

Liver transplantation for hepatocellular carcinoma: the Baylor experience

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Abstract

Background Liver transplantation (LTX) is indicated in selected patients with hepatocellular carcinoma (HCC) and cirrhosis.

Methods We compared the outcome of LTX for patients with and without HCC in 5-year time periods between 1987 and 2007 to reflect the implementation of the Milan tumor selection criteria in 1997 and of the model for end-stage liver disease (MELD) score-based liver allocation in 2002.

Results Of 2350 patients who underwent primary LTX, 330 had HCC. Five-year patient survival for HCC patients was 28.6% in 1987–1992 and 42.3% in 1992–1997, which was 41.4–31.4% lower than that in non-HCC patients ($P < 0.0001$). After 1997, 5-year survival was 76% for HCC patients, similar to the survival for non-HCC patients ($P = 0.8784$). Five-year tumor recurrence dropped from 52.9% (1987–1992) and 48.2% (1992–1997) to 11.4% (1997–2002) and 8.4% (2002–2007) ($P < 0.0001$). Multi-variate analysis for tumor recurrence showed the following significant factors: tumor size >6 cm [hazard ratio (HR) 3.67], ≥ 5 nodules (HR 3.441), vascular invasion (HR 3.18), transplant in 1987–1992 (HR 6.772), and transplant in 1992–1997 (HR 3.059). MELD-based liver allocation reduced median waiting time for LTX for HCC versus non-HCC (35 vs. 111 days; $P = 0.005$) without compromise in patient outcome.

Conclusions The results of LTX for HCC continue to improve and are equal to results in patients without HCC.

Keywords Hepatocellular carcinoma · Survival · Liver transplantation · Outcome

Introduction

Liver transplantation is a well-established treatment modality for hepatocellular carcinoma (HCC) in a selected group of patients with cirrhosis of the liver. With the refinement of the tumor inclusion criteria for transplant, the overall success rate with liver transplantation for patients with HCC has improved over time. With success comes the question of whether we may be too restrictive with our inclusion criteria, thus restricting access to transplantation for patients who might be cured of their malignancy. The utility of a liver biopsy prior to transplantation in order to determine tumor differentiation is still under debate, and the optimal treatment regimen before liver transplantation is yet to be defined. This article describes the trends of development of liver transplantation for HCC at Baylor University Medical Center in Dallas, Texas, USA.

Methods

The present analysis includes patients who underwent primary liver transplantation at Baylor University Medical Center at Dallas between 1 March 1987 and 1 March 2007. Five-year periods during this timeframe were chosen to correspond with the implementation of the Milan tumor selection criteria in 1997 and the implementation of the model for end-stage liver disease (MELD) score-based liver allocation in 2002.

Three hundred thirty patients who underwent primary liver transplantation were found to have HCC in the liver

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explant by pathological examination. During the same time period, 2020 adult patients transplanted the first time did not have HCC. Retransplantation was not attempted in patients with recurrent HCC, and HCC was not observed in patients who underwent retransplantation.

Patient data were collected prospectively and entered into a clinical database. The database is audited routinely for data accuracy, and data entry is ongoing, which explains why part of the data is incomplete, especially for the 2002–2007 era. The current study is an analysis from the database.

Tumor pathology was defined by dedicated liver pathologists. Tumor size was entered as the largest tumor diameter. Edmondson tumor grading was used, with grade I indicating well-differentiated tumors; grade II, moderate differentiation; grade III, poor differentiation; and grade IV, undifferentiated tumors. The presence of vascular invasion was recorded whenever it was found on a micro or macro level.

Statistical data analysis included Fisher's exact test for nonparametric values and the Wilcoxon two-sample test for numeric values. Patient survival, recurrence-free survival, and tumor recurrence rates were estimated using the Kaplan–Meier method.

A Cox multivariate analysis was performed using tumor recurrence as the outcome. Factors studied included age, gender, maximum tumor diameter, number of tumor nodules, vascular invasion, alpha-fetoprotein (AFP), transplant period (1987–1992, 1992–1997, 1997–2002, 2002–2007),

tumor ablation treatment, waiting time, and liver disease etiology of hepatitis B and hepatitis C. Statistical significance was established at P values <0.05 . Analysis was performed using SAS software version 9.1.3. (SAS Institute, Cary, North Carolina, USA).

