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ORIGINAL ARTICLE

Predictors of long-term outcome following liver transplantation for hepatocellular carcinoma: a single-center experience

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Summary

Orthotopic liver transplantation (OLT) is increasingly being applied for cure in patients with cirrhosis and concomitant hepatocellular carcinoma (HCC). In recipients with limited tumor burden, OLT achieves reasonable long-term outcome. This study sought to identify clinical and pathologic variables predictive of long-term disease-free survival and the presence of vascular invasion. From 1992 to 2006, 130 patients underwent OLT for cirrhosis and HCC. Malignancy was diagnosed in 107 patients prior to OLT and in 23 patients on pathologic examination of the explant. Nine clinical and pathologic variables were considered including: TNM stage, nodularity, vascular invasion, Milan criteria, incidental lesion, differentiation, tumor size, preOLT transarterial chemoembolization (TACE), and administration of sirolimus-based immunosuppression. The overall incidence of HCC recurrence was 17% with the majority (82%) being stage III. Cumulatively, tumor recurrence-free survival (RFS) is 84, 74, and 67% at 1, 3, and 5 years respectively. Independent predictors of RFS included stage III and poorly differentiated lesions ($P < 0.05$). Furthermore, stage III tumors and those >3.5 cm in size were predictive of vascular invasion. Importantly, preOLT, TACE and postOLT sirolimus had no influence on survival. Pathologic variables including tumor stage and grade have a significant impact on outcome. Importantly, it seems that TACE and sirolimus had no beneficial effect.

Introduction

Orthotopic liver transplantation (OLT) is increasingly becoming a viable treatment strategy for patients with end-stage liver disease and concomitant hepatocellular carcinoma (HCC). While the incidence of HCC has nearly doubled in the last two decades [1], initial experience with OLT for malignancy was dismal [2,3]. However, changes in recipient selection criteria, reserving OLT for patients with limited tumor burden, have dramatically improved long-term outcome [4]. With the universal application of the model for end-stage liver disease (MELD) system for organ allocation in the United States, patients with HCC have been given increased priority on the waiting list for cadaveric organs [5]. With an adjusted MELD score exclusively for patients with HCC, time to transplantation is dramatically reduced [6].

Cancer recurrence following OLT for HCC is a formidable problem for approximately 20% of patients despite careful preoperative staging and strict patients selection [7]. As such, several tumor-specific variables, including size, grade, and the presence of vascular invasion may predict long-term outcome [8–10]. However, the influence of clinical interventions including transarterial chemoembolization (TACE) and sirolimus-based immunosuppression on HCC recurrence is controversial [11,12]. The current study attempts to identify both clinical and pathologic variables associated with prolonged patient survival, and

determine the incidence of HCC recurrence, following transplantation in this single center selected patient population.

Methods

From 1992 to 2006, 142 patients underwent OLT for end-stage liver disease and concomitant HCC at the University of Colorado Health Sciences Center (UCHSC). Of those, 130 patients with complete records were included in this study. A retrospective review was conducted to identify clinical and pathologic variables associated with long-term survival. Sources of data for the patients in this study included the University of Colorado Transplant Database and patients medical records. This work was approved by the UCHSC Institutional Review Board.

Diagnosis and evaluation

Preoperative diagnosis of all patients included a history and physical exam, laboratory studies, and abdominal ultrasound. Preoperative diagnosis of HCC was based on abdominal computed tomography (CT) or magnetic resonance imaging (MRI) of the abdomen. We do not routinely perform biopsies for diagnosis. Extrahepatic metastasis was excluded based on abdominal/chest CT, MRI, and bone scintigraphy prior to OLT. Final diagnosis of HCC was made by pathological examination of the explanted liver. Patients who demonstrated extrahepatic metastasis, lymph node involvement, or vascular invasion of the portal vein, hepatic vein, or vena cava identified by CT or MRI, were not considered for transplant. Recurrence of HCC was identified using CT, MRI, positron emission tomography, and routine chest X-ray.

