



Liver Transplantation Results for Hepatocellular Carcinoma in Chile

M. Gabrielli, M. Vivanco, J. Hepp, J. Martínez, R. Pérez, J. Guerra, M. Arrese, E. Figueroa, A. Soza, R. Yáñez, R. Humeres, H. Rios, J.M. Palacios, R. Zapata, E. Sanhueza, J. Contreras, G. Rencoret, R. Rossi, and N. Jarufe

ABSTRACT

Hepatocellular carcinoma (HCC) is the most common malignant tumor of the liver. Liver transplantation is the best treatment for HCC; it improves survival, cures cirrhosis, and abolishes local recurrence. We describe the outcomes of patients with HCC who underwent liver transplantation in two liver transplantation centers in Chile.

Methods. This study is a clinical series elaborated from the liver transplantation database of Pontificia Universidad Católica and Clínica Alemana between 1993 and 2009. The survival of patients was calculated using the Kaplan-Meier survival analysis. The significant alpha level was defined as $<.05$.

Results. From 250 liver transplantations performed in this period, 29 were due to HCC. At the end of the study, 25 patients (86%) were alive. The mean recurrence-free survival was 30 months (range 5 months to 8 years). The 5-year survival for patients transplanted for HCC was $>80\%$; however, the 5-year overall survival of patients who exceeded the Milan criteria in the explants was 66%. There was no difference in overall survival between patients transplanted for HCC versus other diagnosis ($P = .548$).

Conclusion. This series confirmed that liver transplantation is a good treatment for patients with HCC within the Milan criteria.

HCC is the most common primary tumor of the liver. It ranks fifth among all malignant tumors in men and eighth in women.¹ Liver cirrhosis for hepatitis B and C as well as alcohol, are the diseases most strongly associated with HCC,² although recently obesity and diabetes have emerged as risk factors.³

Curative treatments for HCC include liver resection and liver transplantation. Radiofrequency ablation may also be curative for small tumors. Other therapies, such as ethanol injection, chemoembolization, and systemic chemotherapy, have generally failed to show good results in terms of survival.⁴ In 1996, a pivotal report from the Milan center in Italy,⁵ showed a 4-year survival of 85% and a recurrence-free survival of 92% for HCC patients with a single tumor measuring ≤ 5 cm in diameter or with no more than 3 tumors each not exceeding 3 cm and no proven vascular invasion who were treated with liver transplantation. Therefore, at present, liver transplantation (LT) is a good treatment for HCC, improving survival, reducing local recurrence rates, and abolishing the underlying cirrhotic liver.⁶ Our aim was to assess the overall survival outcomes

of patients with HCC treated with LT in two centers in Chile.

METHODS

This clinical series from Pontificia Universidad Católica and Clínica Alemana liver transplantation programs included databases elaborated between 1993 and 2009. We obtained demographic characteristics from all patients. The diagnosis of HCC was performed using two dynamic images, alpha-fetoprotein levels, or biopsy. The examined follow-up was 4 years which was achieved in all patients. Survival plots were estimated using the Kaplan Meier method for HCC patients compared with non-HCC patients treated with LT. The survival differences were tested for trends with log-rank tests.

From the Liver transplantation Program, School of Medicine, Pontificia Universidad Católica de Chile (M.G., J.H., J.M., R.P., J.G., M.A., E.F., A.S., R.Y., N.J.), and the Liver transplantation Program, School of Medicine, Clínica Alemana-Universidad del Desarrollo (M.V., R.H., H.R., J.M.P., R.Z., E.S., J.C., G.R., R.R.), Santiago, Chile.

Address reprint requests to Nicolás Jarufe Cassis, MD, Liver Transplantation Program Pontificia Universidad Católica de Chile, Santiago, Chile. E-mail: njarufe@med.puc.cl

The closing date for the survival analysis was August 31, 2009. The SPSS program 15.0 for Windows was used for statistical analyses, with a significant alpha level defined as $<.05$.

RESULTS

In the study period 250 LT were performed, including 27 for HCC. The diagnosis was established preoperatively in 17 patients and by histologic examination of the explanted liver in 12. Liver transplantation for HCC represented 11.6% of all cases; patients were predominantly men, ranging in age from 15 to 71 years (Table 1).

When the diagnosis of HCC was confirmed before liver transplantation surgery, 88% of patients (15) underwent treatment. The 23 procedures performed on this group most frequently included transarterial chemoembolization. In 12 patients, multifocal lesions were detected. The median waiting time for surgery was 12 months (range 2–24). Ten patients exceeded the Milan criteria upon anatomorphologic examination of the explanted liver.

At the end of the study, 25 patients transplanted for HCC were alive, and four (13%) had tumor recurrences all of whom exceeded the Milan criteria in their native explants. The mean recurrence-free survival was 30 months (range 5 months to 8 years). The 5-year overall survival for all patients transplanted for HCC was 86%, and for patients who fulfilled the Milan criteria at explantation it was 94.7%. The 5-year overall survival of patients who exceeded the Milan criteria in their explants was 66%. Figure 1 shows the overall survival for transplanted patients for all diagnoses and Fig 2 for subjects subdivided by diagnosis. The overall survival rates for hepatocellular carcinoma patients transplanted were similar between the centers ($P = .48$).