Results

Of the 2350 patients studied, 330 had HCC. Patient characteristics are shown in Table 1. A higher proportion of HCC than non-HCC patients were male (76.3 vs. 54.9%, $P < 0.0001$). The distribution by race and ethnicity shows the high number of Asians ($P < 0.0001$) and Hispanics ($P = 0.0125$) in the HCC group.

The leading underlying liver diseases were hepatitis C and B in the HCC patients (70.9%). Hepatitis B or C was found in only 38.3% of the non-HCC patients ($P < 0.0001$). The median age at transplant was 54 years in the HCC patients and 49 in the non-HCC patients ($P < 0.0001$).

The proportion of patients who underwent liver transplantation and had HCC increased abruptly from 9 to 9.7% of all primary transplants between 1997 and February 2002 to 26.2% starting in March 2002 ($P < 0.0001$). Out of the 330 patients with HCC, 42 were transplanted between 1987 and 1992, 59 between 1992 and 1997, 58 between 1997 and 2002, and 171 between March 2002 and March 2007 (Table 1).

Table 1 Demographics and disease characteristics for patients with and without HCC

Parameter	Description	<i>N</i>	HCC	Non-HCC	<i>P</i> value
Overall	Total population	2350	330	2020	
Age (years)	Mean	2350	53.5 $\pm$ 8.88	48.69 $\pm$ 10.68	<0.0001
	Median		54	49	
Gender	Male	1360	252 (76.4%)	1108 (54.9%)	<0.0001
	Female	990	78 (23.6%)	912 (45.2%)	
Race	Caucasian	2085	276 (83.9%)	1809 (89.6%)	<0.0001
	Black	179	24 (7.3%)	155 (7.7%)	
	Asian	56	24 (7.3%)	32 (1.6%)	
	Other	29	5 (1.5%)	24 (1.1%)	
Ethnicity	Hispanic	287	46 (16.8%)	241 (15.6%)	0.0125
Etiology	Hepatitis C	872	196 (59.4%)	676 (33.5%)	<0.0001
	Hepatitis B	135	38 (11.5%)	97 (4.8%)	
	Other	1343	96 (29.1%)	1247 (63.7%)	
MELD	Calculated score	2311	13	17	
Transplant period	3/1987–2/1992	468	42 (9.0%)	426 (91.0%)	<0.0001
	3/1992–2/1997	633	59 (9.3%)	574 (90.7%)	
	3/1997–2/2002	597	58 (9.7%)	539 (90.3%)	
	3/2002–2/2007	652	171 (26.2%)	481 (73.8%)	

HCC hepatocellular carcinoma,
MELD model for end-stage liver disease

Table 2 Tumor characteristics across eras

Parameter	Detail	<i>N</i>	1987–1992	1992–1997	1997–2002	2002–2007	<i>P</i> value
Number of nodules	1	172	24 (58.5%)	22 (39.3%)	31 (53.5%)	95 (65.5%)	0.0001
	2	57	5 (12.2%)	16 (28.6%)	10 (17.2%)	26 (17.9%)	
	3	26	1 (2.4%)	4 (7.1%)	7 (12.1%)	14 (9.7%)	
	4	6	0	0	2 (3.4%)	4 (2.8%)	
	≥5	39	11 (26.8%)	14 (25%)	8 (13.8%)	6 (4.1%)	
Maximum tumor size (cm)	0.0–2	100	6 (14.3%)	14 (23.7%)	26 (45.6%)	54 (37%)	<0.0001
	2.1–4	127	10 (23.8%)	22 (37.3%)	21 (36.8%)	74 (50.7%)	
	4.1–6	42	8 (19%)	11 (18.6%)	9 (15.8%)	14 (9.6%)	
	>6	35	18 (42.9%)	12 (20.4%)	1 (1.8%)	4 (2.7%)	
Edmondson tumor grade	I	71	14 (43.8%)	24 (45.3%)	15 (31.2%)	18 (15.8%)	<0.0001
	II	99	10 (31.2%)	22 (41.5%)	21 (43.8%)	46 (40.3%)	
	III	70	5 (15.6%)	7 (13.2%)	10 (20.8%)	48 (42.1%)	
	IV	7	3 (9.4%)	0	2 (4.2%)	2 (1.8%)	
Vascular invasion		50	10 (23.8%)	19 (32.2%)	5 (8.8%)	16 (11.3%)	0.001
Bilobar tumors		64	14 (33.3%)	21 (35.6%)	5 (8.9%)	24 (16.9%)	0.0006
AFP ≥400 IU/mL		39	13 (35.1%)	17 (28.8%)	0	9 (6.5%)	<0.0001
TACE/RFA		119	0	3 (9.7%)	29 (80.6%)	87 (71.9%)	<0.0001