Immunosuppression

Both cadaveric (CAD) and living donor liver transplant (LDLT) were performed using standard techniques [13,14]. Initial maintenance immunosuppression consisted of a triple-drug regimen including cyclosporin, azathioprine and prednisone ($n = 3$) (Table 1). In 1994, this regimen was switched to tacrolimus, mycophenolate mofetil (MMF), and prednisone ($n = 78$). Steroids were administered with 1 g of methylprednisolone intravenously on the day of transplantation and were tapered to 20 mg/day over 3 days. Oral prednisone was started on day 3 (20 mg/day) and tapered over 2 months. Beginning in January of 2000 until July of 2002, a subgroup of patients received sirolimus ($n = 49$) as either primary immunosuppression, in addition to calcineurin inhibitors (CNI), or were converted to sirolimus secondary to CNI toxicity within 6 months of OLT. All patients receiving sirolimus (2 mg/day) as primary immunosuppression postOLT were given three doses of steroids: 1 gm on the day of surgery, 500 mg on postoperative days 2 and 3. With the exception of patients with autoimmune disease, all steroids were discontinued in the sirolimus group on postoperative day 4. Patients receiving sirolimus did not receive MMF.

Table 1. Immunosuppression regimens.

Regimen	No. of patients	Year
CSA + AZA + prednisone	3	1992–1994
TAC + MMF + 3 day steroid taper	78	1995–2006
Sirolimus + CNI + 3 day steroid taper	29	2000–2001
Sirolimus conversion ± CNI	20	2000–2006

CSA, cyclosporin; AZA, azathioprine; TAC, tacrolimus; MMF, mycophenolate mofetil; CNI, calcineurin inhibitors.

Histopathology

Explanted livers included in this study were serially sectioned and examined by an experienced pathologist. Anatomic location, tumor size by maximum diameter of each lesion, tumor number, distribution (unilobar/bilobar), and presence of gross and/or microscopic vascular invasion were documented. Any suspicious or enlarged lymph nodes were also sectioned and evaluated for metastatic disease. Tumors were graded by the degree of differentiation as follows: well-differentiated (grade 1); moderately differentiated (grade 2); poorly differentiated (grade 3) or necrotic [15]. Tumor stage was determined by the revised pTNM classification [16].

Statistical analysis

Survival analysis was performed using the Kaplan–Meier method. Group survival curves were compared using the log-rank test for nonparametric data. Overall, nine clinical and pathologic variables were simultaneously analyzed for independent significance using a multivariate Cox proportional hazard model. A logistic regression model was used to control for covariates when vascular invasion was used as the primary outcome. The pathologic variables considered were as follows: presence of vascular invasion, TNM stage, nodularity (solitary/multinodular), within Milan criteria by explant, incidental tumor, differentiation (well, moderate, poor, necrotic), tumor size by explant. The clinical parameters considered included preOLT TACE and the administration of sirolimus. While there is no statistical difference in long-term outcome between patients treated with sirolimus as a primary immunosuppression regimen and those converted secondary to CNI

toxicity, they are considered together. A *P*-value of ≤0.05 was considered significant. Primary end-points were overall survival, tumor recurrence-free survival (RFS), and presence of vascular invasion. In addition, the largest tumor diameter (cm) was compared by grade via Student's *t*-test.

Results

Histopathology of liver explants

The majority of patients in this cohort had pathologically well-differentiated tumors (46%). Forty-five patients had moderately differentiated lesions, and eight patients had tumors which were poorly differentiated. Sixteen tumors were necrotic and not able to be evaluated secondary to preOLT ablative therapy. Interestingly, over half of these patients were considered stage I ($n = 70$), with 23 lesions being incidental at pathologic evaluation. Thirty-four patients were stage II. Twenty-six patients were stage III and no patients were transplanted with stage IV disease. Vascular invasion was identified in 18% of explanted livers. The majority of tumors were solitary ($n = 88$). Preoperative Child's Classification was also determined with 45 patients as Child's C.

