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Clinical Outcomes of Liver Transplantation for HBV-Related Hepatocellular Carcinoma: Data from the NIH HBV-OLT Study

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Abstract

Background—Hepatitis B virus (HBV)-related hepatocellular carcinoma (HCC) is an indication for orthotopic liver transplantation (OLT) in patients with tumor stage within the UNOS criteria. The number of patients listed for HBV-related HCC is increasing while the number of patients listed for HBV-related cirrhosis is declining presumptively due to the availability of more effective oral nucleos(t)ide analogues. This study presents the final, long-term outcome of patients transplanted for HBV-related HCC in the National Institutes of Health (NIH)-HBV OLT Study Group.

Results—Ninety-eight patients (52.4%) in the NIH-HBV OLT cohort underwent OLT for HBV-related HCC. With a mean follow-up of 36.5 months post-OLT, 12 (12.2%) patients developed recurrence of HCC. Multivariate analysis did not find a statistically significant role of gender, tumor stage at OLT, pre-OLT HCC treatment, recurrence of HBV, or duration of HCC diagnosis pre-OLT in predicting HCC recurrence. Serum alpha-fetoprotein (AFP) level greater than 200 ng/mL at transplant was found to be statistically significant in predicting HCC recurrence ($p=0.003$). HCC recurrence was significantly associated with decreased post-OLT survival.

Conclusion—HCC is the most common indication for OLT in patients with chronic hepatitis B (CHB) in the era of more effective oral antivirals. Serum AFP at the time of OLT is significantly associated with HCC recurrence.

Keywords

Hepatitis B virus; recurrence; liver cancer; risk factors; predictors

INTRODUCTION

Chronic hepatitis B virus (HBV) infection is a major global health problem and affects approximately 2 million persons in the United States (1). The consequences of chronic HBV infection include cirrhosis, liver failure, and hepatocellular carcinoma (HCC). Liver failure due to chronic HBV infection is an important indication for orthotopic liver transplantation (OLT) and presently accounts for approximately 2% of liver transplants performed in the United States (2). HCC is an indication for OLT in patients with tumor stage falling within Milan criteria in whom exception points are granted in the current era of organ allocation based on the Model for End Stage Liver Disease (MELD) (3;4). Recent advances in the therapeutic armamentarium of chronic hepatitis B (CHB) with the availability of more potent oral nucleos(t)ide analogues with lower rates of antiviral drug resistance have decreased disease progression in patients with CHB (5–7). Indeed, it has been reported that the number of patients listed for OLT due to liver failure from CHB has been declining while the number of patients listed for HBV-related HCC has increased (8). Accordingly, increased attention has been paid to possible predictors of recurrent HCC in HBV-related disease, most notably the role of recurrent HBV (9–11).

The National Institutes of Health sponsored study on “Prevention of Hepatitis B Recurrence after Orthotopic Liver Transplantation” (NIH HBV-OLT) includes 15 transplant centers in the United States and provides a unique opportunity to study several issues regarding HBV-related HCC. An earlier report compared the outcomes of 94 patients transplanted for HBV-related HCC to 75 patients transplanted for HBV cirrhosis (12). The current study focused on the final longer-term outcome of the 98 patients transplanted for HBV-related HCC.

MATERIALS AND METHODS

Patient Population

The NIH HBV OLT study enrolled hepatitis B surface antigen (HBsAg) positive patients who were 13 years or older from 15 centers in the United States. At enrollment, all patients were either on the liver transplant waiting list or were within 12 months post-transplant. The study was approved by the Institutional Review Board representing each of the participating centers, and written informed consent was obtained from all patients prior to study entry. For patients enrolled at the time of listing, data were collected prospectively. For patients enrolled after placement on the liver transplant list, data after enrollment were collected prospectively while data prior to enrollment were collected retrospectively up to the time of listing.

A total of 317 patients were enrolled. The patients were listed between 1993 and 2005. A total of 187 patients were transplanted between March 2001 and September 2007. Demographics, clinical, laboratory [blood counts, creatinine, liver panel, prothrombin time/international normalized ratio (INR), alpha-fetoprotein (AFP), hepatitis B serology and HBV DNA], and radiologic (for patients with hepatocellular carcinoma) data, as well as start and stop dates of antiviral therapy and HBIG dosing, were entered into an electronic database. Data were collected at enrollment, transplant listing, and time of transplant, every 6 months while on the transplant waiting list, every 3 months during the first year post-transplant, and every 6 months after the first post-transplant year. Data up to the time of study closure on November 30, 2007 were analyzed.

At each visit, an extra tube of blood was collected for central testing. Samples were centrifuged and stored at –70 degrees C at the participating centers and shipped to the central laboratory at the University of Michigan where they were stored at –80 degrees C prior to testing.

