

Hepatocellular carcinoma recurrence after liver transplantation in a Brazilian multicenter study: clinical profile and prognostic factors of survival

Aline L. Chagas^{a,c}, Guilherme E.G. Felga^d, Marcio A. Diniz^a, Renato F. Silva^e, Angelo A. Mattos^f, Rita C.M.A. Silva^e, Ilka F.S.F. Boin^g, José H.P. Garcia^h, Agnaldo S. Limaⁱ, Julio C.U. Coelho^j, Paulo L. Bittencourt^k, Venâncio A.F. Alves^{b,c}, Luiz A.C. D'Albuquerque^{a,c} and Flair J. Carrilho^{a,c}; Brazilian HCC Study Group

Background Liver transplantation (LT) is the treatment of choice for patients with unresectable early hepatocellular carcinoma (HCC). Post-LT HCC recurrence rates range from 8 to 20% and still impact on overall survival (OS). The aim of our study was to evaluate the impact of HCC recurrence on post-LT survival and analyze prognostic factors among those patients with recurrence.

Patients and methods We carried out a national, multicenter, retrospective cohort study in Brazil. Medical records of 1119 LT recipients with HCC were collected. Data from patients with post-LT HCC recurrence were analyzed and correlated with post-relapse survival.

Results OS of the 1119 patients included in the study was 63% over 5 years. Post-LT HCC recurrence occurred in 86 (8%) patients. The mean time to recurrence was 12 months. Sites of recurrence were extrahepatic in 55%, hepatic in 27%, and both hepatic and extrahepatic in 18%. Recurrence treatment was performed in 50 (64%) cases, mostly with sorafenib. Post-relapse survival rates were 34% at 1 year and 13% at 5 years. Univariable analysis identified α -fetoprotein more than 1000 ng/ml at relapse, recurrence treatment, extrahepatic location, and time to recurrence more than 2 years as prognostic factors. In multivariable analysis, recurrence treatment, extrahepatic location, and time to recurrence more than 2 years were independent predictors of better survival.

Conclusion In a large Brazilian cohort of LT recipients with HCC, post-LT HCC recurrence occurred in 8% and impacted significantly on the OS. Patients with early recurrence presented a worse prognosis. However, treatment of recurrence improved outcomes, highlighting the importance of early diagnosis. *Eur J Gastroenterol Hepatol* 31: 1148–1156
Copyright © 2019 The Author(s). Published by Wolters Kluwer Health, Inc.

Introduction

Hepatocellular carcinoma (HCC) is a common cause of morbidity in patients with cirrhosis and the third leading

cause of cancer mortality worldwide [1]. Liver transplantation (LT) is the treatment of choice for patients with unresectable early HCC, with survival rates of 70% in 5 years [2,3]. Post-transplant HCC recurrence, however, is still a cause of morbidity and mortality among these patients. Even after the adoption of restrictive selection criteria, HCC post-transplant recurrence rates, in most recent studies, range from 8 to 20% [4–7].

Post-transplant HCC recurrence occurs because of progression of occult metastases months or years after transplantation or secondary to the release of tumor cells at the time of surgery [4]. The presence of vascular invasion and satellite nodules in the explant and the size and number of tumors are recognized risk factors related to HCC post-transplant recurrence [5–7]. Generally, HCC relapse occurs within the first 2 years after LT and may be either intrahepatic and/or extrahepatic, especially to bone, lung, and lymph nodes [4–7].

Studies evaluating the impact of HCC recurrence in patients undergoing LT showed a significant reduction in post-transplant survival in these patients. Some factors related to worse prognosis were early recurrence (<2 years after LT) and the presence of bone metastases [7]. The diagnosis of tumor recurrence at an early stage of disease may lead to an increase in survival as it allows surgical or loco-regional treatment with curative intent [4–7]. However, the optimal management of these patients is not well established.

European Journal of Gastroenterology & Hepatology 2019, 31:1148–1156

Keywords: hepatocellular carcinoma, liver neoplasms, liver transplantation, recurrence, relapse, survival analysis

^aDepartment of Gastroenterology, ^bDepartment of Pathology, University of São Paulo School of Medicine, ^cSão Paulo Clinicas Liver Cancer Group, ^dLiver Transplantation Unit, Hospital Israelita Albert Einstein, São Paulo, Brazil, ^eServiço de Gastroenterologia e Unidade de Transplante de Fígado, Hospital de Base – FUNFARME, Faculdade de Medicina de São José do Rio Preto, São José do Rio Preto, ^fDepartment of Gastroenterology, Fundação Universidade Federal de Ciências da Saúde de Porto Alegre, Porto Alegre, ^gUnit of Liver Transplantation, State University of Campinas, Campinas, ^hCeará Unit of Liver Transplantation, Department of Surgery and Liver Transplantation, Federal University of Ceará, Fortaleza, ⁱSchool of Medicine, Federal University of Minas Gerais, Belo Horizonte, ^jSurgery Department, Federal University of Paraná, Curitiba, ^kUnit of Gastroenterology and Hepatology, Portuguese Hospital of Salvador, Bahia and ^lBiostatistics and Bioinformatics Research Center, Cedars Sinai Medical Center, Los Angeles, California, USA

Correspondence to Aline L. Chagas, MD, Department of Gastroenterology, Division of Clinical Gastroenterology and Hepatology, School of Medicine, Hospital das Clínicas, University of São Paulo, São Paulo CEP 05403-000, Brazil
Tel: +55 119 8940 1955; e-mail: alinelchagas@gmail.com

Received 23 January 2019 **Accepted** 9 April 2019

This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NCND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

There are few studies in the literature analyzing the prognostic factors related to survival in patients who developed with post-LT HCC recurrence and the role of relapse treatment.

The aim of our multicenter study was to evaluate the impact of tumor recurrence on the survival of patients with HCC who underwent LT in Brazil, perform a clinical and demographic characterization of patients with post-LT HCC recurrence, and evaluate the prognostic factors related to their survival.

Patients and methods

Study design

We carried out a national, multicenter, retrospective cohort study with data from 13 transplant centers after the introduction of a model for end stage liver disease-based allocation system in Brazil. Medical records of 1368 recipients with HCC transplanted from July 2006 through to July 2015 were compiled.