Recipient characteristics and survival analysis

This study included 111 males and 19 females with cirrhosis and concomitant HCC (Table 2). Mean recipient age was 52 ± 7.5 years (range 36–68). Mean follow-up postOLT was 34 months (median follow-up 26.5 months). While 112 patients were transplanted via CAD donors, 18 recipients underwent transplant from a living donor (LDLT). Not surprisingly, the majority of patients had hepatitis C ($n = 75$) as the primary diagnosis. Seventeen patients suffered from both hepatitis C and alcoholism (ETOH). Additional diagnosis included hepatitis B ($n = 16$), ETOH ($n = 10$), autoimmune hepatitis ($n = 4$), cryptogenic cirrhosis ($n = 4$), hemochromatosis ($n = 2$), nonalcoholic steatohepatitis ($n = 1$), and primary sclerosing cholangitis ($n = 1$). The overall survival rates for this cohort were 88, 75, and 68% at 1, 3, and 5 years, respectively. Tumor RFS rates were 84, 74, and 67% at 1, 3, and 5 years, respectively (Fig. 1a).

Recurrence of HCC occurred in 17 patients (13%) following OLT. Currently, two patients with cancer recurrence remain alive with lung metastasis. The remaining 15 patients are dead. Of these, 12 died as a direct result of cancer recurrence, while three died from other causes including myocardial infarction [1] and stroke [2]. Anatomic sites of tumor recurrence included the liver allograft [8], the lungs [5], the brain [3], and the omentum [1]. Cumulatively, 14 of 17 (82%) recurrences were stage III by explant, with only two patients at stage I and one patient stage II. Interestingly, 11 of 112 CAD recipients

Table 2. Patient and tumor characteristics ($n = 130$).

Age	57.8 (±8.3) range: 40–68
Sex	
M	111
F	19
Stage	
I	70
II	34
III	26
Differentiation	
Well	60
Moderate	45
Poor	8
Necrotic	16
Vascular invasion	24/130
Nodularity	
Solitary	88
Multifocal	42
Milan criteria	
Yes	96
No	34
HCC recurrence	17/130 (13%)
Graft type	
CAD	112
LDLT	18
PreOLT TACE	51/130 (39%)
PostOLT Sirolimus	49/130 (37.7%)

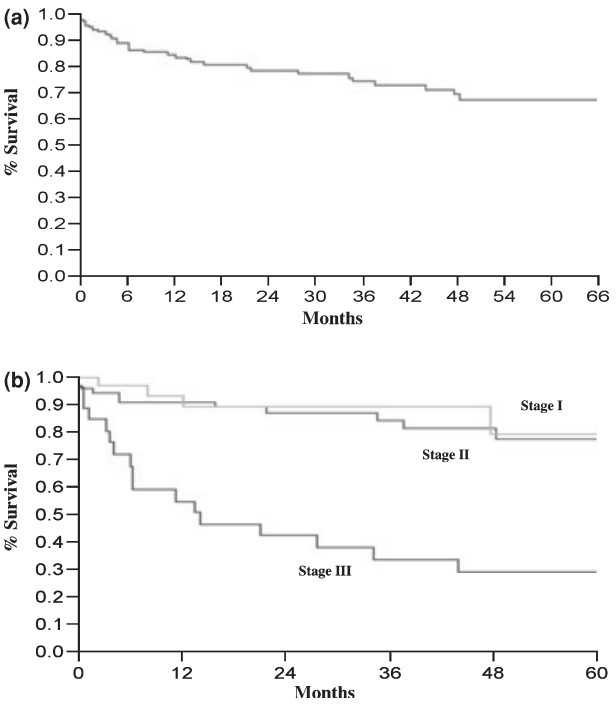

Figure 1 Tumor recurrence-free survival overall (a), and by stage (b).

(9.8%) suffered cancer recurrence compared with six of 18 LDLT recipients (33%). However, these differences were not statistically significant. Not surprisingly, five of six LDLT explants were stage III.

With regard to the patients receiving sirolimus therapy ($n = 49$), only three patients suffered an HCC recurrence. Among these three patients, all had stage III lesions. The average time from initiation sirolimus therapy to tumor recurrence was 12.2 months. Fifty-one patients underwent TACE prior to OLT for purpose of providing a bridge to transplant. As such, four patients with tumors measuring 5 cm underwent repeat TACE. Time on the waiting list for the cohort as a whole is 420 days. Patients undergoing TACE were on the waiting list for an average of 395 days. Conversely, patients not treated with TACE were on the list for an average of 434 days. Importantly, these differences were not significant.

