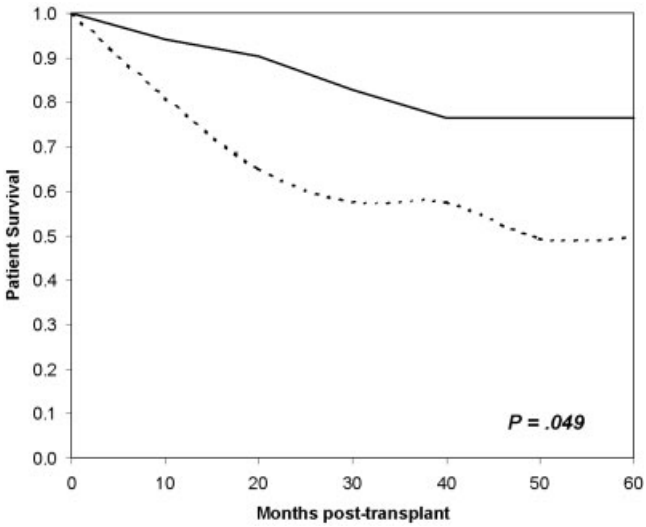

Figure 1. Kaplan-Meier analysis of the survival of patients after transplantation for HCC according to HCV status. All deaths were defined as events. HCV-positive patients had significantly worse prognosis. Median survival in this group (dashed line) was 18.6 months, compared with 32 months in HCV-negative patients (straight line) ($P = 0.05$).

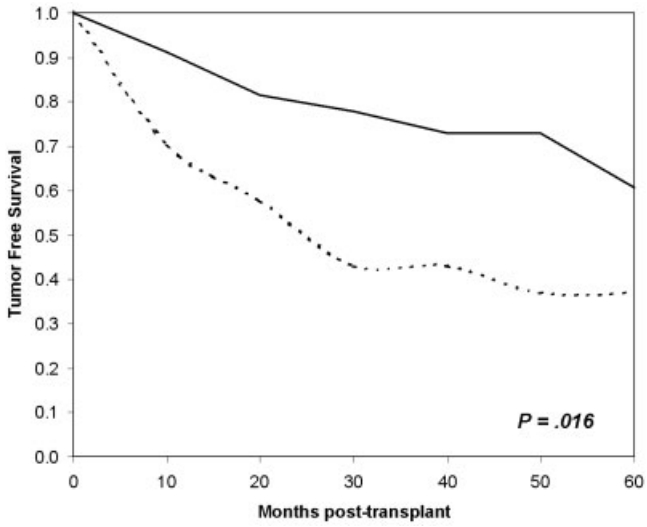

Figure 2. Kaplan-Meier analysis of recurrence-free survival of patients after transplantation for HCC according to HCV status. HCV-positive patients had significantly worse prognosis. Median recurrence-free survival in this group (dashed line) was 17.7 months, compared with 32 months in HCV-negative patients (straight line) ($P = 0.016$).

(n = 1), recurrent HCV (n = 1), metastatic HCC (n = 7), and cerebral vascular accident (n = 1). In group 2, there were 8 deaths, caused by myocardial infarction (n = 2), sepsis (n = 1), metastatic HCC (n = 4), and cerebral vascular accident (n = 1).

Tumor-Free Survival

Tumor-free survival in group 1 at 1, 3, and 5 years was 70.3%, 43%, and 36.8%, respectively, vs. 88.1%, 73%, and 60.8% in group 2 (Fig. 2). Twelve patients (32.4%) developed HCC recurrence in the HCV-positive population, compared with 6 patients (17.6%) in the HCV-negative population. This did not achieve statistical significance. In the HCV negative group, 3 of the 6 recurrences were within the liver compared with 9 of 12 in the HCV-positive group ($P = 0.294$). In a subgroup analysis, tumor-free survival was further examined by stratifying the patients on the basis of Milan criteria. Group 1 patients outside of Milan criteria had a far lower rate of recurrence-free survival (Fig. 3). By contrast, there was no marked difference in tumor-free survival between group 2 patients stratified according to Milan criteria (Fig. 3). Moreover, Cox regression analysis identified HCV infection and vascular invasion as significant independent predictors of tumor-free survival (Table 3).