HCC diagnosis was made on the basis of the American Association for the Study of Liver Diseases diagnostic criteria [8]. After applying the inclusion and exclusion criteria, 1119 patients were eligible for the final analysis. Patients were excluded from the study for the following reasons: incidental HCC diagnosis in explant ($n=122$); incomplete tumor or patient data ($n=91$); unconfirmed HCC diagnosis ($n=14$); mixed tumor (hepatocholangiocarcinoma) diagnosis ($n=14$); and patients who underwent living-donor LT ($n=8$).

The diagnosis of post-transplant HCC recurrence was made on the basis of the following criteria: (a) Image evaluation showing a lesion with typical vascular findings, compatible with intrahepatic or extrahepatic HCC recurrence; (b) Biopsy or result of surgical specimen with anatomopathological diagnosis of HCC in intrahepatic or extrahepatic lesions that appeared after transplantation. The clinical, radiological, and anatomopathological original reports of patients with post-transplant HCC recurrence were analyzed.

No common post-LT HCC screening protocol was adopted in all transplant centers in Brazil and the screening protocol was defined according to each participating center. A survey was conducted, and most centers screened patients for HCC recurrence every 6–12 months with serum α -fetoprotein (AFP) and imaging tests, including chest and abdominal computed tomography, abdominal MRI, abdominal ultrasound, and bone scintigraphy.

Each transplant center received a questionnaire to be filled out with demographic, clinical, laboratory, radiological, and anatomopathological data by review of medical records. The following variables were evaluated: age at transplantation, sex, presence of liver cirrhosis, etiology of chronic liver disease, Child–Pugh [9] and model for end stage liver disease [10] scores at the time of inclusion on the transplant list, pre-LT AFP (serum AFP levels performed ≤ 3 months before LT), and date of transplantation. In relation to post-LT HCC recurrence, we evaluated the date of recurrence, diagnostic methods, tumor recurrence characteristics and location, serum AFP level at the time of relapse, and treatment provided for recurrence.

The primary endpoint was post-relapse survival. The secondary endpoints were overall survival (OS) and disease-free survival (DFS). For OS and DFS, the date of LT was considered zero time and the event of interest was death because of any cause. For post-relapse survival, the time of relapse was considered zero time. Patients who were lost to follow-up were censored.

The study protocol conformed to the ethical guidelines of the 2008 Declaration of Helsinki and was approved by the Institutional Review Board of the University of Sao Paulo School of Medicine (number: 164.120).

Statistical analysis

Patients' characteristics were presented with descriptive statistics such that continuous variables are expressed as mean \pm SD or medians (range), whereas qualitative variables were expressed as frequency (percentage). Cut-offs were defined evaluating the effect of the continuous variable on the log of hazard ratio (HR) from a multivariable Cox regression fitted using restricted splines of third degree with knots defined on the basis of quantiles. The post-relapse survival curves were presented using the Kaplan–Meier method [11]. The median survival times and their 95% confidence intervals (CIs) are also reported. Proportional hazards Cox [12] simple and multivariable regression were fitted, considering different centers as strata. The proportional hazards hypothesis was tested through the Schoenfeld residuals [13].

For all statistical analyses, a P value less than 0.05 was considered statistically significant. The data were analyzed using the statistical program R, version 3.3.2, Vienna, Austria [14]. The statistical methods of this study were reviewed by a statistician not masked (DMA).

Results

Post-transplant hepatocellular carcinoma recurrence and survival

OS of the 1119 patients in this nationwide series was 79% (95% CI: 76.69–81.52) in 1 year, 72.5% (95% CI: 69.72–75.26) in 3 years, and 63% in 5 years (95% CI: 58.81–65.97). Post-LT HCC recurrence was observed in 8% (86/1119). The DFS was 94.4% in 1 year (95% CI: 92.95–95.95), 89.8% in 3 years (95% CI: 87.71–91.94), and 88.3% in 5 years (95% CI: 85.93–90.74).

At the end of the study, among the 86 patients with post-LT HCC recurrence, 20 patients were alive and 66 died. In 94% (62/66), death was related to HCC recurrence. Post-LT tumor recurrence had a major impact on the survival of patients transplanted with HCC (Fig. 1). Post-relapse survival was 34% in 1 year (95% CI: 24.46–46.18), 18% in 3 years (95% CI: 10.25–30.08), and 13% in 5 years (95% CI: 6.38–25.72). The median post-relapse survival was 9.6 months.

Clinical and demographic characteristics

The clinical, laboratory, radiological, and anatomopathological characteristics of the 86 patients with post-LT HCC recurrence are summarized in Table 1. The majority of patients were men (78%; 67/86), with a median age of

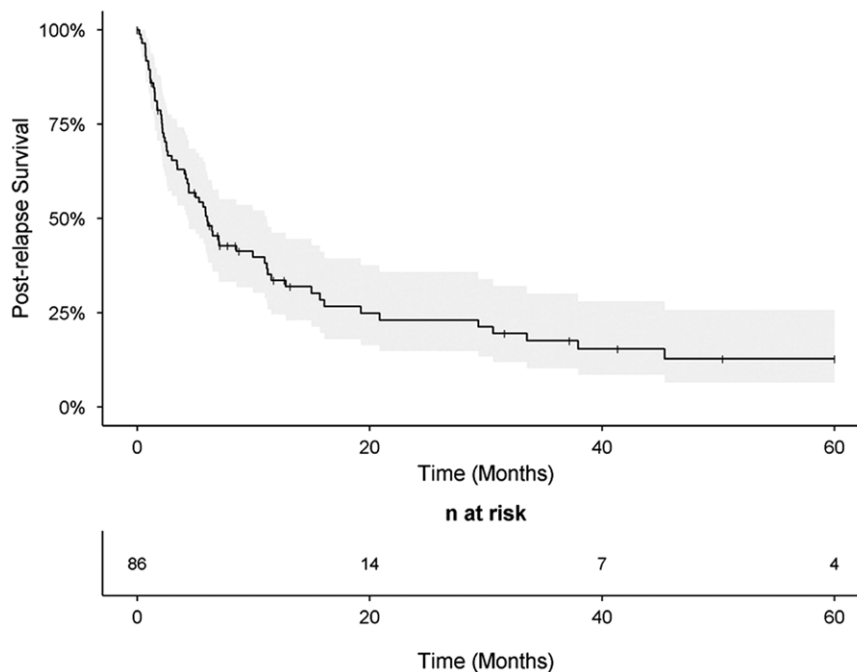


Fig. 1. Post-relapse survival curve in patients with hepatocellular carcinoma recurrence after liver transplantation.