Predictors of overall patient survival

Univariate analysis revealed that stage III tumors by liver explant are significantly associated with higher mortality compared with either stage I or II ($P = 0.0002$). Furthermore, poorly differentiated tumors ($P < 0.0001$), as well as the presence of vascular invasion ($P < 0.0001$), and tumor size >3.5 cm ($P = 0.004$) had a negative impact on survival. Conversely, tumor burden within the Milan criteria by explant had a positive impact on overall survival ($P = 0.0075$). Nodularity, preOLT TACE, incidental lesions, and postOLT sirolimus therapy were not significant. Multivariate analysis revealed that stage III and poorly differentiated tumors were independent predictors of survival following transplantation ($P < 0.05$).

HCC recurrence-free survival

By univariate analysis, stage III tumors were strongly associated with a lower disease-free survival ($P < 0.0001$, Table 3). Five-year RFS survival for recipients with stage III tumors is 29%, vs. 79 and 77% for stage I and II, respectively (Fig. 1b). Similarly, poorly differentiated tumors ($P < 0.0001$), the presence of vascular invasion ($P < 0.0001$), beyond the Milan criteria by explant ($P = 0.007$), and tumor size >3.5 cm ($P = 0.0018$) were also associated with lower disease-free survival. Five-year RFS for recipients with poorly differentiated lesions is 14%, compared with 79% in those with well-differentiated pathology (Fig. 2a). Patients with vascular invasion by explant have a 35% 5-year survival vs. 75% in those that do not (Fig. 2b). Nodularity, preOLT TACE, incidental lesions, postOLT sirolimus therapy were not significant. Multivariate analysis revealed stage III and poorly differentiated tumors were independent predictors of HCC disease-free survival following OLT (Table 4). Interestingly, comparing tumor size (cm) by grade, poorly differentiated lesions were significantly larger (mean = 8.3 cm)

Table 3. Univariate analysis of factors affecting HCC recurrence-free survival.

Variables	Hazard ratio	95% confidence interval	*P*-value
Stage III	5.05	2.43–10.51	**<0.0001**
Vascular invasion	4.74	2.39–9.39	**<0.0001**
Milan criteria (no.)	3.25	1.65–6.40	**0.0007**
Poorly differentiated	8.53	3.02–24.08	**<0.0001**
Tumor Size (>3.5 cm)	3.07	1.27–16.89	**0.0018**
TACE	0.55	0.26–1.19	0.13
Sirolimus	0.53	0.25–1.11	0.93
Multifocal	1.17	0.56–2.42	0.68
Incidental tumor	0.58	0.22–1.52	0.27

HCC, concomitant hepatocellular carcinoma; TACE, transarterial chemoembolization. Bold figures are the factors maintaining statistical significance ($P < 0.05$).

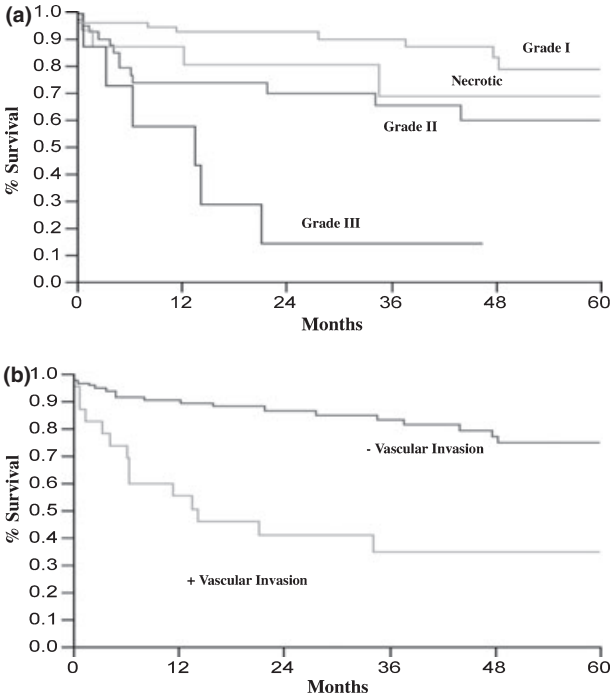

Figure 2 Recurrence-free survival by degree of differentiation (a) and the presence of vascular invasion (b).

Table 4. Multivariate analysis of factors affecting HCC recurrence-free survival.