DISCUSSION

Liver transplantation has emerged as an accepted modality for the treatment of HCC.[24,26,27] Poor outcomes reported in earlier series of liver transplants for HCC demonstrated the need for better selection criteria to improve survival.[28] To this end, recipient and tumor characteristics such as size, number, lobar distribution, and vascular invasion have been extensively studied.[29-33] In 1996, Mazzaferro et al.[23] reported excellent outcomes for patients with small HCCs. Their selection criterion was limited to patients with unresectable (defined either anatomically or by a limited hepatic reserve) single tumors <5 cm, or patients with up to 3 tumors, the largest of which was <3 cm. Their promising results have been validated by other reports.[34-38] Wide acceptance of what is now known as the Milan criteria eventually led to the United Network for Organ Sharing (UNOS) modification of organ allocation policies for HCC in 1998.[24,39] Whether the Milan criteria, and the resulting UNOS policies, are too restrictive has been a controversial issue without a clear resolution.[34,39-42]

Our results suggest the Milan selection criteria may be too limiting, preventing the benefits of transplantation from being extended to selected patients with larger tumors. This study showed a marked difference in tumor-free survival for patients with HCV and HCC when they were stratified according to the Milan selection guidelines. However, these guidelines were not able to predict a statistically significant survival difference for those patients whose tumors were not associated with HCV infection. This suggests that the Milan criterion loses predictive power when applied to patients without HCV infection. A plausible explanation for this stems from the characteristics of the patient population that was the basis for the Milan criteria. Of the 48 patients in the study of Mazzaferro et al.,[23] 45 (95%) had HCV-associated cirrhosis.[23] Cirrhosis caused by other etiologies was not evaluated.

The molecular mechanism underlying HCC is currently unknown. The activation of cellular oncogenes, reactivation of tumor suppressor genes, overexpression

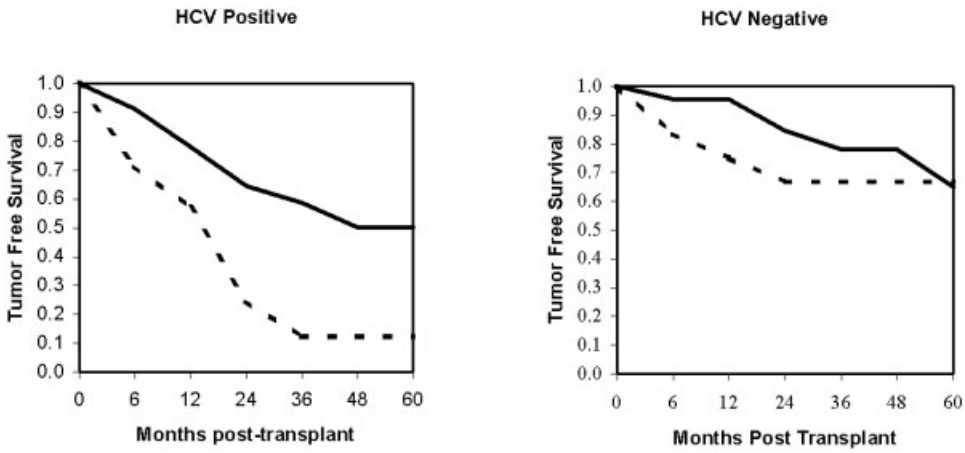

Figure 3. Kaplan-Meier analysis of recurrence-free survival of HCV-positive and HCV-negative patients after transplantation for HCC according to Milan criteria. Median recurrence-free survival in HCV-positive patients outside Milan criteria group (dashed line) was 12.6 months, significantly worse when compared with 29.7 months in HCV-positive patients within Milan criteria (straight line) ($P = 0.014$). Median recurrence-free survival in HCV-negative patients outside Milan criteria group (dashed line) was 26 months, and this was not significantly different when compared with 35.1 months in HCV-negative patients within Milan criteria (straight line) ($P = 0.21$).