58 years at the time of transplant. The etiology of liver disease was hepatitis C virus in 69%. The median time on the transplant list was 9.6 months. Ten (12%) patients were included after 'downstaging'. At diagnosis, in imaging studies, most patients had uninodular HCC (54%, 46/85), with a mean size of the largest tumor of 33 mm (± 12.08), and 74% (63/85) of the patients fulfilled the Milan criteria. During the waiting list period, HCC treatment was performed in 69% (59/85) of cases and most underwent transarterial chemoembolization.

In relation to post-transplant immunosuppression, most patients received a combination therapy (calcineurin inhibitor + purine inhibitor). Calcineurin inhibitor monotherapy was used in 21% and mammalian target of rapamycin (mTOR) inhibitors alone or in combination with other medications were used in 24%.

In explant analysis, different from diagnosis, only 22 (26%) patients had one nodule and 33.5% had multifocal HCC (>3 nodules). The average size of the largest tumor was 32 mm (± 16.23) and HCC was moderately differentiated in 63% (53/84) of cases. In explant, only 42% (36/85) of patients were within Milan criteria. Vascular invasion was described in 62% (53/85) of patients, being microvascular in 41 cases and macrovascular in nine cases. In three cases, the type of vascular invasion was not described.

Clinical features of post-transplant hepatocellular carcinoma recurrence

The clinical characteristics of patients with post-LT HCC recurrence and post-relapse management are summarized in Table 2. In the majority of patients, the diagnosis was made in the first 2 years after transplantation (85%, 73/86). Forty-seven patients (55%, 47/85) had extrahepatic HCC recurrence, with the most common sites being lung (40%, 19/47), bones (25.5%, 12/47), and peritoneum (8.5%, 4/47). Twenty-three patients (27%, 23/85)

had only hepatic recurrence and 15 (18%, 15/85) patients hepatic and extrahepatic recurrence. The majority of patients (74%, 51/69) had elevated AFP (>10 ng/ml) at the time of relapse and the median AFP value was 235 ng/ml (1–60 500 ng/ml).

Treatment of post-LT HCC recurrence was performed in 64% (50/78) of cases. Sorafenib was the most frequent treatment, indicated for 37% (29/78) of patients. Surgery was the treatment of choice in 8% (6/78), one patient was treated with radiotherapy, and 18% (14/78) underwent combined treatment (e.g. surgery + systemic treatment \pm radiotherapy). Exclusive palliative care was indicated for 28 (36%) patients.

Prognostic factors of post-liver transplantation hepatocellular carcinoma recurrence survival

We analyzed the prognostic factors related to survival among patients who had post-LT HCC recurrence. The AFP level at relapse was an important prognostic factor. Patients with AFP more than 1000 ng/ml had a worse survival rate compared with patients with AFP less than 1000 ng/ml ($P=0.01$; Fig. 2). The site of post-LT HCC recurrence also had an impact on survival. Patients who had extrahepatic recurrence had better survival than patients with hepatic or hepatic+extrahepatic recurrence ($P<0.001$; Fig. 3).

Patients who were treated had a better survival compared with untreated patients ($P<0.001$). In Fig. 4, the importance of performing treatment of recurrence in survival is shown. Among the patients treated, those who underwent systemic therapy with sorafenib had a worse survival rate than patients who received radiotherapy, combined therapy, or surgery ($P=0.008$).

Analyzing the impact of time to relapse on survival, we observed that patients with early recurrence (<24 months) had a worse survival rate compared with patients with late recurrence ($P=0.02$; Fig. 5).

Table 1. Clinical characteristics of patients with hepatocellular carcinoma recurrence after liver transplantation

	N (%) or mean ± SD
Age at transplant (years)	58 ± 9.26
Sex (male)	67 (78)
Etiology of liver disease	
HCV	59 (69)
Alcohol	10 (12)
HBV	7 (8)
NAFLD	1 (1)
Cryptogenic	3 (3)
Coinfection	1 (1)
Other	5 (6)
Number of nodules, diagnosis	
1	46 (54)
2 a 3	33 (39)
>3	6 (7)
Size of largest nodule diagnosis (mm)	33.27 ± 12.08
Milan criteria, diagnosis	63 (74)
Bridge treatment	59 (69)
TACE	45 (69)
PEI/RFA	6 (10)
Surgery	1 (2)
Combined	7 (12)
AFP pretransplantation (ng/ml)	
Mean ± SD	1.076 ± 4.793
Median (minimum–maximum)	88 (3.6–40 800)
Post-transplant immunosuppression	
Calcineurin inhibitors	17 (21)
Combined therapy	45 (55)
mTOR inhibitors	20 (24)
Number of nodules, explant	
0	2 (2.5)
1	22 (26)
2–3	32 (38)
>3	28 (33.5)
Size of the largest nodule explant (mm)	32.45 ± 16.23
Milan criteria, explant	36 (42)
Vascular invasion, explant	53 (62)
Type of vascular invasion	
Microvascular	41 (50)
Macrovascular	9 (11)
No vascular invasion	32 (39)
Satellites nodules, explant	28 (34)
Degree of tumor differentiation, explant	
Complete necrosis	2 (2)
Well differentiated	5 (6)
Moderately differentiated	53 (63)
Poor differentiated	24 (29)

AFP, α-fetoprotein; HBV, hepatitis B virus; HCV, hepatitis C virus; mTOR, mammalian target of rapamycin; NAFLD, non-alcoholic fatty liver disease; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation; TACE, transarterial chemoembolization.

