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ORIGINAL ARTICLE

Superiority of transplantation versus resection for the treatment of small hepatocellular carcinoma

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Summary

The best therapy for hepatocellular carcinoma (HCC) is still debated. Hepatic resection (HR) is the treatment of choice for single HCC in Child A patients, whereas liver transplantation (LT) is usually reserved for Child B and C patients with single or multiple nodules. The aim of this study was to compare HR and LT for HCC within the Milan criteria on an intention-to-treat basis. Forty-eight patients were treated by LT and 38 by HR. The median time on the waiting list for transplantation was 118 days. The estimated overall survival was significantly higher ($P = 0.005$) in the LT group than in the HR one. The estimated freedom from recurrence was also significantly higher ($P < 0.0001$) for LT patients than for HR ones. Indeed, the probability of HCC recurrence after resection was higher than after transplantation achieving 31% and 76% for HR and 2% and 2% for LT at 3 and 5 years after surgery. Multivariate analysis confirmed that transplantation was superior to resection in terms of patient's survival and risk of HCC recurrence. We conclude that LT is superior to HR for small HCC in cirrhotic patients assuming that LT should be performed within 6–10 months after listing to reduce the dropouts for reasons of tumor progression.

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cause of mortality from cancer worldwide and is responsible for about 1 million deaths yearly [1]. This neoplasm is almost always associated with cirrhosis at least in developed countries and recognizes chronic hepatitis C and B infection, alcoholic cirrhosis and hemocromatosis as the main risk factors. Liver resection and transplantation are considered the only two potentially curative treatments for this cancer [2,3]. Hepatic resection (HR) has achieved improvement in survival within the past decade as a result of advances in diagnosis and surgical management of HCC [4]. However, the long-term prognosis remains poor, and the 5-year overall survival rate ranges between 33% and 44% [5], with a 5-year cumulative recurrence rate of 80% to 100% [6]. Liver transplantation (LT) could be viewed as the optimal treatment for HCC because of the widest possible resection margins for tumor and removal of the underlying cirrhotic parenchyma being at risk for the recurrence of HCC; transplantation is also a definitive cure for cirrhosis and its related complications [7]. Hepatic transplantation for HCC performed within well-defined oncologic criteria has shown long-term results comparable with those of transplantation for non-HCC patients [8,9]. However, the chronic shortage of donors' organs together with the increasing number of patients awaiting transplantation makes this therapeutic option less available to the individual patients [10]. Owing to the limited organ supply,

many liver transplant centers usually make a selection to resect patients with Child–Pugh A chronic liver disease and single nodule HCC and to reserve transplantation for those with impaired liver function and small oligonodular HCC considered within the currently accepted criteria for transplantation [11,12]. The aim of this study was to compare the results of HR and LT for HCC diagnosed within the Milan criteria preoperatively on an intention-to-treat basis in a single center over a 10-year period.

Patients and methods

Between 1996 and 2005, a total of 86 patients affected by HCC, defined within the Milan criteria by preoperative staging, were evaluated by charts review. The decision on how to proceed with resection was based on the age of the patient (all case older than 68 years) or functional liver reserve (Child A patients or initial Child B without portal hypertension and with normal bilirubin). Inclusion criteria for transplantation (age <68 years and tumor within the Milan criteria irrespectively of functional liver reserve and presence of portal hypertension) were those adopted by the Nord Italia Transplant program (http://www.nitp.org/), which is the organ procurement organisation (OPO) that coordinates LT in our geographical area.

Liver transplantation for HCC

From 1996 to 2005, 48 patients underwent LT for HCC at the Department of Surgery and Transplantation of the University of Udine, Italy (46 from heart beating cadaveric and two from living related donors). The diagnosis of HCC was based on preoperative imaging studies (ultrasound and computed tomography (CT) scan). No HCC biopsy was performed according to our center's policy. All patients were cirrhotic; twenty-six (54%) and six (12%) cases, respectively, were HCV (one HIV positive) and HBV positive, 13 (27%) patients had alcoholic cirrhosis, three cases were diagnosed with cryptogenetic cirrhosis. Child Pugh score was A, B and C in 42%, 41% and 17% of cases, respectively. The median MELD score was 14. All the HCC cases listed for transplantation fulfilled the Milan criteria preoperatively, as our policy is to exclude from transplantation cases exceeding those criteria. All cases eligible for transplantation underwent preoperative HCC treatment with trans-arterial-chemoembolization (TACE) as a measure to control tumor growing while the patient was on the waiting list. Only two patients dropped out from the liver waiting list for reasons of tumor progression. Immunosuppressive regimen was based on calcineurin inhibitors (tacrolimus or cyclosporine) associated with steroids usually discontinued 3 months after transplantation.