DISCUSSION

This is the first Chilean cooperative clinical series of liver transplantation for hepatocellular carcinoma. In this study, there was no significant difference in survival between transplant patients with versus without HCC. The ten patients who exceeded the Milan criteria displayed shorter survival than those who did not exceed them, but because of the

Table 1. Demographic Characteristics

	HCC	Other Diagnosis
Transplants (n)	27	223
Age (years)	56*	48
Male (%)	77.8*	44.7
Female (%)	22.2	55.3*
Cause of liver disease		
Hepatitis C virus (%)	44*	15.7*
Hepatitis B Virus (%)	0	1.3**
Alcohol (%)	31*	10.7
Child-Pugh class n (%)		
A	8	—
B	17	—
C	4	—

* $P < .05$; **Not significant.

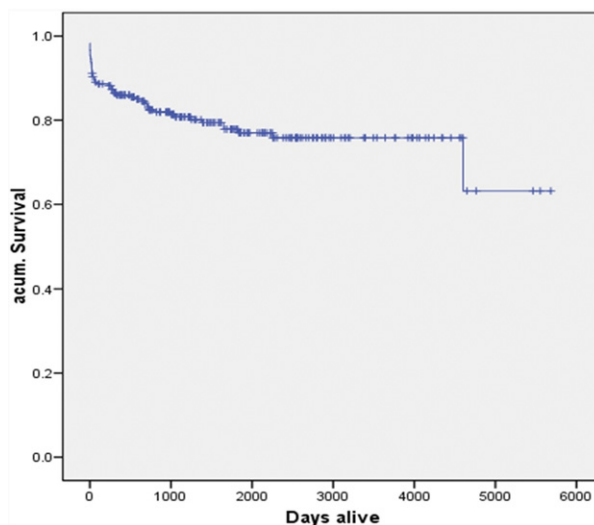


Fig 1. Overall survival for all transplanted patients.

small sample sizes they did not significantly alter the overall survival of HCC patients. In 1997, Figueras et al⁷ reported the results of a prospective study regarding liver transplantation as the primary treatment for patients with small HCC versus without HCC. They did not observe a significant difference in survival between the groups.

The risk of HCC among patients with chronic hepatitis C is high, namely 2%–8%.⁸ In the present study, 44% of patients with HCC bore hepatitis C virus; no patients with hepatitis B virus had HCC. A Brazilian study⁹ reported a rate of 31.1% of HCC patients bearing hepatitis C virus and 13.3% bearing hepatitis B virus.

An important issue in liver transplantation for HCC is the time a waiting a suitable graft. Some studies have reported that waiting time represents an important prog-

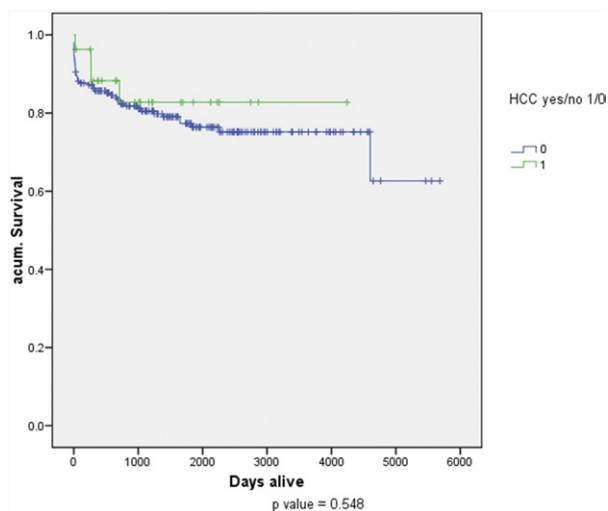


Fig 2. Overall survival for transplanted patients according to diagnosis: hepatocellular carcinoma (HCC) versus other diagnosis.

nostic factor for survival.^{10,11} In the present study, the mean waiting time was 12 months. Llovet et al¹² reported that 23% of waiting patients dropped out of the list during the first 6 months owing to tumor progression. In Chile there is a shortage of donors, so waiting times are prolonged, exceeding the 6 months recommended for transplantation in HCC. Therefore, most patients in the present series underwent one or more pretransplant bridge therapies.

Liver transplantation is an effective option for HCC patients meeting the Milan criteria. Several published reports have shown 3-year disease-free survival rates of 70%.^{13,14} In the present series, the 3-year survival for patients transplanted for HCC was >80%. Nevertheless, one should consider that in a significant percentage of our patients, the diagnosis of HCC was made as an incidental finding in the explanted liver biopsy; liver damage was the indication for the transplantation.

The time between the last imaging and transplantation was >6 months in some cases, because they were referred from other centers where there were no resources for frequent imaging tests. This fact may explain the high number of cases who were outside the Milan criteria in this series (34%). Although their survival was lower than that of candidates meeting the Milan criteria, the 66% 5-year survival rate remains significant.

In conclusion, this study yielded results consistent with the available literature showing that liver transplantation is the best therapy for HCC with remarkable long-term survival among cases that meet the Milan criteria.

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