Data on tumor burden at listing, interventions for cancer, and dropout rate while on the waiting list were further evaluated. Explant pathology reports were evaluated by one of the investigators to determine fulfillment of United Network for Organ Sharing (UNOS) criteria and University of California, San Francisco (UCSF) criteria (13). The primary outcomes were HCC recurrence and survival following transplantation.

Hepatitis B Testing

All laboratory tests except for HBV DNA, antiviral- and HBIG- resistance mutations were performed at the participating centers. Serum HBV DNA levels were quantified by the Cobas Amplicor HBV Monitor assay (Roche Molecular Systems, Inc., Branchburg, NJ) at the central laboratory. The lower limit of detection of this assay is 200 copies/mL. Samples with values >100,000 copies/mL were diluted 1:1,000 to 1:100,000 fold and retested. For patients with missing central laboratory samples, HBV DNA results at the participating centers were used and the results converted into log₁₀ copies/mL using conversion formulae provided by the manufacturer.

Statistical Analyses

Categorical data were presented as number and percent and compared using chi-square test or Fisher's exact test as appropriate. Continuous variables were expressed as mean and standard deviation (SD) unless specified otherwise, and were compared using t-test or Mann-Whitney U-test. Serum HBV DNA level was expressed as copies/mL and logarithmically transformed. Continuous variables were dichotomized taking the median as cutoff value, except for serum HBV DNA, where the cutoff used was 5 log₁₀ copies/mL. Univariate analyses of factors associated with HCC recurrence post-transplant were performed using Kaplan-Meier analysis with log rank test. For this purpose patient demographics, HCC diagnosis time, tumor stage at listing and at OLT, pretransplant treatment for HCC, transplant center, level of AFP at OLT, and presence of HBV recurrence were analyzed. Variables that had a p value of < 0.2 on univariate analysis were entered into a Cox regression hazards model. Forward and backward logistic regression was performed to determine the independent predictors of HCC recurrence. All statistical analyses were performed using SPSS v. 14.0.8 statistical software (SPSS, Inc., Chicago, IL).

RESULTS

Characteristics of Study Patients

Of the 187 patients transplanted in the NIH HBV OLT study, 98 patients (52.4%) underwent OLT for HBV-related HCC and comprised the cohort for the current study. Characteristics of the study cohort are summarized in Table 1. Seventy-three patients (74.5%) with known HCC at listing comprised the largest group compared to 17 patients (17.3%) who developed HCC on the waiting list and 8 patients (8.2%) diagnosed with incidental HCC on explant liver. In all three groups, males predominated. The mean age of 55 years was similar across all the groups. Though Asians were most prevalent overall, among individual groups, Asians predominated only in the group with known HCC at listing, whereas Caucasians predominated in the other two groups.

Laboratory tests at the time of listing and transplantation are also summarized in Table 1. HBV DNA was undetectable in 50% at the time of listing and increased slightly to 56.3% at the time of transplant. HBV DNA greater than 5 log₁₀ copies/mL was present in 41.3% of patients with available sera for analysis at the time of transplant. In patients with detectable HBV DNA, mean HBV DNA was 4.1 log₁₀ copies/mL at the time of transplantation. Anti-HCV was detectable in five patients. Anti-HDV was detectable in one patient. No patient tested positive for anti-HIV. The mean serum AFP increased from 262 ng/mL at the time of

listing to 448 ng/mL by the time of transplant. Among the different groups, the group with incidental HCC was characterized by significantly lower serum AFP measurements compared to the other groups with known HCC. While waiting on the transplant list, there was no significant deterioration in clinical status as measured by mean CTP scores, and the mean MELD score increased slightly from 13.2 at listing to 15.4 by the time of transplant.

Data regarding the use of antiviral therapy is summarized in Table 1. At the time of listing, 61 patients (62.2%) had been receiving antiviral therapy for HBV. By the time of transplantation, 76 patients (74.5%) were receiving antiviral therapy, of which 14 patients (18.4%) had documented viral breakthrough.

Tumor staging before transplantation (based on computed tomography/magnetic resonance [CT/MR] imaging studies at the participating centers) and after transplantation (based on explant pathology) are summarized in Table 2. Among the 73 patients with known HCC at listing, information regarding tumor stage was available in 67 patients. Of these 67 patients, 51 patients (76.1%) had tumors within the Milan criteria and 16 patients (23.9%) had tumors outside the Milan criteria. Applying the UCSF criteria to the radiologic findings, 53 patients (79.1%) had tumors within the UCSF criteria, and 14 (20.8%) had tumors outside the UCSF criteria. Among the 17 patients diagnosed with HCC while on the waiting list, information on tumor stage was available in 14 patients. Of these 14 patients, 10 had tumors within the Milan criteria and 12 had tumors within the UCSF criteria. Seventeen patients had “unknown” stage of tumor before transplant because of missing or inadequate data in 9 patients and tumor diagnosis after transplantation in 8 patients.