AFP alpha-fetoprotein, TACE/RFA transarterial chemoembolization/radiofrequency ablation

Most tumors were diagnosed before transplantation. The proportion of incidental tumors was 21.4% in 1987–1992, 42.4% in 1992–1997, 36.2% in 1997–2002, and 12.7% in 2002–2007 ($P < 0.0001$).

Evolution of tumor characteristics

The trends in tumor characteristics over time are shown in Table 2. In terms of tumor nodules, 172 of 300 patients had 1 tumor (57.3%), 57 had 2 (19%), 26 had 3 (8.7%), 6 had 4 (2%), and 39 had ≥5 tumors (13%). The proportion of single tumors increased from 58.5% in 1987–1992 to 65.5% in 2002–2007, while the proportion of patients with ≥5 tumors decreased from 26.8 to 4.1% ($P < 0.0001$). At the same time, the proportion of tumors <2 cm in diameter increased from 14.3 to 37%, with a concomitant decrease in tumors >6 cm from 42.9 to 2.7% ($P < 0.0001$).

Microscopic tumor grading showed a decline in the proportion of well-differentiated tumors, from 43.8% in 1987–1992 to 15.8% in 2002–2007 ($P < 0.0001$). However, data entry in the latter group is ongoing, and data are missing on 57 patients. Vascular invasion was found in 23.8% of patients in 1987–1992 and in 32.2% in 1992–1997; it declined to 8.9% in 1997–2002 and 11.3% in 2002–2007 ($P = 0.0010$).

Serum AFP was ≥400 IU/mL in 35.1% of patients transplanted in 1987–1992, 28.8% in 1992–1997, and only 6.5% in 2002–2007 ($P < 0.0001$).

Neoadjuvant treatment

Neoadjuvant treatment was applied differently across eras. While none of the patients received neoadjuvant treatment before 1992 and only 3 (9.7%) received neoadjuvant treatment between 1992 and 1997, the proportion was 80.6% in 1997–2002 and 71.9% after 2002 ($P < 0.0001$). Treatment included transarterial chemoembolization in 64 patients and radiofrequency ablation in 55 patients.

Adjuvant therapy

Intraoperative chemotherapy was given in 87.9% of the patients transplanted before 1992 with tumors known before transplantation. The proportion declined to 85.3% in 1992–1997 and 70.3% in 1997–2002. It was 86.1% after 2002 ($P = 0.1583$).

Postoperative chemotherapy was administered in 81% of the patients before 1992. The proportion decreased to 78% in 1992–1997 and further to 62.1% in 1997–2002 and 54.5% after 2002 ($P = 0.0008$).