Hepatic resection for HCC

From 1996 to 2005, 38 patients, affected by HCC resulting within the limit of the Milan criteria after pre-operative staging, underwent HR at the Department of Surgery and Transplantation of the University of Udine, Italy. The diagnosis of HCC was based on preoperative imaging studies (ultrasound and/or CT scan); no HCC biopsy was performed. All patients had cirrhosis; 20 (53%) and six (16%) cases, respectively, were HCV and HBV positive, 13 (34%) patients had alcoholic cirrhosis. Child Pugh score was A in 74%, B in 26% of cases, respectively, none was Child Pugh score C. The median MELD score was 11. HRs were always performed by two senior surgeons (F. B. and A. U.) using the intermittent pedicle clamping technique (15–20 min followed by 5-min reperfusion) with the aid of Ligasure™ or by kellyclasia.

Statistical analysis

Quantitative variables were compared with the Student or Mann–Whitney test according to their distributions. For comparison of qualitative variables chi-squared or Fisher's test was used after assumptions were verified. The time to event (death or tumor recurrence) was calculated from the day of indication of surgery (for the HR group) or inclusion into the waiting list (for the LT group). Data accrual was closed on March 23, 2006.

Because the comparative study was not randomized, analysis of survival and time to HCC recurrence for LT and HR groups was performed using Cox proportional hazard models, after we verified the proportional hazards assumption, to obtain an estimate of the treatment effect adjusted by prognostic covariates [13]. Multivariate stepwise analyses included all variables significant at $P \leq 0.10$ in a univariate analysis [14]. Retention in the stepwise model required that the variable be significant at $P \leq 0.05$ in a multivariate analysis [15]. The variables considered as possible prognostic factors (Table 1) were age, gender, alcoholic assumption, hepatitis B virus, and C virus infections status, Child–Pugh scores, HCC focal status, tumor grading, HCC nodules number and diameter, Milan histological criteria satisfied, tumor-node-metastasis (TNM) tumor staging classification, microvascular invasion and nodules capsulation.

Graphical representations of time to tumor recurrence and to death for LT and HR groups, which account for Cox regression model adjustment, were used [16,17].

Statistical analyses were performed with STATA/SE 9.0 for Windows (Statacorp LP, College Station, TX, USA).

Table 1. Characteristics of liver transplantation (LT) and hepatic resection (HR) samples.

	LT (#48)	HR (#38)	*P*-value
Gender (M/F)	42/6	28/10	NS
Median age (range)	56 (37–67)	65 (48–79)	<0.0001
Child–Pugh (%)			
A	41	74	Fisher's test
B	42	26	0.002
C	17	0	
Viral serology (%)			
HCV	54	53	NS
HBV	12.5	13	NS
Alcoholism (%)	27	34	NS
Points out of Milan criteria at pathology (%)	27	0	<0.0001
Multifocal hepatocellular carcinoma (HCC) (%)	65	16	<0.0001
Number of nodules (mean ± SD)	2.0 ± 1.1	1.2 ± 0.5	<0.0001
Diameter (cm) of nodules (mean ± SD)	3.7 ± 2.5	3.5 ± 1.1	NS
HCC grading (%)			
G1	2	24	Fisher's test
G2	76	31	<0.0001
G3	22	37	
G4	0	8	
TNM (%)			
T1	17	5	Fisher's test
T2	46	92	<0.0001
T3	27	3	
T4	10	0	
Tumor capsule (%)	18	47	0.004
Vascular invasion at histology (%)	8	29	0.01