After transplantation, information regarding tumor stage from explant pathology was available in all 98 patients (Table 2). In 73 patients with known HCC at listing, 41 patients (56.2%) had tumors within the Milan criteria and 53 patients (72.6%) had tumors within the UCSF criteria. In 17 patients diagnosed with HCC while awaiting transplantation, 12 had tumors within the Milan criteria and 14 had tumors within the UCSF criteria. In the 8 patients with incidental HCC on explant pathology, 5 had tumors within the Milan criteria, and 6 had tumors within the UCSF criteria. Twelve patients diagnosed with HCC at listing and two patients diagnosed with HCC while awaiting transplantation were reported to have “no HCC” on explant pathology (11 of whom had received treatment of their HCC pre-transplantation), and these 14 patients were included in the “inside Milan criteria” group for analysis. None of the 11 patients with “no HCC” on explant who had received treatment of HCC pre-transplantation developed recurrent HCC post-transplantation. Thus, in total, explant pathology found that 58 patients (59.1%) had tumors within the Milan criteria and 73 patients (74.4%) had tumors within the UCSF criteria.

Four patients had tumor stages outside of Milan criteria and inside UCSF criteria (so called “downstageable” tumors) based on radiologic imaging prior to transplant. On explant pathology, 15 patients had tumors that met these criteria (12 patients had known HCC at listing, 2 patients were diagnosed with HCC while awaiting transplantation, and 1 patient had a large HCC diagnosed incidentally on explant).

Information regarding macrovascular portal vein invasion was present in 71 of 90 patients with known HCC pre-transplant and 85 of 98 patients on explant pathology (Table 2). Prior to transplant, macrovascular portal vein invasion was evident radiographically in 4 patients. On explant pathology, macrovascular portal vein invasion was detected in 10 patients.

Treatment of HCC Pre-transplantation

Pre-transplant surgical and/or radiological interventional therapies of HCC are summarized in Table 3. Prior to listing, 58 patients with known HCC had undergone treatment of their

tumors. Of these 58 patients, 8 patients (13.8%) underwent surgical resection, 44 patients (75.9%) had undergone “other” treatments as listed in Table 3, and 6 patients (10.3%) underwent a combination of both surgical and “other” treatment.

After listing and while awaiting transplantation, 48 patients underwent treatment of their tumors. Of these 48 patients, 4 patients (8.3%) underwent surgical resection. Forty-four patients (91.7%) underwent “other” therapies as listed in Table 3. Of these 44 patients, 38 patients had known HCC at the time of listing, and 6 patients were diagnosed with HCC while waiting on the transplant list.

HCC Recurrence

Clinical outcomes following transplantation are summarized in Table 4. During a mean follow-up of 36.5 months, recurrent HCC developed in 12 patients (12.2%). Of these 12 patients, 10 patients had HCC diagnosed prior to listing and two patients were diagnosed with HCC while listed for transplantation. None of the patients with incidental HCC had HCC recurrence. Recurrent HBV developed in 8 patients (8.1%), 4 had HCC diagnosed prior to listing, 2 were diagnosed with HCC while listed for transplantation, and 2 were diagnosed with HCC on explant pathology.

A comparison of clinical characteristics between patients with and without HCC recurrence is summarized in Table 5. There was no significant difference in patient demographics (gender, age, or race) between patients who developed HCC recurrence and those who did not. Neither the time of HCC diagnosis (prior to listing, while listed, or on explant pathology) (See also Figure 1), tumor stage by Milan criteria determined at the time of listing (See also Figure 2), tumor stage determined on explant pathology, presence of macrovascular invasion on explant pathology, nor HCC treatment prior to transplant was predictive of HCC recurrence. The development of HBV recurrence was also not associated with HCC recurrence. Of the 8 patients with HBV recurrence, only two had HCC recurrence. Neither pre-transplant HBV replicative status nor use of antiviral therapy pre-transplant was predictive of HCC recurrence. None of the patients with HCV or HDV coinfection had HCC recurrence, but only 5 patients had HCV coinfection and only 1 patient had HDV coinfection. HCV and HDV status was not tested in all patients.

Serum AFP level > 200 ng/mL at the time of transplant significantly predicted HCC recurrence ($p=0.003$) (See also Figure 3). In a multivariate analytic model, serum AFP level at OLT was found to be significantly predictive of HCC recurrence (Table 6). However, gender, tumor stage at OLT, pre-OLT treatment of HCC, transplant center, or when HCC was diagnosed was not predictive of HCC recurrence.