Variables	Hazard ratio	95% confidence interval	*P*-value
Stage III	4.77	2.01–11.32	**0.0034**
Poorly differentiated	3.5	1.13–10.85	**0.049**

Table 5. Univariate analysis of factors predictive of vascular invasion.

Variables	Odds ratio	95% confidence interval	*P*-value
Stage III	53.74	15.43–187.25	**<0.0001**
Milan criteria (no.)	4.78	1.88–12.18	**0.0001**
Tumor size (>3.5 cm)	7.71	2.66–22.36	**0.0002**
Poorly differentiated	0.852	4.42–164.81	**0.03**
Multifocal	2.05	0.83–5.06	0.12
Incidental tumor	0.17	0.02–1.30	0.08

Table 6. Multivariate analysis of factors predictive of vascular invasion.

Variables	Odds ratio	95% confidence interval	*P*-value
Stage III	37.73	10.5–136.07	**<0.0001**
Tumor size (>3.5 cm)	3.67	0.96–14.01	**0.05**

than either moderate (3.4 cm) or well-differentiated tumors (3.3 cm, $P < 0.05$).

Clinicopathologic predictors of vascular invasion

Univariate analysis was also employed to identify pathologic predictors of vascular invasion in the explanted liver. Factors considered included: tumor stage, nodularity, Milan criteria by explant, incidental lesions, tumor size (>3.5 cm), and differentiation. Importantly, tumor size >3 cm ($P = 0.0002$), stage III lesions (<0.0001), poor differentiation ($P = 0.03$), and pathologically within the Milan criteria ($P = 0.0001$) were predictive of vascular invasion (Table 5). Controlling for all other variables by logistic regression, stage III lesions and tumor size >3.5 cm were exclusively predictive of the presence of vascular invasion in the specimen (Table 6).

Discussion

Chronic inflammation in the cirrhotic liver promotes a severely dysplastic field [17]. While OLT offers the advantage of complete hepatic resection, cancer recurrence is reportedly as high as 60% [18]. However, the actual incidence of recurrent disease varies between centers. Roayaie *et al.* documented an 18% incidence of tumor recurrence with a 5-year survival of 22% [19]. The majority of patients with recurrence had vascular invasion in the explant. Conversely, preliminary experience at the University of Pittsburgh suggests recurrent HCC is much closer to 40% in a cohort of patients transplanted during the 1980s [10]. The cumulative experience from the UNOS database notes recurrence at approximately 8%, with a 5-year survival of 42%, compared with 72% in those without HCC [20].

While the experience with OLT for malignancy continues to expand, several clinical and pathologic variables have been identified which independently influence long-term outcome. Among these, increasing tumor size [9], TNM stage [21], differentiation [22], and the presence of vascular invasion [23] are consistently associated with HCC recurrence and survival. A study by Zavaglia *et al.* revealed that histologic grade and vascular invasion are strong predictors of tumor recurrence [24]. Importantly, tumor size itself may be an important predictor of the presence of vascular invasion [9] and degree of differentiation [8]. Recently, a report for the United Kingdom suggested that the best predictive cutoff, with regard to the tumor size and disease-free survival, is 3.5 cm in largest diameter [25]. Interestingly, multinodularity was not associated with HCC re-emergence after transplant.

This single-center experience identifies several pathologic variables strongly associated with both long-term outcome and the presence of vascular invasion in the explanted liver. These data confirm previous findings that pathologic progression of disease has the highest predictive capacity. By multivariate analysis, stage III and poorly differentiated tumors were independently associated with a reduction in HCC RFS. Five-year outcome by univariate comparison for either factor is <35%. Furthermore, poorly differentiated lesions are significantly larger in size. While it is our bias that vascular invasion is an important prognostic factor, tumor size has been implicated as a predictor the presence of vascular invasion on explant analysis [8]. Our experience extends previous findings that a size threshold of 3.5 cm is prognostically important and that multinodularity has no influence on outcome. As such, we have identified stage III lesions and those >3.5 cm in size as predictive of the presence of vascular invasion. Thus, total tumor burden appears to be more influential than multifocality.