Results

Liver transplantation for HCC

Liver transplantation for HCC between 1996 and 2005 accounted for 16% of all transplants performed at the Department of Surgery and Transplantation of the University of Udine, Italy. There were 42 (87.5%) males and six (12.5%) females, with a mean age at transplantation of 56.1 years (SD = 7.31 years). The median waiting list time was 118 days, with two drop-outs for HCC progression. Those two patients had a multifocal tumor (three nodules <3-cm diameter) that dropped out despite TACE in both cases, respectively, at 78 and 92 days after listing. Pathological tumor staging, according to the American Liver Tumor study Group Modified TNM staging classification [18], was T1 in 17%, T2 in 46%, T3 in 27% and T4a in 10% of cases. Thirty-five percent and 65% of patients had, respectively, monofocal and multifocal HCC and 27% of cases exceeded the Milan criteria after pathological examination of the surgical specimen. The mean number and diameter of HCC nodules were 2.0 ± 1.1 and 3.7 ± 2.5 cm at pathology versus 1.8 ± 0.9 and 2.7 ± 1.2 cm at CT-scan (respectively $P = 0.17$ and $P = 0.03$). The average necrosis of HCC nodules as a result of pretransplant TACE was 38 ± 40%. Microvascular invasion was present in four cases (8%) and the HCC nodules were capsulated in 18% of cases. Tumor grading was G1 in 2%, G2 in 76%, G3 in 22% of cases. Ten patients died after transplantation, five (10%) within 1 months from the transplant (four died of multi-organ failure and one for graft failure caused by hepatic vein thrombosis), one each died of pontine demielinization and sepsis, respectively, 6 and 14 months after transplantation and two died of late recurrence of HCV. Only one patient died of metastatic HCC to the lung 14 months after transplantation without evidence of disease within the liver graft. This patient was a T4a/G2 with microvascular invasion and developed multiple lung metastasis 2 months after the transplant despite preoperative negative pulmonary CT scan. No cases of HCC recurrence within the liver were encountered at a median follow-up of 21 months (range: 1–85 months). The 1, 3 and 5 years estimated overall survival rates were, respectively, 84%, 78% and 72%, median survival was not reached after 5 years. One, 3 and 5 years estimated overall survival rates were, respectively, 89%, 84% and 76% for T1 and T2 pathological staging considered together and 76%, 68% and 68% for T3 and T4a pathological staging also considered together. The overall survival curves of T1-T2 and T3-T4a groups were not significantly different (Log rank test: $P = 0.28$). Median survival was not also reached after 5 years for both T1-T2 and T3-T4a. The estimated 1-, 3- and 5-year freedom for recurrence probabilities were 98%, 98% and 98%, respectively.

Hepatic resection for HCC

There were 28 (73.7%) males and 10 (26.3%) females, with a mean age at surgery of 64.5 years (SD = 7.05 years). Types of resections performed were wedge resections in 17 cases (45%), mono-segmentectomy in 13 cases (34%), bi-segmentectomy in seven cases (18%) and one left hepatectomy (3%). The minimal margin from the tumor to the cut surface was more than 1 cm in 26% and <1 cm in 68% of cases. At pathological examination of the specimen, tumor stage was T1 in 5%, T2 in 92% and T3 in 3% of cases. Eighty-four percent and 16% of patients had, respectively, monofocal and multifocal HCC. The mean number and diameter of HCC nodules were 1.2 ± 0.5 and 3.5 ± 1.1 cm at pathology. HCC nodules were capsulated in 18 cases (47%). Tumor grading was G1 in 24%, G2 in 31%, G3 in 37% and G4 in 8% of cases. Eleven cases (29%) had microvascular invasion at pathological exami-

nation of the resected specimen. Early (within 30 days after surgery) operative mortality was 5% (two out of 38) and was because of peritoneal bleeding and peritonitis in one case each. Seven cases (18%) died of terminal hepatic failure at a median follow-up of 29 months after HR (range: 1–71 months). Thirteen cases (34%) experienced HCC recurrence within the liver at a median follow-up of 36 months (range: 10–84 months); of these, three (23%) died of recurrent metastatic HCC at 66 ± 12 (mean ± SD) months after resection. Eight percent of resected cases (three out of 38) died of recurrent HCC. Sixteen patients (42%) died of cause unrelated to the liver disease; of these six (37.5%) had recurrent HCC at the moment of death; a majority of these patients died of cardiovascular disease reflecting the older age of the resection group. Finally, 10 patients (26%) were alive at a median follow-up of 30 months (range: 15–70) from surgery none with recurrent HCC. The 1, 3 and 5 years estimated overall survival rates were, respectively, 82%, 61% and 27%; median survival was reached at 44 months. One, 3 and 5 years estimated overall survival rates were, respectively, 81%, 60% and 28% for T1 and T2 pathological staging considered together; median survival was also reached at 44 months for T1-T2. Only one patient was T3 with a survival time of 42 months. The 1-, 3- and 5-year freedom for recurrence probabilities were 97%, 75% and 37%, respectively.