Post-OLT Survival

During a mean follow-up of 36.5 months, 12 patients (12.2%) died (Table 4). Of these 12 patients, 8 patients were diagnosed with HCC prior to listing, 3 patients were diagnosed with HCC while listed, and 1 patient was diagnosed with incidental HCC on explant. The cause of death was recurrent HCC (5 patients), followed by non-liver related causes (3 patients), followed by recurrent HBV, liver-related non-HCC, peri-transplant complications, and unknown causes (1 patient each).

HCC recurrence significantly impacted survival with more patient deaths occurring in the group with HCC recurrence compared to no HCC recurrence (50% versus 6.9%, $p<0.001$) (Table 7 and Figure 4).

DISCUSSION

We present the longer term follow-up of 98 patients transplanted for HBV-related HCC in the NIH-HBV OLT study consortium. During the study period (March 2001 to September 2007), HCC replaced HBV cirrhosis as the leading indication for OLT in 52.4% of the patients with CHB. This finding confirms earlier observations noting an increase in the number of patients with CHB listed for HCC as compared to a declining number of patients listed for end-stage cirrhosis since the year 2000 (8). This trend is almost certainly due to the increasing use of more effective HBV antiviral therapy with stronger potency and less risk for viral resistance. Prior studies have shown that effective suppression of HBV replication can decrease disease progression in patients with advanced CHB (14), resulting in improvement in liver function and a decrease in the MELD score of patients with HBV on the transplant waiting list (15;16). The majority of patients in our study cohort (74.5%) were taking HBV antiviral medications by the time of transplantation. Greater than half (56.3%) of the patients had detectable HBV DNA at the time of transplantation with a mean level of 4.1 log₁₀ copies/mL. However, since fewer than 20% had documented viral breakthrough by the time of transplantation, this high rate of HBV DNA detection was likely not due to viral resistance, but a reflection of inadequate duration of therapy (median 15.5 months, range 0 to 94) to fully suppress viral replication by the time of transplantation. Indeed, 16 of 76 patients receiving antiviral therapy at the time of transplant had been on treatment for less than 6 months. Despite this, there was no significant deterioration in clinical status of the patients as reflected by stable Child-Turcotte-Pugh (CTP) and MELD scores while awaiting transplantation.

While awaiting transplantation, there was apparent progression of tumor stage with more patients falling out of Milan or UCSF criteria when comparing tumor stage at/during listing to tumor stage on explant pathology. Whether this apparent progression is real or related to the variation in accuracy between radiological staging prior to transplant compared to histological staging on explant pathology is not clear. However, the overall increase in the mean serum AFP while awaiting transplantation would appear to support true tumor progression despite the fact that most of the patients (74.4%) received treatment of HCC prior to transplantation. The most common treatment modalities were local ablation utilizing transarterial chemotherapy (TAC), radiofrequency ablation (RFA), or transarterial embolization (TAE). That tumor stage progressed despite multiple administrations of adjuvant local therapy is not surprising, as these modalities are considered “non-curative”, and response rates for TAC or TAE have only ranged between 16% and 60% with fewer than 2% of treated patients ever achieving a durable response (17–19). An unusually high percent of patients (12/90, 13.3%) with known tumors had surgical resection prior to transplant. Eight of the 12 patients had HCC resection before listing. Although the explant liver revealed cirrhosis in almost all patients, it is possible that some of these patients did not have cirrhosis when HCC was first diagnosed.

Overall, HCC recurrence occurred in 12.2% of the patients during a mean follow-up of 36.5 months in our series. The mean time to recurrence after transplantation was 17.6 months. In our study, serum AFP at the time of transplantation was the only predictor of HCC recurrence. Pre-transplant serum AFP has previously been described as a predictor of HCC recurrence after OLT (20–23). In fact, pre-transplant serum AFP was deemed significant enough by Korean investigators to potentially warrant inclusion in a scoring system to determine candidacy for liver transplantation (24). Pre-transplant serum AFP is a biologically plausible marker for predicting HCC recurrence, as elevated serum AFP may be a better indicator of viable tumor mass in AFP-secreting tumors than tumor size on imaging in patients who have received extensive loco-regional treatment (25).