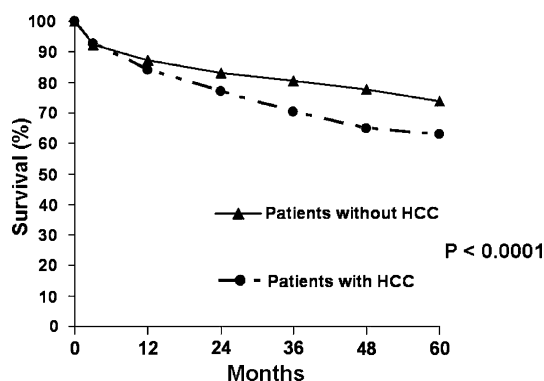
Waiting time to transplant

The overall median waiting time to transplant was 59 days for patients with HCC (mean = 1135.1 days) compared with 98 days for non-HCC patients (mean = 1169.3 days) ($P = 0.3954$). The waiting time was similar for HCC and non-HCC patients across eras, except for patients

Table 3 Waiting time to transplant across eras

Time period	HCC	N	Waiting time (days)			P value
			Median	Mean	Range	
1987–1992	Yes	40	10	192.4	0–72	0.0795
	No	413	13	230.4	0–176	
1992–1997	Yes	59	145	334.7	2–402	0.4077
	No	572	127	314.1	0–1413	
1997–2002	Yes	57	275	330.1	2–882	0.1386
	No	538	236.5	294.6	0–2752	
2002–2007	Yes	169	35	290.1	0–2344	0.005
	No	480	111	337.3	0–3914	

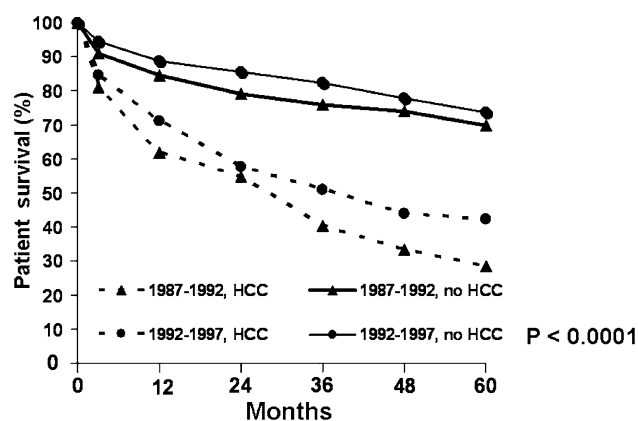
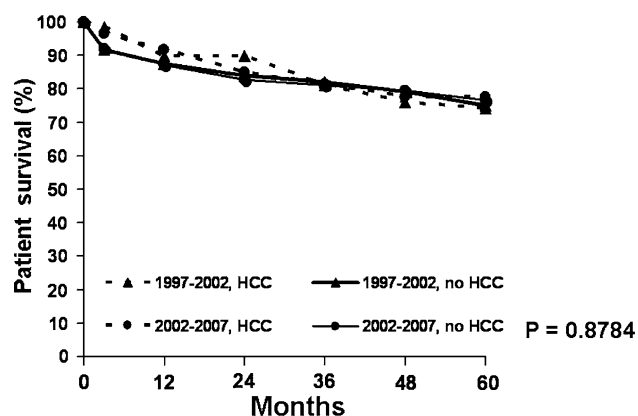
HCC hepatocellular carcinoma

**Fig. 1** Overall Kaplan–Meier patient survival. HCC hepatocellular carcinoma

transplanted after implementation of the MELD score-based allocation in 2002, when the median waiting time of patients with HCC was significantly shorter, at 35 days (mean = 290.1 days), compared with 111 days for non-HCC patients (mean = 337.3 days) ($P = 0.005$) (Table 3).

Patient survival posttransplant

Overall Kaplan–Meier survival (Fig. 1) was lower in HCC patients than in non-HCC patients ($P < 0.0001$). Patients with HCC had a survival of 83.9% at 1 year and 63% at 5 years and a median survival of 97.6 months, compared with 87.1% at 1 year and 73.8% at 5 years and a median survival of 144.7 months in non-HCC patients. However, the survival of patients with HCC was markedly inferior to that of non-HCC patients by almost 30% at 5 years in patients transplanted before 1997 (Fig. 2) ($P < 0.0001$). Survival was 61.9% at 1 year and 28.6% at 5 years for HCC patients transplanted in 1987–1992, compared with 84.7 and 70%, respectively, for non-HCC patients during the same time period. In 1992–1997, 1-year patient survival for HCC patients was 71.2% and 5-year survival was

**Fig. 2** Kaplan–Meier patient survival for patients transplanted before March 1997**Fig. 3** Kaplan–Meier patient survival for patients transplanted from March 1997

42.3%, compared with 88.6 and 73.7%, respectively, in non-HCC patients.