Significant controversy exists over whether preOLT TACE and postOLT sirolimus-based immunosuppression have an impact on cancer recurrence and ultimately mortality [11,12,26,27]. Importantly, our experience not only corroborates previous observations underscoring the important contribution of specific pathologic variables [28,29], but fails to show a survival benefit for either preOLT TACE or sirolimus therapy following transplantation. Five-year survival for those undergoing preOLT chemoembolization is 73%, compared with 63% for those who did not. Similarly, patients treated with sirolimus postOLT had a 75% 5-year survival, compared to 60% in those who received standard immunosuppres-

sion. While recipients subject to either therapy have an empirically lower mortality, these differences were not univariately significant. Furthermore, controlling for pathologically advanced disease, neither TACE nor sirolimus were independent predictors of survival. However, these findings may be secondary to a modest sample size. Furthermore, despite the lack of significance, both sirolimus-based immunosuppression and preOLT TACE trended toward positive long-term outcome. Whether these therapies actually have a true survival benefit remains questionable.

While these data are interesting, we acknowledge several limitations. As this is a single-center retrospective experience that spans 14 years, we were unable to obtain complete records for 12 recipients who were excluded from this study. Furthermore, an additional six patients were radiographically diagnosed with HCC prior to OLT that ultimately had no evidence of malignancy in the explant specimen. While our experience with sirolimus following OLT for HCC is relatively large, these 49 patients are not a homogeneous group. Approximately 40 patients received sirolimus immediately postOLT as a primary immunosuppressive agent in conjunction with CNI. Conversely, nine patients were converted to sirolimus secondary to calcineurin toxicity. Finally, the 51 patients who received preoperative chemoembolization are a reasonably uniform cohort in that no alternative forms of locoregional therapy were administered prior to transplant. However, despite the lack of impact on disease-free survival, it is unknown whether TACE prior to transplant impacts time on the waiting list and/or overall dropout at our center.

With a cancer recurrence rate of 13% over this time period, and overall 5-year survival near 70%, our approach to OLT for HCC has changed dramatically. Specifically, the constant evolution of immunosuppressive strategies have clearly contributed to our overall outcome. Cumulatively, this study suggests that stage III and poorly differentiated tumors have a significant impact on HCC recurrence and ultimately survival. Furthermore, stage III lesions and tumors >3.5 cm are independent predictors of vascular invasion. Unfortunately, preOLT chemoembolization and postOLT sirolimus-based therapy had no beneficial effect on long-term outcome.

Authorship

MAZ wrote paper, designed the study, collected data. JFT analyzed data, contributed to the study design. MW analyzed data. TB analyzed data. JC collected data. FW collected data. TS collected data. WB analyzed data, contributed to the study design. IK analyzed data, contributed to the study design.

References

1. El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. *N Engl J Med* 1999; **340**: 745.
2. Iwatsuki S, Starzl TE, Sheahan DG, *et al.* Hepatic resection versus transplantation for hepatocellular carcinoma. *Ann Surg* 1991; **214**: 221.
3. Olthoff KM, Rosove MH, Shackleton CR, *et al.* Adjuvant chemotherapy improves survival after liver transplantation for hepatocellular carcinoma. *Ann Surg* 1995; **221**: 734.
4. 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.
5. Wiesner RH, Freeman RB, Mulligan DC. Liver transplantation for hepatocellular cancer: the impact of the MELD allocation policy. *Gastroenterology* 2004; **127**: S261.
6. Yao FY, Bass NM, Ascher NL, Roberts JP. Liver transplantation for hepatocellular carcinoma: lessons from the first year under the model for end-stage liver disease (MELD) organ allocation policy. *Liver Transpl* 2004; **5**: 621.
7. Zimmerman M, Busuttil RW. Long-term efficacy of percutaneous thermal ablation for patients with recurrent hepatocellular carcinoma. *Nat Clin Pract Gastroenterol Hepatol* 2006; **3**: 250.
8. Pawlik TM, Delman KA, Vauthey JN, *et al.* Tumor size predicts vascular invasion and histologic grade: implications for selection of surgical treatment for hepatocellular carcinoma. *Liver Transpl* 2005; **11**: 1086.
9. Lohe F, Angele MK, Gerbes AL, Lohrs U, Jauch KW, Schauer RJ. Tumour size is an important predictor for the outcome after liver transplantation for hepatocellular carcinoma. *Eur J Surg Oncol* 2005; **31**: 994.
10. Marsh JW, Dvorchik I, Subotin M, *et al.* The prediction of risk of recurrence and time to recurrence of hepatocellular carcinoma after orthotopic liver transplantation: a pilot study. *Hepatology* 1997; **26**: 444.
11. Porrett PM, Peterman H, Rosen M, *et al.* Lack of benefit of pre-transplant locoregional hepatic therapy for hepatocellular cancer in the current MELD era. *Liver Transpl* 2006; **12**: 665.
12. Kneteman NM, Oberholzer J, Al Saghier M, *et al.* Sirolimus-based immunosuppression for liver transplantation in the presence of extended criteria for hepatocellular carcinoma. *Liver Transpl* 2004; **10**: 1301.
13. Trotter JF, Wachs M, Everson GT, Kam I. Adult-to-adult transplantation of the right hepatic lobe from a living donor. *N Engl J Med* 2002; **346**: 1074.
14. Stegall MD, Mandell S, Karrer F, Kam I. Liver transplantation without venovenous bypass. *Transplant Proc* 1995; **27**: 1254.
15. Edmondson H, Steiner P. Primary carcinoma of the liver: a study of 100 cases among 48,900 necropsies. *Cancer* 1954; **1**: 462.