Univariable and multivariable analyses

The univariable analysis identified AFP more than 1000 ng/ml on relapse as a negative prognostic factor and the treatment of HCC relapse, extrahepatic recurrence site, and time to relapse more than 24 months as protective factors (Table 3). In the multivariable analysis, relapse time more than 24 months HR: 0.31 (95% CI: 0.12–0.85), extrahepatic recurrence HR: 0.45 (95% CI: 0.23–0.86), and treatment of relapse (HR: 0.27; 95% CI: 0.14–0.54) remained as independent factors of better post-relapse survival.

Discussion

We carried out a multicenter study that evaluated the results of LT in more than 1000 patients with HCC. This is the first study in Brazil that analyzed the characteristics and prognostic factors related to survival among patients with post-transplant HCC recurrence. We showed the

Table 2. Characteristics of hepatocellular carcinoma recurrence after liver transplantation

	N (%) or mean ± SD
Time to relapse (months)	12 ± 9.31
≤24	73 (85)
>24	13 (15)
Location	
Hepatic	23 (27)
Hepatic + extrahepatic	15 (18)
Extrahepatic	47 (55)
Lung	19 (40)
Bones	12 (25.5)
Peritoneum	04 (8.5)
Linfonodal	02 (4)
Multiple sites	05 (11)
Other	05 (11)
AFP at relapse (ng/ml)	
Mean ± SD	6 636.8 ± 15 174.5
Median (minimum–maximum)	235 (1–60 500)
AFP at relapse (ng/ml)	
≤10	18 (26)
10–100	11 (16)
100–400	10 (14)
400–1000	8 (12)
>1000	22 (32)
Treatment of relapse	
Yes	50 (64)
No	28 (36)
Type of treatment – relapse	
Sorafenib	29 (37)
Surgery	6 (8)
Radiotherapy	1 (1)
Combined treatment	14 (18)
Exclusive palliative care	28 (36)

AFP, α-fetoprotein.

role of relapse treatment, recurrence location, and time to relapse in their outcomes.

Post-transplant HCC recurrence was observed in 8% (86/1119) of patients. The rate of tumor recurrence found here is similar to the data reported from other centers [4,15,16]. In older studies, LT in patients with HCC was indicated for more advanced tumors. The post-transplant HCC recurrence rate was as high as 50% [17–20]. Since the adoption of more restrictive criteria for transplantation, the rate of recurrence observed in most studies varies from 8 to 20% [4–7,21]. In the multicenter Latin American study, the relapse rate at 1, 3, and 5 years was 7.3, 12.8, and 15%, respectively, at a mean time of 13 months [22]. In the experience of the Paul Brousse Hospital, France, in 493 HCC patients undergoing LT, the recurrence rate was 14.2%, with an average time of 17 months post-transplant, and 70% of the relapses occurred in the first 2 years [23]. Agopian *et al.* [24] found tumor recurrence in 117/865 (13.5%) of patients transplanted with HCC, between 1984 and 2013, at the University of California at Los Angeles. The mean time between transplantation and relapse was 15 months. In 2015, De’Angelis *et al.* [15] published a systematic review of post-transplant HCC recurrence. The mean relapse rate in 61 studies was 16%, with the mean time between transplantation and relapse of 13 months (1–132 months).

In this study, the mean time between transplantation and the diagnosis of recurrence was 12 months, and in the majority of patients (85%, 73/81), relapse diagnosis occurred within the first 2 years after LT. In terms of the localization of post-transplant HCC recurrence, the majority of the patients in our series had extrahepatic

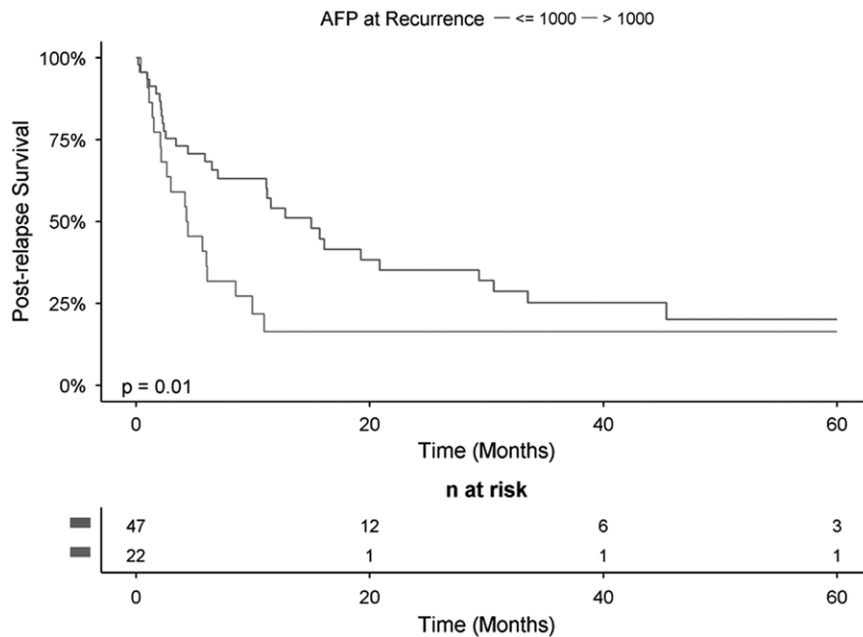


Fig. 2. Post-relapse survival curve according to serum α -fetoprotein (AFP) levels at diagnosis of recurrence: AFP up to 1000ng/ml versus AFP more than 1000ng/ml.