Patient survival curves were similar between patients with HCC and patients without HCC starting in 1997 (Fig. 3): the Kaplan–Meier patient survival was 91.3% at 1 year and 76% at 5 years for HCC patients; it was 87.3% at 1 year and 75.5% at 5 years in patients without HCC ($P = 0.8784$).

The Kaplan–Meier survival of patients who were alive at 1 year after transplant also showed inferior results: this group of patients with HCC had a 5-year survival of 75.1%, and the non-HCC patients had a 5-year survival of 84.7% ($P < 0.0001$) (Fig. 4). Again, when comparing different transplant eras, the survival difference was 24–36% lower in HCC patients before 1997. There was no survival difference between HCC and non-HCC patients in transplants performed after 1997: the 5-year survival was 83.3% for HCC patients and 86.5% for non-HCC patients ($P = 0.2163$).

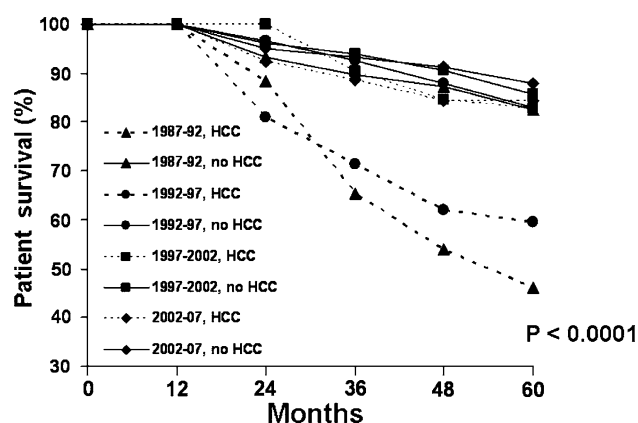


Fig. 4 Kaplan–Meier survival of patients who were alive 1 year after transplant

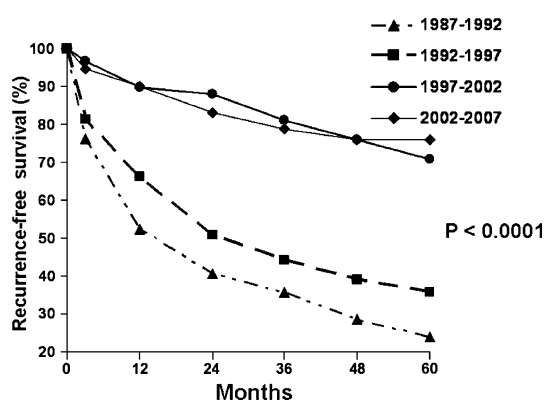


Fig. 5 Kaplan–Meier tumor recurrence-free survival

Recurrence-free survival

The Kaplan–Meier tumor recurrence-free survival also improved over time (Fig. 5), from 52.4% at 1 year and only 23.8% at 5 years in patients transplanted before 1992 to 66.1 and 35.6%, respectively, in 1992–1997; the tumor recurrence-free survival markedly increased to 87.7% at 1 year and 70.7% at 5 years in 1997–2002, and further to 90.1 and 75.8%, respectively, in 2002–2007 ($P < 0.0001$).