16. Greene FL, Page DL, Fleming ID, *et al. AJCC Cancer Staging Manual*, 6th Edition. New York: Springer, **2002**: 131.
17. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? *Lancet* 2001; **357**: 539.
18. Schlitt HJ, Neipp M, Weimann A, *et al.* Recurrence patterns of hepatocellular and fibrolamellar carcinoma after liver transplantation. *J Clin Oncol* 1999; **17**: 324.
19. Roayaie S, Schwartz JD, Sung MW, *et al.* Recurrence of hepatocellular carcinoma after liver transplant: patterns and prognosis. *Liver Transpl* 2004; **10**: 534.
20. Yoo HY, Patt CH, Geschwind JF, Thuluvath PJ. The outcome of liver transplantation in patients with hepatocellular carcinoma in the United States between 1988 and 2001: 5-year survival has improved significantly with time. *J Clin Oncol* 2003; **21**: 4329.
21. Shimoda M, Ghobrial RM, Carmody IC, *et al.* Predictors of survival after liver transplantation for hepatocellular carcinoma associated with Hepatitis C. *Liver Transpl* 2004; **10**: 1478.
22. Jonas S, Bechstein WO, Steinmuller T, *et al.* Vascular invasion and histopathologic grading determine outcome after liver transplantation for hepatocellular carcinoma in cirrhosis. *Hepatology* 2001; **33**: 1080.
23. Hemming AW, Cattral MS, Reed AI, Van Der Werf WJ, Greig PD, Howard RJ. Liver transplantation for hepatocellular carcinoma. *Ann Surg* 2001; **233**: 652.
24. Zavaglia C, De Carlis L, Alberti AB, *et al.* Predictors of long-term survival after liver transplantation for hepatocellular carcinoma. *Am J Gastroenterol* 2005; **100**: 2708.
25. Grasso A, Stigliano R, Morisco F, *et al.* Liver transplantation and recurrent hepatocellular carcinoma: predictive value of nodule size in a retrospective and explant study. *Transplantation* 2006; **81**: 1532.
26. Decaens T, Roudot-Thoraval F, Bresson-Hadni S, *et al.* Impact of pretransplantation transarterial chemoembolization on survival and recurrence after liver transplantation for hepatocellular carcinoma. *Liver Transpl* 2005; **11**: 767.
27. Zhou J, Fan J, Wang Z, *et al.* Conversion to sirolimus immunosuppression in liver transplantation recipients with hepatocellular carcinoma: report of an initial experience. *World J Gastroenterol* 2006; **12**: 3114.
28. Kishi Y, Sugawara Y, Tamura S, *et al.* Impact of incidentally found hepatocellular carcinoma on the outcome of living donor liver transplantation. *Transpl Int* 2006; **19**: 720.
29. Sotiropoulos GC, Malago M, Molmenti EP, *et al.* Hilar lymph nodes sampling at the time of liver transplantation for hepatocellular carcinoma: to do or not to do? *Transpl Int* 2007; **20**: 141.