HBV recurrence has been reported to be associated with HCC recurrence after OLT (9–11). The mechanistic explanation of this possible relationship remains unclear, and it is intriguing to speculate whether recurrence of HCC gives rise to recurrence of HBV (as suggested by Faria et al) or whether recurrence of HBV leads to recurrence of HCC. The suggested explanation for the former scenario as discussed by Faria et al involves recrudescence of HBV replication from covalently closed circular (ccc) DNA in tumor cells. In our study cohort, we did not find a significant relation between recurrence of HBV and recurrent HCC. Indeed, only 2 of 12 patients with recurrent HCC had virological evidence of HBV recurrence. Perhaps our inability to demonstrate an association is due to the small number of recurrent HBV cases in our cohort and the use of antiviral therapy in nearly all patients. Indeed, prior studies noting a potential association between HBV recurrence and HCC recurrence were characterized by a low frequency of use of antiviral therapy and high rate of HBV recurrence in contrast to our study. Also, some studies have suggested that antiviral therapy prevents HCC recurrence in patients who have had surgical resection of their tumors (26;27).

Prior studies have also found tumor burden (size and number of tumor foci), the presence of macro- or microvascular invasion on explant pathology, and the degree of tumor differentiation to be predictive of HCC recurrence (20;22;28–32). Contrary to these reports, we did not find an association between tumor stage (either Milan or UCSF criteria) determined based on pre-transplant radiology or post-transplant explant pathology, and recurrence of HCC. Although there was a trend towards more HCC recurrence in patients transplanted with tumor stages outside Milan and/or UCSF criteria, this trend did not reach statistical significance. Additionally, recurrent HCC was also seen in patients transplanted with tumor stage within Milan criteria in our study cohort. This observation would support the notion that tumor stage alone is not completely predictive of tumor recurrence, but that tumor recurrence likely involves multiple additional factors including tumor biology and host factors. Our observation that serum AFP is highly predictive of tumor recurrence would support the importance of tumor biology.

In an earlier report of this cohort, post-transplant survival was not diminished in patients with HCC recurrence. In the current study which extended the duration of post-transplant follow-up from a median of 18.3 to 36 months and a maximum from 32.7 to 77 months post-transplant survival was significantly associated with HCC recurrence ($p < 0.001$). Of the 12 patients who died, 5 had recurrent HCC. These data highlight the importance of adequate duration of follow-up in assessing post-transplant outcomes.

The current study has some limitations, most notably being the lack of standardized protocols for HCC treatment pre-transplantation and variations in waiting time to transplantation. However, the NIH-HBV OLT study consortium offers a unique “real world” assessment of HCC recurrence in CHB patients undergoing OLT in the U.S. during an era when most patients received antiviral therapy pre-transplant and all except one patient received combination prophylaxis of antiviral therapy and hepatitis B immune globulin post-transplant.

In conclusion, HCC is now the most common indication for OLT in patients with CHB in this era of effective HBV antiviral medications. Serum AFP at the time of transplantation is significantly associated with HCC recurrence in our cohort. Tumor stage beyond Milan or UCSF criteria showed a trend towards a higher rate of HCC recurrence, but did not reach statistical significance. Our finding that HCC recurrence is not associated with HBV recurrence in an era when almost all patients received antiviral prophylaxis also merits confirmation.

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ABBREVIATIONS

AFP	alpha-fetoprotein
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CHB	chronic hepatitis B
CTP	Child Turcotte Pugh
HBeAg	hepatitis B e antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HDV	hepatitis D virus
INR	international normalized ratio
MELD	model for endstage liver disease
NIH	National Institutes of Health
OLT	orthotopic liver transplantation
RFA	radiofrequency ablation
TAC	transarterial chemotherapy
TAE	transarterial embolization
UNOS	United Network for Organ Sharing

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No. at risk:		Time after Transplantation (month)					
HCC at Listing:	73	62	51	35	19	7	
Diagnosed on the List:	17	12	11	10	5	4	
Diagnosed at OLT:	8	7	4	3	3	3	

Figure 1.
Post-transplant HCC recurrence as a function of time of HCC diagnosis. ($p=0.253$)

No. at risk:

Outside Milan and UCSF:	25	20	14	11	6	2
In Milan:	58	48	42	31	18	12
Outside Milan In UCSF:	15	13	10	6	3	1

Figure 2.
HCC recurrence as a function of tumor stage on explant liver. ($p=0.103$)

No. at risk:

AFP level at OLT >200 ng/mL:	59	50	40	30	18	10
AFP level at OLT 20-200 ng/mL:	21	17	16	11	7	4
AFP level at OLT <20 ng/mL:	17	13	9	6	2	0

Figure 3.
HCC recurrence as a function of serum AFP at transplant. ($p=0.003$)

No. at risk:

HCC Recurrence (+):	12	8	6	6	6	4
HCC Recurrence (-):	86	74	63	46	27	14

Figure 4.
Survival as a function of HCC recurrence. ($p < 0.001$)