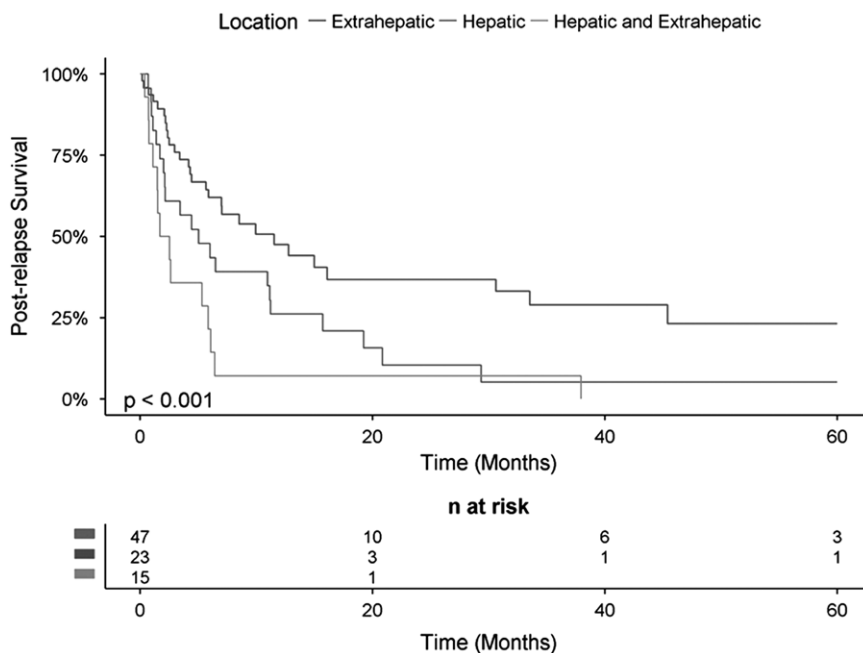


Fig. 3. Post-relapse survival curve according to the location of hepatocellular carcinoma recurrence after liver transplantation.

recurrence (55%, 64/78), with the most common sites being lung (40%), bone (25.5%), and peritoneum (8.5%). Several studies in the literature reported similar results, with a higher frequency of extrahepatic post-transplant HCC recurrence [4,12,23,24]. In a systematic review, in 1021 patients with post-transplant HCC relapse, 67% had extrahepatic recurrence [15]. According to the literature, the frequency of only extrahepatic recurrence ranges from 50 to 60%; hepatic and extrahepatic 30–40% and only hepatic 15–40%. In patients with extrahepatic recurrence, the most affected sites are the lungs (40–60%), bones (25–30%), lymph nodes (~10%), adrenals (~10%), and peritoneum (~10%), in agreement with the results found in our study [4,15]. This draws attention to

the need for a more comprehensive HCC screening after LT, including AFP, total abdominal and chest scans, and bone scintigraphy.

As shown in this study and also by other groups, the majority of post-transplant HCC recurrences occur within the first 2 years [4,12]. Thus, the current recommendations for screening are that computed tomography or MRI and AFP should be performed every 6–12 months after transplant in the first 3–5 years [4,25,26]. Some groups suggested the stratification of patients according to the risk of relapse for performing the screening [26]. However, post-transplant HCC screening, how it should be performed, and whether it is cost-effective is still a matter of debate in the literature and there are no prospective,

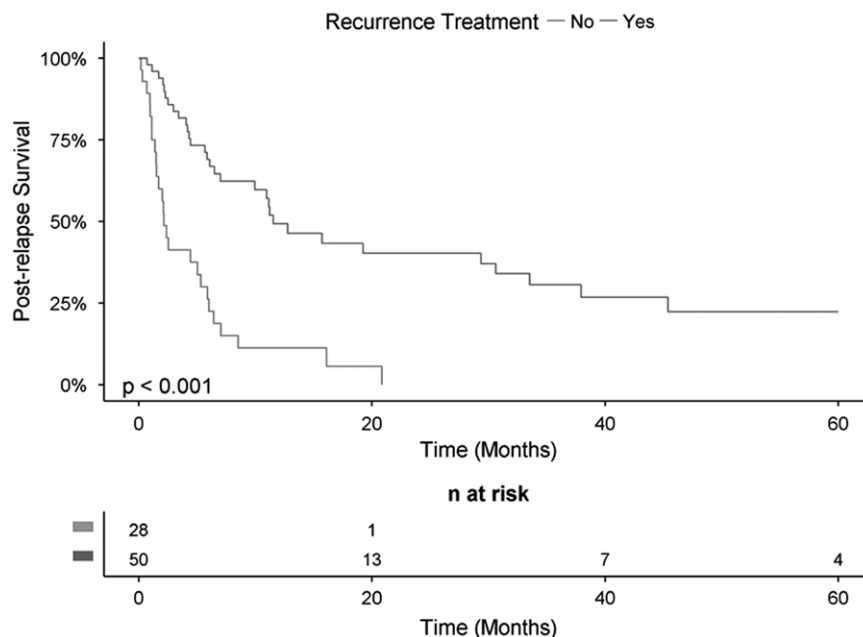


Fig. 4. Post-relapse survival curve according to post-transplant hepatocellular carcinoma recurrence treatment.

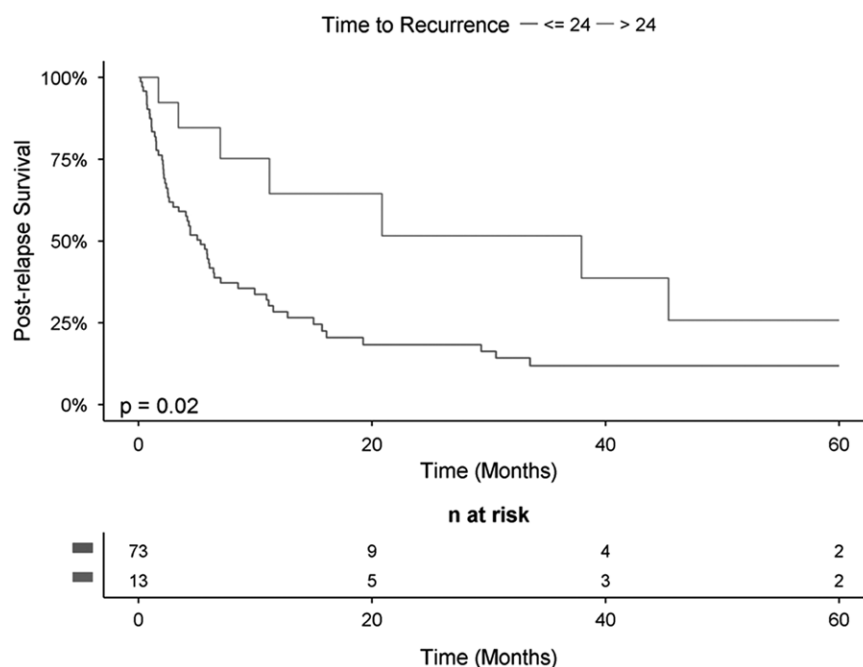


Fig. 5. Post-relapse survival curve according to time to relapse in patients with hepatocellular carcinoma recurrence after liver transplantation.

randomized studies assessing this issue [8,23]. The aim of screening is to detect relapse at an initial stage, when surgical or loco-regional treatment with curative intent can be performed. In Brazil, there is no national HCC post-LT screening protocol. As this is a retrospective study, one limitation of our study is that no common screening protocol was adopted by all participant transplant centers included in the study. Nevertheless, most groups performed post-LT screening in HCC patients every 6–12 months, with serum AFP and various combinations of imaging tests.