Comparison of liver transplantation and hepatic resection

The characteristics of LT and HR samples are compared in Table 1. Patients treated by HR were significantly older and had a capsulated tumor more frequently than transplanted cases. As expected, LT patients had a Child–Pugh score significantly different from the resected counterpart ($P = 0.002$); most of the patients who underwent resection were Child A. Moreover, transplanted cases had a higher number of HCC nodules with also a larger diameter (only 16% of resected cases had more than one nodule of HCC, while 65% of transplant cases were multifocal); 13 (27%) transplant cases and no one resection cases were out of the Milan criteria at pathological examination of the specimens. Resected cases showed vascular invasion more frequently than HCC treated by transplantation (29% vs. 8%, $P = 0.01$); the four vascular invasion in the LT group were G2 in three cases and G3 in one case; the 11 vascular invasion in the HR group were G2, G3 and G4, respectively, in two, seven and two cases, showing that most of the tumors with vascular invasion were also less differentiated (82% G3-G4). Notably, HCC grading levels were differently distributed in the LT and HR samples, with statistical significance ($P < 0.0001$) and with more of less differentiated cases in the HR group. TNM typology was also differently distributed in the LT and HR samples, with statistical significance ($P < 0.0001$). More patients treated by HR were T2, while T3 and T4a were more frequent among liver transplanted cases. HCC recurrence was more frequent after resection than after transplantation being, respectively, 34% and 2% ($P < 0.0001$) of cases. LT patients had a recurrence free time significantly higher than the HR ones ($P < 0.0001$). Most of the liver-related deaths (78%) in the HR group were caused by progression of cirrhosis. Only two transplanted cases died of cirrhosis caused by HCV recurrence. The operative mortality, defined as death within 30 days from surgery, was 10% after transplantation and 5% after resection (P = NS).

Prognostic factors that displayed significant associations ($P \leq 0.10$) with survival or time to HCC recurrence in the univariate proportional hazards model are shown in Table 2. These variables comprised the eligible pool of predictors for stepwise proportional hazards model used to predict survival and time to HCC recurrence.

Four variables were eligible for inclusion by the model predicting survival (Table 2). The Cox final model included only treatment. The estimated overall survival was significantly higher after transplantation than after resection (Fig. 1). Liver resected patients showed a hazard ratio 2.7 times [$P = 0.008$, $CI_{95\%}$: (1.30–5.62)] higher than the transplanted ones.

Table 2. Proportional hazards analysis of prognostic factors against survival and time to hepatocellular carcinoma recurrence ($P \leq 0.10$).

	Survival			Recurrence		
Characteristic	Hepatic resection (HR)	*P*	95% CI	HR	*P*	95% CI
Treatment*	2.70	0.008	(1.30–5.62)	17.78	0.006	(2.30–137.58)
Age	1.04	0.057	(1–1.09)	1.12	0.003	(1.04–1.21)
Child–Pugh scores	0.45	0.013	(0.24–0.84)	0.35	0.069	(0.11–1.09)
Vascular invasion**	2.09	0.062	(0.96–4.53)			

*Liver transplantation as reference category; **Not having as reference category.

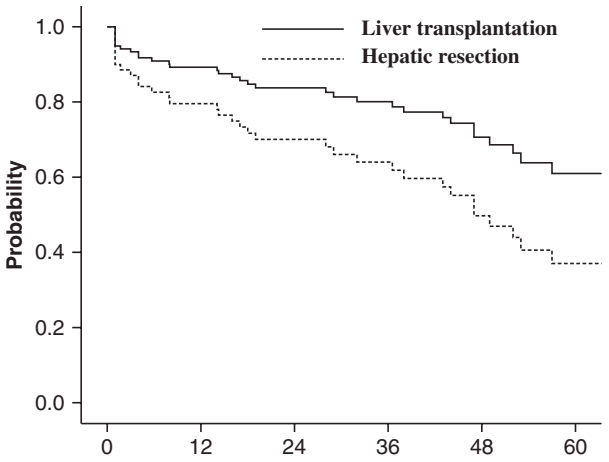

Figure 1 Graphical representation of the overall survival curves by treatment group, which account for Cox regression adjustment.