Table 1

Characteristics of Patients Transplanted for HBV-related HCC

	HCC At Listing	HCC Diagnosed on Waiting List	HCC Diagnosed on Explant	Total
No. of Patients (%)	73 (74.5)	17 (17.3)	8 (8.2)	98 (100)
Male (%)	56 (76.7)	13 (76.5)	7 (87.5)	76 (77.6)
Age, years	55.2 ± 10.5	55.5 ± 7.8	55.4 ± 6.5	55.3 ± 9.7
Race (%)				
Caucasian	18 (24.7)	12 (70.6)	6 (75)	36 (36.7)
Asian	48 (65.8)	5 (29.6)	1 (12.5)	54 (55.1)
African American	4 (5.5)	0	1 (12.5)	5 (5.1)
Other	3 (4.1)	0	0	3 (3.1)
Labs At Listing				
HBeAg (+)	18/61 (29.5)	4/16 (25)	4/8 (50)	26/85 (30.6)
HBV DNA Detectable	31/65 (50.8)	7/15 (46.7)	3/6 (50)	43/86 (50)
HBV DNA >5 log ₁₀ c/mL	24/65 (36.9)	6/15 (35.3)	2/6 (33.3)	32/86 (37.2)
HBV-DNA [Log ₁₀ copies/ml]	3.7 ± 2.2	4.1 ± 2.4	4.5 ± 3.1	3.8 ± 2.3
Hgb	13 ± 2.2	13 ± 1.3	11.3 ± 1.4	12.9 ± 1.9
WBC	4.5 ± 1.5	4.7 ± 2.0	6.4 ± 5.1	4.7 ± 2.1
Platelet	105 ± 57.1	80 ± 41.3	70.7 ± 33.4	98.1 ± 54.2
Albumin g/dl	3.4 ± 0.7	3.0 ± 0.5	2.5 ± 0.6	3.2 ± 0.7
AST U/L	81 ± 96	94 ± 54.5	132 ± 91	87.6 ± 90.8
ALT U/L	76 ± 90	70.3 ± 42.1	89.4 ± 71	76.1 ± 82
Bilirubin mg/dL	1.8 ± 3.4	2.6 ± 2.9	8.8 ± 13.1	2.5 ± 5.0
Alk Phosp U/L	140 ± 98.2	174 ± 83	180 ± 100	148 ± 96.5
Creatinine mg/dL	0.9 ± 0.7	1.1 ± 1.1	1.7 ± 2.3	1.0 ± 0.9
INR	1.2 ± 0.3	1.3 ± 0.4	1.9 ± 0.6	1.3 ± 0.1
Anti-HCV (+)	2/60 (3.3)	3/14 (82.4)	0/8 (0)	5/82 (6.1)
Anti-HDV (+)	1/13 (7.7)	0/5 (0)	0/5 (0)	1/23 (4.3)
HIV (+)	0/60 (0)	0/16 (0)	0/8 (0)	0/84 (0)
AFP (ng/mL)	302 ± 1282	194 ± 635	13.4 ± 13.1	262 ± 1140
AFP (log ₁₀)	1.4 ± 0.11	1.35 ± 0.19	0.93 ± 0.18	1.39 ± 0.94
CTP Score	6.5 ± 1.9	8.5 ± 1.8	11 ± 2.7	7.7 ± 2.5
MELD score	13.6 ± 4.7	11.2 ± 5.5	13.1 ± 10.3	13.2 ± 7.4
Labs At Transplantation				
HBeAg (+)	16/57 (28.1)	4/15 (26.7)	2/18 (25)	22/80 (27.5)
HBV DNA Detectable	36/61 (59)	5/11 (45.5)	4/18 (50)	45/80 (56.3)
HBV DNA >5 log ₁₀ c/mL	28/61 (45.9)	2/11 (18.2)	3/8 (37.5)	33/80 (41.3)
HBV-DNA [Log ₁₀ copies/ml]	4.3 ± 2.1	2.7 ± 1.6	4.0 ± 2.8	4.1 ± 2.2
Hgb	12.8 ± 2.8	12 ± 1.7	10.9 ± 1.0	12.5 ± 2.6