Post-transplant tumor recurrence has a major impact on HCC transplant survival, and is associated with a median survival of less than 1 year after diagnosis [12]. Post-transplant HCC recurrence usually occurs in a

multifocal and rapidly evolving way because of the associated immunosuppressive medication, showing a reserved prognosis and leading to death in the vast majority of cases [12,26,27]. In this study, patients who developed relapse had a high mortality, with a median post-recurrence survival of 9.6 months and a 5-year survival of 13%.

In the European Registry of Transplantation, tumor recurrence was the cause of death in 11% of patients who underwent LT [28]. Other studies have also shown the impact of HCC relapse on post-transplant survival [4,7]. According to a systematic review that included 1021 cases of post-transplant HCC relapse, the median post-recurrence survival was 13 months (0.1–112.5 months) [15]. In the study carried out at Beaujon Hospital, France, all patients

Table 3. Prognostic factors of post-relapse survival

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Time to relapse >24 months	0.38 (0.16–0.94)	0.035	0.31 (0.12–0.85)	0.023
Extrahepatic recurrence	0.61 (0.33–1.12)	0.112	0.45 (0.23–0.86)	0.015
Hepatic and extrahepatic recurrence	0.96 (0.34–2.69)	0.931	1.05 (0.24–4.68)	0.948
AFP at relapse (ng/ml)				
>100	1.76 (0.85–3.67)	0.130	1.58 (0.79–3.17)	0.197
>200	1.69 (0.82–3.48)	0.152		
>400	1.63 (0.81–3.27)	0.171		
>1000	1.71 (0.8–3.66)	0.163		
Treatment of relapse	0.31 (0.16–0.61)	0.001	0.27 (0.14–0.54)	<0.001
Types of treatment				
Sorafenib	1.12 (0.24–5.28)	0.887	–	–
Combined therapy	0.86 (0.23–3.21)	0.824		

AFP, α -fetoprotein; CI, confidence interval; HR, hazard ratio.

with relapse died at a median time of 6.5 ± 5 months [29]. In the experience of the Paul Brousse Hospital, France, the median post-recurrence survival was 19 months, with survival in the first, third, and fifth year of 65, 26, and 5%, respectively [23]. In the Latin American Multicenter Study of Transplantation and HCC, tumor recurrence was the main cause of death in HCC patients who underwent liver transplantation and the mean postrecurrence survival was 12 months (5–26 months) [22]. This draws attention to the major impact of HCC relapse on the survival of transplanted patients with this tumor and the importance of the evaluation of prognostic factors related to the risk of relapse in the selection of patients with HCC for LT.

There are few studies in the literature evaluating the impact of post-LT HCC recurrence treatment and no prospective, randomized, controlled study. Thus, the treatment strategies in this group of patients are still not well established. According to data published in some studies and in the systematic review performed by De'Angelis and colleagues, surgical treatment is safe and effective in patients with localized/unifocal HCC recurrence, both extrahepatic and intrahepatic, being the treatment of choice in these patients [4,12,15,25].

According to the available studies, with the limitation of being nonrandomized retrospective studies, patients with recurrence, in whom it is possible to perform surgical or loco-regional treatment with curative intent, have better survival compared with patients who can only receive palliative treatments (transarterial chemoembolization, sorafenib, radiotherapy, among others) or exclusive palliative care [12,15]. In a study published by Bodzin *et al.* [30], in 857 HCC transplant patients, post-transplant tumor recurrence occurred in 12.4% of the patients. Patients who underwent surgical treatment had a median survival of 27.8 months, significantly higher than patients who underwent nonsurgical treatment (10.6 months) and patients who received only exclusive palliative care (3.7 months, $P < 0.001$).

In the study of the French group, which aimed to evaluate the impact of surgical treatment of post-LT HCC recurrence on survival, the majority of patients (72.9%) had extrahepatic recurrence. The surgical resection of the

relapse, involving cases of hepatic and extrahepatic recurrence, was performed in 31.4% of patients and they had a median survival of 35 months, significantly higher than the survival observed in patients in whom treatment was not possible (15 months; $P < 0.001$). Other factors related to a better prognosis in this study were AFP less than 100 ng/ml at the time of relapse, recurrence in an extrahepatic location, and unifocal recurrence [23]. Sapisochin *et al.* [31] published a study that brought together the experience of two centers: one from Canada and another from Spain. In 121 patients with post-LT HCC recurrence, the factors related to better survival after relapse were treatment of recurrence with curative intent, AFP less than 100 ng/ml at the time of relapse diagnosis, and late recurrence (>12 months). In this study, we found similar results. Patients with AFP less than 1000 ng/ml and with extrahepatic recurrence had a better prognosis. Extrahepatic recurrence was an independent factor related to survival.

Time to recurrence was an important prognostic factor in our series. Patients with early recurrence had a worse survival rate compared with patients with late recurrence. Time to recurrence more than 24 months was an independent prognostic factor related to better survival on multivariable analysis. Other authors have reported similar results [26].