TABLE 3. Cox Regression Analysis*

Variable	Relative risk	95% CI Lower	95% CI Upper	*P* value
Hepatitis C virus	2.568	1.166	5.653	0.019
Vascular invasion	4.865	2.098	11.283	0.0

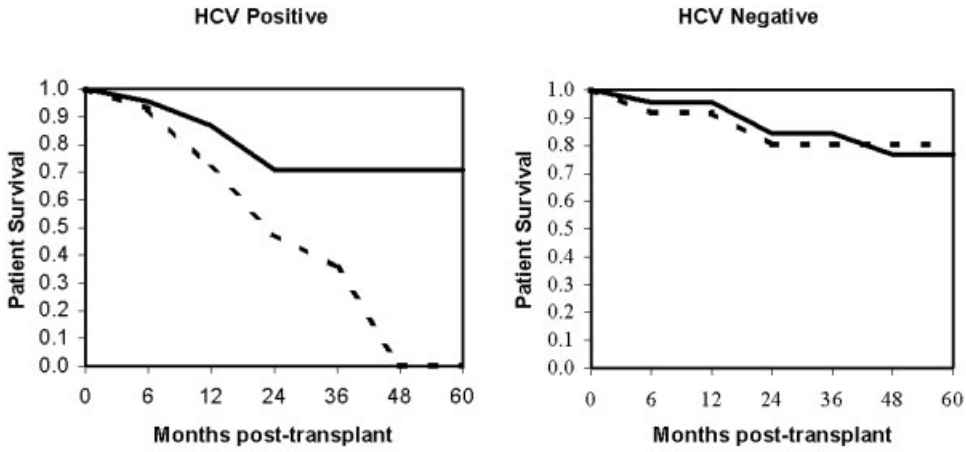

Figure 4. Kaplan-Meier analysis of patient survival of HCV-positive and HCV-negative patients after transplantation for HCC according to Milan criteria. Mean patient survival in HCV-positive patients outside Milan criteria group (dashed line) was 23.8 ± 5.5 months, significantly worse when compared with 61.4 ± 5.5 months in HCV-positive patients within Milan criteria (straight line) ($P = .007$). Mean patient survival in HCV-negative patients outside Milan criteria group (dashed line) was 42.1 ± 5.1 months, and this was not significantly different when compared with 85.1 ± 10.8 months in HCV-negative patients within Milan criteria (straight line) ($P = .784$)

of growth factors, possibly telomerase activation, and DNA mismatch repair defects may contribute to the development of HCC.[43] Many studies have indicated that HCV plays a role in the development of HCC through various mechanisms.[7-10] From our clinical standpoint, this study suggests a marked difference in the pattern and aggressiveness of HCC recurrence in a cohort of patients with HCV-HCC exceeding the Milan criteria. This is evident in patient survival and tumor-free survival outcomes. Whether this stems from the biological behavior of HCV is unknown.

It is well established that cirrhosis from any cause is a risk factor for the development of HCC.[2,44] In the general population, HCV-associated cirrhosis is shown

to carry the highest risk of HCC development, with an estimated rate as high as 7.8-28% at 5 and 10 years from the diagnosis of cirrhosis.[7] Recurrence of HCV after liver transplantation is a universal event, with most patients showing some degree of fibrosis and precirrhotic changes by 5 years.[45] In the general population, progression to clinically important hepatitis and cirrhosis related to HCV infection is an indolent process that takes, on average, 10 and 21.2 years, respectively.[46] In contrast, after transplantation, progression to cirrhosis is an accelerated process attributable to the presence of the viral infection in the background of immune suppression.[47,48] Perhaps the accelerated progression of histopathological changes associated with viral infection under immunosuppression is also related to an accelerated HCC tumor recurrence.[49] This notion is supported by our results, which indicate that hepatitis C is an independent significant predictor of HCC recurrence in Cox regression analysis.

Our results demonstrate vascular invasion and hepatitis C to be statistically significant independent predictors of tumor recurrence and survival. The patients in group 2 were significantly older and had significantly more bilobar distributions of tumor. Interestingly, this cohort had a favorable outcome when compared with the patients in group 1, despite having a higher prevalence of factors that typically predict poorer outcomes. Certainly, a limitation of this study is the small number of patients, which prevents extensive analysis of tumor characteristics as a risk factor for recurrence.

Considering that study of Mazzaferro et al.[23] was essentially limited to patients with HCV, and that HCV is an independent variable for poor prognosis, application of the Milan criteria to patients with HCC that is not associated with HCV may preclude them from the survival advantage offered by transplantation. With the acknowledgment of the limitations of this study, in particular the inherent bias of a retrospective study and the relatively small sample size, we believe that there may be a benefit in a careful and methodical expansion of the Milan criteria for HCC in the non-HCV setting. Further studies are needed to confirm these findings and to address the specific extent of any expansion under consideration.

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