	HCC At Listing	HCC Diagnosed on Waiting List	HCC Diagnosed on Explant	Total
WBC	5.0 ± 2.6	5.8 ± 5.0	5.9 ± 4.8	5.2 ± 4.5
Platelet	103 ± 51	78 ± 40	64 ± 36	95.6 ± 50
Albumin g/dl	3.4 ± 0.7	2.9 ± 0.7	2.4 ± 0.2	3.2 ± 0.7
AST U/L	175 ± 368	83 ± 65	104 ± 81	153 ± 320
ALT U/L	123 ± 230	60 ± 63	75 ± 63	108 ± 202
Bilirubin mg/dL	2.1 ± 4.1	2.9 ± 3.0	9.7 ± 12.2	2.9 ± 5.4
Alk Phosp U/L	146 ± 113	173 ± 87	191 ± 88	155 ± 111
INR	1.3 ± 0.5	1.5 ± 0.6	1.5 ± 0.2	1.3 ± 0.5
AFP (ng/mL)	495 ± 1718	401 ± 845	11.8 ± 15.3	448 ± 1530
AFP (log ₁₀)	1.51 ± 0.11	1.52 ± 0.28	0.82 ± 0.17	1.45 ± 0.09
CTP Score	7.6 ± 2.6	7.5 ± 2.3	10.5 ± 0.7	7.7 ± 2.5
MELD score	16.2 ± 7.8	13.3 ± 6.4	15.0 ± 8.4	15.4 ± 8.1
Antiviral Therapy				
Antiviral Rx at listing	48 (65.8)	7 (41.2)	6 (75)	61 (62.2)
Antiviral Rx at OLT	56 (76.7)	14 (82.4)	6 (75)	76 (74.5)
Duration of Rx (mos)	23.7 ± 21.8	21.7 ± 20.5	25.5 ± 28.1	23.5 ± 21.8
Virological Breakthru	11/56 (19.6)	1/14 (7.1)	2/6 (33.3)	14/76 (18.4)

Table 2

Summary of tumor staging before and after transplantation.

	Before Transplantation				After Transplantation (explant pathology)			
	HCC At Listing (n=73)	HCC Diagnosed on Waiting List (n=17)	HCC Diagnosed on Explant (n=8)	Total (n=98)	HCC At Listing (n=73)	HCC Diagnosed on Waiting List (n=17)	HCC Diagnosed on Explant (n=8)	Total (n=98)
Milan Criteria								
Inside Milan	51	10	na	61/81 (75.3)	41	12	5	58/98 (59.1)
Outside Milan	16	4	na	20/81 (24.7)	32	5	3	40/98 (45.5)
UCSF Criteria								
Inside UCSF	53	12	na	65/81 (80.2)	53	14	6	73/98 (74.4)
Outside UCSF	14	2	na	16/81 (19.8)	20	3	2	25/98 (25.5)
Unknown	6	3	8	17	0	0	0	0
Outside Milan and inside UCSF	2/67	2/14	0	4/81	12/73	2/17	1/8	15/98
Portal Vein Invasion								
No	56	11	0	67/90	56	12	7	75/98
Yes	1	3	0	4/90	7	2	1	10/98
Unknown	16	3	0	19/90	10	3	0	13/98

Table 3

Pre-transplant treatment of HCC.

	Prior to Listing	While Listed		
	HCC At Listing (n=73)	HCC At Listing (n=73)	HCC Diagnosed on Waiting List (n=17)	Total (n=90)
HCC Treatment	58	42	6	48
Surgical Treatment Alone	8	4	0	4
Other Treatment	44	38	6	44
Arterial Chemotherapy	22	20	2	22
Embolization only	6	3	1	4
RFA only	7	5	2	7
TACE only	1	2	0	2
RFA + TACE/embolization/ETOH	8	7	1	8
Systemic Chemotherapy	0	1	0	1
Surgery + Other Treatment	6	0	0	0

RFA=radiofrequency ablation, TACE=transarterial chemoembolization, ETOH=ethanol

Table 4

Clinical outcomes of patients transplanted for HCC.

	HCC At Listing (n=73)	HCC Diagnosed on Waiting List (n=17)	HCC Diagnosed on Explant (n=8)	Total (n=98)
Total Duration of FU, (Mos)	36.7 ± 18.4	34.3 ± 24.5	39.3 ± 29.3	36.5 ± 20.3
No. with HCC Recurrence	10	2	0	12 (12.2)
No. with HBV Recurrence	4	2	2	8 (8.1)
No. died	8 (10.9)	3 (17.6)	1 (12.5)	12 (12.2)
Cause of death				
Recurrent HCC	3	2	0	5
Recurrent HBV	0	1	0	1
Liver related	1	0	0	1
Non-liver Related	2	0	1	3
Peri-transplant	1	0	0	1
Unknown	1	0	0	1

Table 5

Comparison of patients with and without HCC recurrence.