We have also shown that treatment of HCC recurrence (surgical and nonsurgical) has benefits in terms of survival. Patients undergoing treatment had a significantly better survival rate compared with untreated patients ($P < 0.001$) and recurrence treatment was an independent prognostic factor related to better prognosis. However, in our series, treatment was only performed in 64% (50/78) of the cases with tumor recurrence. As this is a retrospective, multicenter study, some data such as performance status, comorbidities, and other factors that, along with the tumor stage, could preclude recurrence treatment, were, unfortunately, not available for analysis. Also, it was not possible to adequately evaluate the impact of surgical treatment with curative intent on survival as only six (8%) patients received this treatment. Sorafenib was the most frequent treatment, recommended in 82% (41/50) – in 29 as the sole treatment and in 12 in association with other therapeutic modalities. Among patients who received treatment, those who underwent systemic treatment with sorafenib had a worse survival rate than patients who received combined therapy or surgical treatment. However, we can not conclude, on the basis of these results, that a treatment is better than the other. Probably, patients who received only sorafenib were those with contraindications to surgical or loco-regional treatment and with more advanced tumors; thus, a worse survival rate was expected.

Some studies have shown the safety and efficacy of using sorafenib, with or without an mTOR inhibitor, in the palliative treatment of post-transplant HCC recurrence, also with benefit in terms of survival [27,32,33]. According to a systematic review on the subject, the median survival with sorafenib was 12.1 months and that with sorafenib plus mTOR inhibitor was 18 months compared with a median survival of 3.3 months in patients who received only exclusive palliative care [15].

The main limitations of this study were the fact that it was a retrospective cohort based on real-life reports from

13 centers. Most importantly, review of all radiological and anatomopathological evaluation was not possible and some data were not available. However, this nationwide effort from a large country came up with a clinical presentation of a large number of patients, from several transplant centers, from different regions of the country.

Conclusion

In this large series of HCC patients submitted to liver transplantation in Brazil, HCC post-LT recurrence occurred in 8% and had a major impact, with a survival of only 13% in 5 years. Patients with early recurrence presented a worse prognosis. However, treatment of post-transplant HCC recurrence increased survival, calling attention to the importance of post-transplant HCC screening, allowing for the detection of recurrence at an earlier stage, which enables the possibility of treatment with curative intent.

Acknowledgements

The Brazilian HCC Study Group: The following principal local investigators enrolled patients in the Brazilian National Survey of Liver Transplant for Hepatocellular Carcinoma: Aline Chagas, Luciana Oba Onishi Kikuchi, Luiz Augusto Carneiro D'Albuquerque, Flair José Carrilho (Division of Clinical Gastroenterology and Hepatology and Division of Digestive Organs Transplantation, Hospital das Clínicas, Department of Gastroenterology, School of Medicine, University of São Paulo, São Paulo); Guilherme Eduardo Gonçalves Felga, Marcio Dias de Almeida (Liver Transplantation Unit, Hospital Israelita Albert Einstein, São Paulo); Rita de Cássia Martins Alves da Silva, Renato Ferreira da Silva (Gastroenterology Division and Liver Transplantation Unit, Hospital de Base – FUNFARME, School of Medicine of São José do Rio Preto, São José do Rio Preto); Mariana Bina Possato, Ilka de Fátima Santana Ferreira Boin (Department of Digestive Surgery of the State University of Campinas, and University Hospital of Campinas, Campinas); Maria Lucia Zanotelli (Liver Transplantation Unit of the Santa Casa de Misericórdia de Porto Alegre, Porto Alegre); Gustavo de Sousa Arantes Ferreira, Julio Cezar Uili Coelho (University Hospital of the Federal University of Paraná, Curitiba); Paulo Everton Garcia Costa, José Huygens Parente Garcia (Liver Transplantation Unit of Ceará, Department of Surgery and Liver Transplantation, Federal University of Ceará, Fortaleza); Paulo Reichert (Hospital São Vicente de Paulo, Passo Fundo); Paulo Lisboa Bitencourt (Hospital Português da Bahia, Salvador); Carlos Eduardo Sandoli Baia, Débora Raquel Benedita Terrabuio (Hospital de Transplantes do Estado de São Paulo – Euryclides de Jesus Zerbini, São Paulo); Gabriela Foinquinos, Sylene Coutinho Rampche de Carvalho, Leila Maria Moreira Beltrão Pereira (Instituto do Fígado de Pernambuco, Recife); Adriano Cláudio Pereira de Moraes, André Luís Conde Watanabe (Liver Transplantation Unit of the Instituto de Cardiologia do Distrito Federal, Distrito Federal); Agnaldo Soares Lima (School of Medicine, Federal University of Minas Gerais, Belo Horizonte); and Ângelo Alves de Mattos (Department of Gastroenterology,

Federal University of Health Sciences of Porto Alegre, Porto Alegre).

A.L.C.: designed research, performed research, collected data, and wrote the paper. G.E.G.F.: performed research, collected data, and wrote the paper. M.A.D.: analyzed data and wrote the paper. R.F.S., A.A.M. and R.C.M.A.S.: designed research, collected data, and wrote the paper. I.F.S.F.B.: collected data and wrote the paper. J.H.P.G., A.S.L., P.L.B. and J.C.U.C.: collected data. V.A.F.A.: designed research and wrote the paper. L.A.C.D.A.: study coordinator and designed research. F.J.C.: study coordinator, designed research, and wrote the paper.

Conflicts of interest

There are no conflicts of interest.