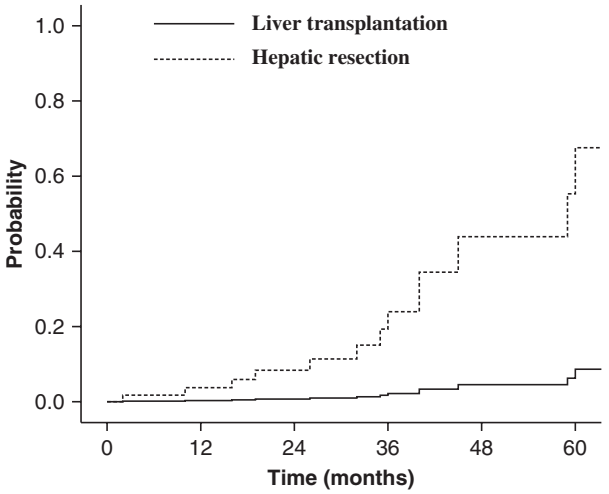

Figure 2 Graphical representation of the hepatocellular carcinoma recurrence probabilities by treatment group, which account for Cox regression adjustment.

Three variables were eligible for inclusion by the model predicting the time to HCC recurrence (Table 2). The final model also included only treatment. Graphical representation of the HCC recurrence probabilities after HR and LT, which accounts for Cox regression adjustment, is shown in Fig. 2. The estimated freedom from recurrence was also significantly higher for LT patients than for HR ones (Fig. 3). Liver resected patients showed a hazard ratio 17.78 times [$P = 0.006$, $CI_{95\%}$: (2.30–137.58)] higher than the transplanted ones.

Discussion

This study was designed as an analysis of patients affected by cirrhosis and HCC. We compared 48

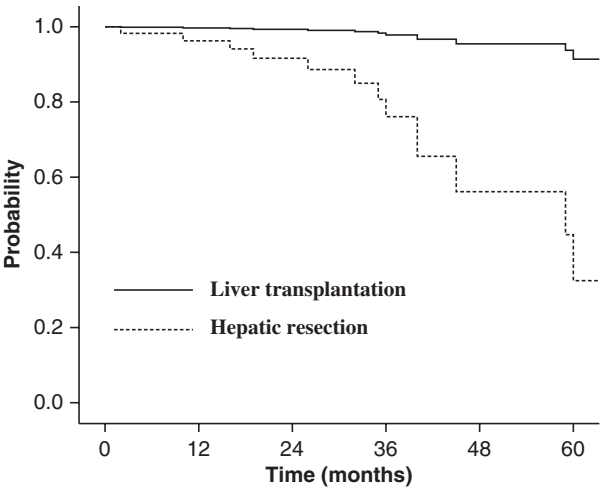

Figure 3 Graphical representation of the time to recurrence curves by treatment group, which account for Cox regression adjustment.

patients who were treated by LT and 38 cases subjected to HR; both cohorts were diagnosed preoperatively with an HCC considered within the Milan criteria [8] for transplantation. The main objective of this study was to compare the overall survival and freedom from recurrence of the patients and the risk of HCC recurrence in each of the two groups. This is a very important topic because of the fact that HR and LT are practical options for patients affected by cirrhosis and HCC, especially in the setting of a patient with Child A cirrhosis, while cases with decompensated liver disease may be candidate only for transplantation [19]. The dilemma whether to resect or transplant these subset of patients is even more compelling because of the shortage of organs and limitation of resources [20,21]. The two populations studied were comparable in terms of gender with a majority of male patients and etiology of the liver disease being predominantly related to viral cirrhosis. Not surprisingly, patients treated by resection were older than transplanted cases, as several studies [22,23] have shown that age does not have any particular significance in the peri-operative mortality in patients who undergo liver resection, while older age has a major impact on early post-transplant survival. As expected, more patients in the transplant group had advanced stage cirrhosis (Child–Pugh B and C), while resected cases were mainly Child–Pugh A. The tumor characteristics showed a higher frequency of multifocal HCC and a greater number of nodules in the transplant cohort; however, no difference was noted in the mean diameter of nodules between the two groups; also, transplanted cases were more frequently better differentiated and appeared with microscopic vascular invasion less commonly than cases