Tumor recurrence rate

The overall Kaplan–Meier tumor recurrence rate was 9.1% at 1 year, 14.3% at 2 years, 17.4% at 3 years, and 21.3% at 5 years. However, the tumor recurrence rate was higher in patients transplanted in the first 10 years (1987–1997) than thereafter (1997–2007) (Fig. 6). The Kaplan–Meier tumor recurrence rate was 26% at 1 year and 52.9% at 5 years for patients transplanted in 1987–1992; it was 19.7 and 48.2% at 1 and 5 years, respectively, in 1992–1997; and it dropped sharply to 3.5 and 11.4% in 1997–2002 and to 4.2 and 8.4% in 2002–2007 ($P < 0.0001$). The difference in tumor

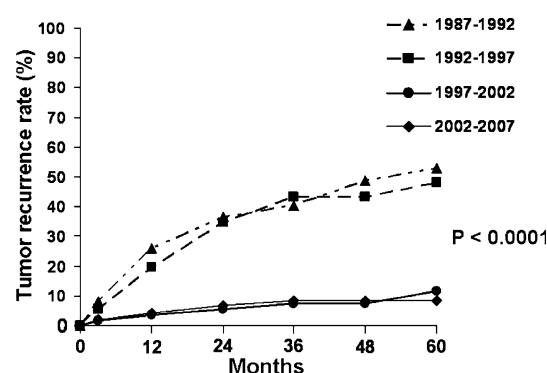


Fig. 6 Kaplan–Meier tumor recurrence rate

recurrence rates between 1997–2002 and 2002–2007 was not statistically significant ($P = 0.7273$).

Multivariate analysis

The results of the multivariate analysis for risk factors for tumor recurrence (censored for death) are shown in Table 4. The following were found to be significant risk factors for tumor recurrence: maximum tumor size >6 cm, with a hazard ratio (HR) of 3.67 ($P = 0.0005$), ≥ 5 tumor nodules (HR 3.441, $P = 0.0004$), vascular invasion (HR 3.181, $P = 0.0012$), transplant in 1987–1992 (HR 6.772, $P = 0.004$), and transplant in 1992–1997 (HR 3.059, $P = 0.0496$). Age >60 , gender, AFP ≥ 400 IU/mL tumor grade, preoperative ablation, waiting time >90 days, hepatitis B and/or C as underlying etiology, and transplant in 1997–2002 were not found to be significant contributing factors.

As we restricted the multivariate analysis to patients transplanted in 1997–2007 only, the only factor found to be significant was ≥ 5 tumor nodules (HR 8.751, $P = 0.003$), while tumor size and the presence of vascular invasion did not reach statistical significance (Table 4).

Discussion

Liver transplantation has become a legitimate treatment for HCC in cirrhotic patients [1–5]. The evolution of the outcomes in our program parallels the trends witnessed worldwide. The initial results with liver transplantation were quite poor [4, 6–12], with tumors recurring in more than half of the patients within 5 years of transplant. This was indeed dismal, as there is no effective treatment for recurrent HCC after transplant. The patient survival was less than 30% at 5 years. Even when eliminating early mortality, which is mainly caused by factors unrelated to HCC, initial survival rates were poor in HCC patients compared with non-HCC patients. The United States

Table 4 Multivariate analysis for risk factors for tumor recurrence in HCC patients who received liver transplants

Variable	1987–2007			2002–2007 only		
	HR	95% CI	<i>P</i> value	HR	95% CI	<i>P</i> value
Age > 60 years	1.386	0.68–2.81	0.3645	0.274	0.05–1.40	0.1202
Male gender	1.251	0.61–2.58	0.5456	0.613	0.15–2.49	0.4939
Tumor >6 cm	3.670	1.76–7.65	0.0005	4.081	0.39–42.50	0.2394
≥5 tumors	3.441	1.74–6.82	0.0004	8.751	2.09–36.68	0.0030
Vascular invasion	3.181	1.58–6.42	0.0012	3.105	0.85–11.32	0.0860
AFP ≥400 IU/mL	1.254	0.58–2.70	0.5618	1.057	0.11–10.42	0.9619
Well-differentiated tumor	0.988	0.49–1.98	0.9729	1.161	0.26–5.10	0.8435
Pretransplant ablation	0.718	0.29–1.76	0.4691	0.486	0.14–1.66	0.2495
LTX 3/1987–2/1992 ^a	6.772	1.84–24.95	0.0040	NA	NA	NA
LTX 3/1992–2/1997 ^a	3.059	1.00–9.34	0.0496	NA	NA	NA
LTX 3/1997–2/2002 ^a	1.110	0.38–3.25	0.8490	0.630	0.17–2.32	0.4866
Waiting time >90 days	0.694	0.34–1.40	0.3072	1.436	0.40–5.10	0.5755
Hepatitis B	1.235	0.51–3.00	0.6411	4.292	0.92–20.11	0.0645
Hepatitis C	1.618	0.77–3.41	0.2052	0.852	0.22–3.34	0.8186