References

- 1 Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, *et al.* Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015; 136:E359–E386.
- 2 Bruix J, Reig M, Sherman M. Evidence-based diagnosis, staging, and treatment of patients with hepatocellular carcinoma. *Gastroenterology* 2016; 150:835–853.
- 3 Forner A, Reig M, Bruix J. Hepatocellular carcinoma. *Lancet* 2018; 391:1301–1314.
- 4 Sapisochin G, Bruix J. Liver transplantation for hepatocellular carcinoma: outcomes and novel surgical approaches. *Nat Rev Gastroenterol Hepatol* 2017; 14:203–217.
- 5 Roberts JP. Tumor surveillance-what can and should be done? Screening for recurrence of hepatocellular carcinoma after liver transplantation. *Liver Transpl* 2005; 11 (Suppl 2): S45–S46.
- 6 Schwartz M, Roayaie S, Llovet J. How should patients with hepatocellular carcinoma recurrence after liver transplantation be treated? *J Hepatol* 2005; 43:584–589.
- 7 Zimmerman MA, Grhobrial M, Tong MJ, Hiatt JR, Cameron AM, Hong J, Busuttill RW. Recurrence of hepatocellular carcinoma following liver transplantation: a review of preoperative and postoperative prognostic indicators. *Arch Surg* 2008; 143:182–188.
- 8 Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. *Hepatology* 2011; 53:1020–1022.
- 9 Pugh RNH, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* 1973; 60:649–649.
- 10 Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, *et al.* A model to predict survival in patients with end-stage liver disease. *Hepatology* 2001; 33:464–470.
- 11 Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958; 53:457–481.
- 12 Cox DR. Regression models and life-tables. In: Kotz S, Johnson NL, editors. *Breakthroughs in statistics*. New York, NY: Springer; 1992. pp. 527–541.
- 13 Schoenfeld D. Partial residuals for the proportional hazards regression model. *Biometrika* 1982; 69:239–241.
- 14 Team RC. *R language definition*. Vienna, Austria: R Foundation for Statistical Computing; 2016.
- 15 De'Angelis N, Landi F, Carra MC, Azoulay D. Managements of recurrent hepatocellular carcinoma after liver transplantation: a systematic review. *World J Gastroenterol* 2015; 21:11185–11198.
- 16 Hollebecque A, Decaens T, Boleslawski E, Mathurin P, Duvoux C, Pruvot FR, Dharancy S. Natural history and therapeutic management of recurrent hepatocellular carcinoma after liver transplantation. *Gastroenterol Clin Biol* 2009; 33:361–369.
- 17 Ringe B, Pichlmayr R, Wittekind C, Tusch G. Surgical treatment of hepatocellular carcinoma: experience with liver resection and transplantation in 198 patients. *World J Surg* 1991; 15:270–285.
- 18 Iwatsuki S, Starzl TE, Sheahan DG, Yokoyama I, Demetris AJ, Todo S, *et al.* Hepatic resection versus transplantation for hepatocellular carcinoma. *Ann Surg* 1991; 214:221–228.

- 19 Bismuth H, Chiche L, Adam R, Castaing D, Diamond T, Dennison A. Liver resection versus transplantation for hepatocellular carcinoma in cirrhotic patients. *Ann Surg* 1993; 218:145–151.
- 20 Moreno P, Jaurieta E, Figueras J, Benasco C, Rafecas A, Fabregat J, et al. Orthotopic liver transplantation: treatment of choice in cirrhotic patients with hepatocellular carcinoma? *Transplant Proc* 1995; 27:2296–2298.
- 21 Bhorri S, Mazzaferro V. Current challenges in liver transplantation for hepatocellular carcinoma. *Best Pract Res Clin Gastroenterol* 2014; 28:867–879.
- 22 Piñero F, Tisi Baña M, de Ataide EC, Hoyos Duque S, Marciano S, Varón A, et al. Latin American Liver Research, Education and Awareness Network (LALREAN). Liver transplantation for hepatocellular carcinoma: evaluation of the alpha-fetoprotein model in a multi-center cohort from Latin America. *Liver Int* 2016; 36:1657–1667.
- 23 Fernandez-Sevilla E, Allard MA, Selten J, Golse N, Vibert E, Sa Cunha A, et al. Recurrence of hepatocellular carcinoma after liver transplantation: is there a place for resection? *Liver Transpl* 2017; 23:440–447.
- 24 Agopian VG, Harlander-Locke M, Zarrinpar A, Kaldas FM, Farmer DG, Yersiz H, et al. A novel prognostic nomogram accurately predicts hepatocellular carcinoma recurrence after liver transplantation: analysis of 865 consecutive liver transplant recipients. *J Am Coll Surg* 2015; 220:416–427.
- 25 Clavien PA, Lesurtel M, Bossuyt PM, Gores GJ, Langer B, Perrier A. OLT for HCC Consensus Group. Recommendations for liver transplantation for hepatocellular carcinoma: an international consensus conference report. *Lancet Oncol* 2012; 13:11–22.
- 26 Roayaie S, Schwartz JD, Sung MW, Emre SH, Miller CM, Gondolesi GE, et al. Recurrence of hepatocellular carcinoma after liver transplant: patterns and prognosis. *Liver Transpl* 2004; 10:534–540.
- 27 Rahimi RS, Trotter JF. Liver transplantation for hepatocellular carcinoma: outcomes and treatment options for recurrence. *Ann Gastroenterol* 2015; 28:323–330.
- 28 Adam R, Karam V, Delvart V, O'Grady J, Mirza D, Klempnauer J, et al. All the contributing centers (www.eltr.org) and the European Liver and Intestine Transplant Association (ELITA). Evolution of indications and results of liver transplantation in Europe. A report from the European Liver Transplant Registry (ELTR). *J Hepatol* 2012; 57: 675–688.
- 29 Irtan S, Barbier L, Francoz C, Dondéro F, Durand F, Belghiti J. Liver transplantation for hepatocellular carcinoma: is zero recurrence theoretically possible? *Hepatobiliary Pancreat Dis Int* 2016; 15: 147–151.
- 30 Bodzin AS, Lunsford KE, Markovic D, Harlander-Locke MP, Busuttil RW, Agopian VG. Predicting mortality in patients developing recurrent hepatocellular carcinoma after liver transplantation: impact of treatment modality and recurrence characteristics. *Ann Surg* 2017; 266:118–125.
- 31 Sapisochin G, Goldaracena N, Astete S, Laurence JM, Davidson D, Rafael E, et al. Benefit of treating hepatocellular carcinoma recurrence after liver transplantation and analysis of prognostic factors for survival in a large Euro-American Series. *Ann Surg Oncol* 2015; 22:2286–2294.
- 32 Na GH, Hong TH, You YK, Kim DG. Clinical analysis of patients with hepatocellular carcinoma recurrence after living-donor liver transplantation. *World J Gastroenterol* 2016; 22:5790–5799.
- 33 Nagai S, Mangus RS, Kubal CA, Ekser B, Fridell JA, Klingler KR, et al. Prognosis after recurrence of hepatocellular carcinoma in liver transplantation: predictors for successful treatment and survival. *Clin Transplant* 2015; 29:1156–1163.