treated by resection. Cillo *et al.* [24] showed that moderately and well-differentiated HCC fare well after transplantation also when exceeding the commonly accepted criteria for transplantation. The number of cases found to be out of the Milan criteria at pathological specimen evaluation was higher in the transplant cohort. Interestingly, although more patients treated by HR were T2, patients in T3 and T4a were more commonly encountered in liver transplanted cases (Table 2), HCC recurrence was more frequent after resection than transplantation (34% vs. 2% $P < 0.0001$) with a probability of HCC recurrence of 63% 5 years after resection versus 2% after transplantation. However, HCC was the primary cause of death in only 23% of cases with HCC recurrence after resection, while the single case of HCC relapse after transplantation died of metastatic disease, confirming that tumor recurrence after transplantation has a very aggressive biological behaviour probably because of the younger age of the patient and immunosuppressive therapy [25–27], while resected cases probably fare better as a result of higher applicability of alternative therapies to control less aggressive tumor recurrence [28]. Although only 26% of the resected HCC had a free margin >1 cm, none of the tumors had a positive resection margin and the width of the margin does not seem to have any significance for recurrence [29]. The high mortality in the HR series caused by progression of cirrhosis and general causes unrelated to the liver disease reflects the progression of cirrhosis in the absence of LT and the older age of the resected population, as reported in the literature [30]. In our series, the surgical related mortality was not different between transplantation and resection, although some authors suggested that LT might be burdened by higher operative risks [31]. Overall survival and freedom from recurrence were both significantly higher in the transplanted population than after HR.

Multivariate analysis showed that liver resected patients had a hazard ratio of dying and having an HCC recurrence 2.7 times [$P = 0.008$, $CI_{95\%}$: (1.30–5.62)] and 17.78 times [$P = 0.006$, $CI_{95\%}$: (2.30–137.58)], respectively, compared to the transplanted ones.

A French study [32] showed results similar to the present series also when salvage LT was attempted in cases of HCC recurrence after primary resection. The authors concluded that primary LT should remain the ideal choice of treatment of a cirrhotic patient with HCC even when tumor is resectable. A study from Bigourdan *et al.* [33], comparing resection and transplantation for HCC patients with Child A cirrhosis, concluded that LT resulted in overall survival and freedom from recurrence generally better than HR. However, this assumption should take into account the limited availability of organs for transplantation. Majno *et al.* [20] showed that life expectancy was 8.8 years for primary transplantation versus 7.8 years for resection eventually followed by salvage transplantation, with a calculated use of grafts at 5 years of 52% for primary transplantation versus 23% for salvage transplantation; they concluded suggesting that this strategy may be a rational way to cope with lengthening of the waiting list. Moreover, Llovet *et al.* [10] reported no difference in long term survival of transplantation versus resection for HCC on an intention to treat basis, probably because of a higher incidence of drop outs on the waiting list. In our experience, we had only two dropouts for reasons of tumor recurrence in the liver waiting list. Hepatic tumors listed for transplantation were always treated with TACE while waiting for a donor and were transplanted within a mean of <4 months from listing, which compares favourably with waiting time reported in the literature for HCC [34]; moreover, living donation was performed in two cases and could be used as a strategy to reduce the waiting list time [35]. According to Sarasin *et al.* [36], when compared to HR, LT for otherwise resectable HCC offers substantial survival benefit among well-targeted subgroups of patients as long as an organ donor is available within a maximal 6–10 months time delay. Also series [37,38] reporting similar long term survival between transplanted and resected patients within the commonly accepted criteria for transplantation showed a higher tumor recurrence after resection, with salvage LT available only in 16.2% of cases [19].

We conclude that LT in our experience is superior to HR for the treatment of small HCC in cirrhotic patients. It might be suggested that removing the entire cirrhotic liver during transplantation provides a more accurate and radical oncologic criterion than resecting the detectable HCC nodule leaving the remnant cirrhotic liver that probably hinders some neoplastic foci undetectable with the current diagnostic methods [39–41]. An effort to transplant HCC patients within 6–10 months after listing is a mainstay to reduce the risk of dropouts because of tumor progression; this goal has been achieved (median waiting list time of 118 days with only two drop outs for HCC progression) in the setting of a region with a high volume of donor's organ without damaging the prioritization of non-HCC patients.

Authorship

UB designed the study, analyzed the data and wrote the paper. MI and FS analyzed the data and wrote the paper. GLA, EB, CA and AR analyzed the data. DL, FB, AU and APB collected the data. DA and VB designed the study.

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