Statistically significant results are in bold

HR hazard ratio, CI confidence interval, AFP alpha-fetoprotein, LTX liver transplantation, NA not applicable

^a 3/2002–2/2007 period; hazard ratio of 1

Department of Health and Human Services did not recognize HCC as a valid indication for liver transplantation until 2001 [12]. The acceptance came with the major improvement in the results, as shown by better patient survival and lower recurrence rates over time [13–15].

Our study shows a dramatic improvement in patient survival and tumor recurrence-free survival, as well as a reduction in the HCC tumor recurrence rate, starting in 1997. The patient survival rate equaled that of non-HCC patients starting in 1997, and the early tumor recurrence rate (before 1 year posttransplant) dropped from 26 to 4%, reinforcing the idea that transplantation for HCC is a justified use of a scarce resource, the donor livers.

The major improvement in results coincided with the implementation of the Milan tumor selection criteria [16, 17]. The adoption of the Milan criteria is considered to improve survival by selecting patients with lower tumor burdens and thus better tumor differentiation and better tumor biology [16]. Paradoxically, in our study there was a lower proportion of well-differentiated tumors in patients transplanted in the latter years than before 1997. This should theoretically have resulted in worse outcomes. However, at the same time, there was a decrease in incidental tumors, due to improved pretransplant HCC screening and improvements in imaging [17, 18], as well as the introduction of neoadjuvant treatments for known tumors.

A multivariate analysis of all the patients for factors contributing to tumor recurrence showed tumor size >6 cm, ≥5 tumor nodules, vascular invasion, and

transplant in the earlier eras as significant factors. Neoadjuvant treatments were not a protective factor for tumor recurrence, as reported before [19]. We deliberately chose tumor recurrence as the outcome for the multivariate analysis, rather than patient survival, in order to avoid as much as possible factors not related to HCC that can influence posttransplant survival. Indeed, tumor size, number of nodules [20–25], poor tumor differentiation [23, 24, 26–30], and vascular invasion [8, 24, 31–37] are associated with poor patient survival, as previously reported. Tumor differentiation was not a significant risk factor for tumor recurrence in our study. Interestingly, when analyzing only the group of patients transplanted after 1997, only the number of tumor nodules (≥5) was a significant factor contributing to tumor recurrence, while vascular invasion and tumors >6 cm lost significance (vascular invasion was close to being a significant factor). However, before 1997 tumors >6 cm included much larger lesions than those included with the implementation of the Milan criteria (data not shown). Pretransplant ablation reduced the risk of tumor recurrence by half in 2002–2007, though this was statistically not significant.

The introduction of the MELD score-based allocation of donor livers for transplantation resulted in improved access for transplantation for patients with HCC. As seen elsewhere, the waiting time from listing to transplantation was significantly shorter in patients with HCC when compared with non-HCC patients in the MELD-based allocation [38, 39]. This resulted in an increase in the proportion of the patients transplanted for HCC [38], without altering the

overall survival posttransplant [40]. On the other hand, there was no improvement in either posttransplant survival or recurrence rate with shorter waiting times. We did not find a shorter waiting time (<90 days) to be a protective factor for posttransplant tumor recurrence.

Of note, this is an ongoing, prospective research database. Thus, data entry is ongoing, with some of the data entries missing, especially for patients transplanted after 2002. Nevertheless, the volume of data was adequate to enable analysis.

In conclusion, the results of liver transplantation for HCC continue to improve and are equal to those obtained in patients without HCC, with concomitant improvement in the access of HCC patients to transplantation. Further studies are necessary to evaluate neoadjuvant treatment options in the context of expansion of the tumor acceptance criteria.

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