	(+) HCC Recurrence (n = 12)	(-) HCC Recurrence (n = 86)	Total (n = 98)	p [*]	p ^{**}
Male (%)	11 (91.7)	65 (75.6)	76 (77.6)	0.211	0.18
Age (yrs)	51.8 ± 11.9	55.8 ± 9.4	55.3 ± 9.7	0.195	0.49
Race				0.653	0.789
Caucasian	4 (33.3)	32 (37.2)	36 (36.7)		
Asian	6 (50.0)	48 (55.8)	54 (55.1)		
African American	1 (8.3)	4 (4.7)	5 (5.1)		
Other	1 (8.3)	2 (2.3)	3 (3.1)		
Time of HCC Diagnosis				0.532	0.525
Prior to Listing	10	63	73		
While on the List	2	15	17		
On explant	0	8	8		
Milan at the time of listing				0.235	0.167
Inside Milan	5/9 (55.6)	46/58 (79.3)	51/67 (76.1)		
Outside of Milan	4/9 (44.4)	12/58 (20.7)	16/67 (23.9)		
Unknown	3/12 (25.0)	28/86 (32.6)	31/98 (31.6)		
Tumor Stage on Explant				0.113	0.103
Inside Milan	5/12 (41.7)	53/86 (61.6)	58/98 (59.1)		
Outside of Milan and inside UCSF	1/12 (8.3)	14/86 (16.2)	15/98 (15.3)		
Outside of UCSF and Milan	6/12 (50)	19/86 (22)	25/98 (25.5)		
(+) Vascular Invasion (Explant)	2/10 (20.0)	8/10 (80.0)	10/98 (10.2)		0.413
HCC Rx Prior to Transplant	10 (83.3)	57 (66.2)	67/90 (74.4)	0.234	0.204
HBV Recurrence	2 (16.6)	6 (6.9)	8 (8.1)	0.251	0.515
HBV Replication Status					
HBeAg (+) at OLT	3/11 (27.2)	19/69 (27.5)	22/80 (27.5)		0.854
HBV DNA (+) at OLT	5/11 (45.4)	40/69 (57.9)	45/80 (56.2)		0.472

	(+) HCC Recurrence (n = 12)	(-) HCC Recurrence (n = 86)	Total (n = 98)	p [*]	p ^{**}
HBV DNA > 5 log ₁₀ at OLT	3/11 (27.2)	30/69 (43.4)	33/80 (41.2)		0.379
Median serum AFP (ng/mL) at OLT (range)	50.3 (2.1–2402)	11.3 (1.5–10,006)	15.9 (1.5–10,006)	0.824	
Serum AFP at OLT > 200 ng/mL	6/12 (50.0)	11/85 (12.9)	17/97 (17.5)	0.006	0.001
Serum AFP at OLT > 20 ng/mL	8/12 (66.6)	30/85 (35.2)	38/97 (39.1)	0.040	0.035
Serum AFP at OLT > 16 ng/mL	10/12 (83.3)	37/85 (43.5)	47/97 (48.4)	0.010	0.012
Serum AFP (log ₁₀)	1.7 (0.7–3.4)	1.1 (0.2–4.0)	1.2 (0.2–4.0)	0.201	0.08
Other viral markers					
Anti-HCV (+)	0/10	5/72 (6.9)	5/82 (6.0)		0.463
Anti-HDV (+)	0/1	1/22 (4.5)	1/23 (4.3)		0.823
Antiviral therapy at the time of OLT	10 (83.3)	65 (75.6)	75 (76.3)	0.493	0.410
Virologic breakthrough prior to OLT	2 (20)	12 (18.4)	14	0.602	0.588
Post-OLT HBV prophylaxis	12	85	97	0.228	0.055
HBIG only	0	4 (4.7)	4 (4.1)		
HBIG + antiviral therapy	11 (91.7)	81 (95.3)	92 (94.8)		
Antiviral therapy only	1 (8.3)	0	1 (1.0)		
Type of antiviral Rx post-OLT				0.109	0.088
LAM	9	58	67		
ADV/TDF	0	13	13		
ETV	2	3	5		
LAM+ADV/TDF	1	6	7		
Other	0	1	1		

Results expressed as number (%) or mean ± SD unless specified otherwise

* Chi-Square, Fishers exact test or Student-t test as appropriate

** Log rank test

Table 6

Analytic model of predictors for HCC recurrence

	Univariate Analysis	Multivariate Analysis	
	p value	Hazard Ratio (95% CI)	p-value
Gender	0.180	6.01 (0.73–49.1)	0.094
Tumor staging at OLT	0.103	1.18 (0.62–2.23)	0.601
Treatment for HCC Pre-OLT	0.204	2.56 (0.39–16.55)	0.322
Transplant Center	0.019	0.96 (0.91–1.01)	0.174
Serum AFP level at OLT	0.003	2.92 (1.43–5.94)	0.006
HCC diagnosis time	0.525	1.32 (0.28–6.08)	0.721

Table 7

Factors affecting post-OLT survival

Factor	p-value
HCC Recurrence	< 0.001
HBV Recurrence	0.067
Tumor Stage at OLT	0.381
AFP level at OLT	0.518
Rx for HCC pre-OLT	0.80
Diagnosis time	0.628