ORIGINAL ARTICLE

An Intention-To-Treat Analysis of Liver Transplantation for Hepatocellular Carcinoma Using Organ Procurement Transplant Network Data

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Single-center studies have shown acceptable long-term outcomes following orthotopic liver transplantation (OLT) for hepatocellular carcinoma (HCC) when tumors are within the Milan criteria. However, the overall survival and waiting list removal rates have not been described at a national level with pooled registry data. To evaluate this, a retrospective cohort of patients listed for OLT with a diagnosis of HCC between January 1998 and March 2006 was identified from Organ Procurement Transplant Network data. Analysis was performed from the time of listing. Adjusted Cox models were used to assess the relative effect of potential confounders on removal from the waiting list as well as survival from the time of wait listing. A total of 4482 patients with HCC were placed on the liver waiting list during the study period. Of these, 65% underwent transplantation, and 18% were removed from the list because of tumor progression or death. The overall 1- and 5-year intent-to-treat survival for all patients listed was 81% and 51%, respectively. The 1- and 5-year survival was 89% and 61% for those listed with tumors meeting the Milan criteria versus 70% and 32% for those exceeding the Milan criteria ($P < 0.0001$). On multivariate analysis, advanced liver failure manifested by Child-Pugh class B or C increased the risk of death, while age $<$ 55 years, meeting the Milan criteria, and obtaining a liver transplant were associated with better survival. The current criteria for liver transplantation of candidates with HCC lead to acceptable 5-year survival while limiting the dropout rate. ***Liver Transpl 15:859-868, 2009.*** © **2009 AASLD.**

Received February 14, 2008; accepted February 19, 2009.

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide.[1] The incidence of HCC is rising in the United States and is projected to further increase over the next 2 decades.[2] Patients with cirrhosis are at the highest risk for developing this malignancy, with chronic hepatitis C virus (HCV) infection being the primary etiology responsible for the increasing incidence of HCC.[3] Surveillance programs in patients with cirrhosis enable the detection of HCC at stages at which curative treatments, such as liver transplantation, can be applied.[4]

In appropriately selected patients with HCC, orthotopic liver transplantation (OLT) has been shown to be an excellent treatment, and it is the only therapy that simultaneously treats the cancer and the underlying liver disease. In the early experience of liver transplantation for HCC, the outcomes were often dismal, largely because of transplantation of recipients with advanced tumors resulting in high rates of tumor recurrence and poor survival.[5] In a seminal study by Mazzaferro and colleagues,[6] a 4-year survival of 85% among 35 HCC patients was reported for liver recipients with a solitary

Abbreviations: AFP, alpha-fetoprotein; CI, confidence interval; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; MELD, Model for End-Stage Liver Disease; OLT, orthotopic liver transplantation; OPTN, Organ Procurement Transplant Network, RFA, radiofrequency ablation; TACE, transarterial chemoembolization; TNM, Tumor-Node-Metastasis; UNOS, United Network for Organ Sharing.

This work was supported in part by DK 064909 (to Jorge A. Marrero).

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DOI 10.1002/lt.21778
Published online in Wiley InterScience (www.interscience.wiley.com).

tumor ≤ 5 cm or with 3 or fewer tumors each ≤ 3 cm; these criteria are now commonly called the Milan criteria. Subsequent to these findings, the United Network for Organ Sharing (UNOS) in the United States adopted these criteria to determine priority for transplanting patients with HCC. In 2002, UNOS adopted the Model for End-Stage Liver Disease (MELD) system for the allocation of deceased donor livers. Patients with HCC within the Milan criteria are given priority by being assigned a higher exception MELD score, currently 22 points for liver candidates with stage II HCC.

The majority of the data on outcomes with OLT for HCC have been derived from single-center studies. The 5-year survival rates from the time of listing have ranged from 47% to 62% when withdrawals from the waiting list are included and from 61% to 74% when withdrawals from the waiting list are excluded.[7] Expanding the criteria for HCC has been proposed by some authors in light of favorable results noted in single-center studies with variable durations of follow-up.[8] However, in most regions, candidates that exceed the Milan criteria are not given priority on the transplant waiting list in comparison with those that meet the Milan criteria. The rate of removal from the transplant waiting list due to either tumor progression or death is an important factor to consider when one is evaluating organ allocation policy and has been estimated to range from 20% to 30%.[4]

The aims of the present study were to evaluate the waiting list removal rates for liver candidates with HCC, the intent-to-treat survival of liver candidates with HCC, and to identify predictors of survival for both candidates on the waiting list and liver transplant recipients through the use of pooled data collected by the Organ Procurement Transplant Network (OPTN). While many studies have evaluated posttransplant survival, an intention-to treat analysis starting at the time of listing was utilized to provide a better understanding of the overall efficacy of liver transplantation for patients with HCC.

PATIENTS AND METHODS

Patients

Data from all adult patients 18 years of age or older with an initial date of registration for deceased donor liver transplantation between January 1998 and March 2006 with a primary, secondary, or tertiary diagnosis of HCC were captured from the OPTN/UNOS database. Identified study subjects included those that developed HCC while waiting for transplantation. Patients with incidental tumors were excluded because the diagnosis of HCC was not known until after transplantation. Demographic, UNOS region, diagnosis, laboratory data, Child-Pugh class, underlying liver disease etiology, tumor burden, and pretransplant treatment data were recorded at the time of initial listing. Candidates listed since 1998 were included because it was the first year in which the Milan criteria were adopted by UNOS and transplant centers in the United States. Overall survival and time to removal from the transplant waiting list were available for all patients. Patients were followed to death, loss to follow-up, withdrawal from the waiting list, or the end of the observation period on December 31, 2006. All deaths were confirmed by evaluation of the Social Security Death Master File. Tumor staging was performed according to the American Liver Tumor Study Group Modified Tumor-Node-Metastasis Staging Classification (http://www.unos.org/policiesandbylaws2/policies/docs/policy_8.doc; accessed December 18, 2007), which is currently being utilized by UNOS.

The pre-MELD era was defined as the era of those listed for OLT prior to February 27, 2002, and the post-MELD era was defined as the era of those listed on or after February 27, 2002. Waiting time was defined as the time from initial listing until removal from the list due to a transplant being performed from either a living or deceased donor. Dropouts were defined as those patients removed from the list because of tumor progression and/or death. The waiting time before dropout was the time from initial listing until removal from the list due to tumor progression or death.

Statistical Analyses

Data were expressed as mean ± standard deviation unless otherwise indicated. We compared the pre-MELD and post-MELD eras with respect to demographics, laboratory and tumor data, pretransplant treatment, and overall survival. The Mann-Whitney test was utilized to compare continuous variables without a normal distribution; otherwise, these variables were compared by *t* tests. Categorical variables were compared with chi-square tests. Survival was analyzed from the initial date of listing and included dropouts from the waiting list (ie, intent-to-treat analysis), unless otherwise indicated. Unadjusted patient survival following liver transplantation for HCC was compared with Kaplan-Meier analysis with a log-rank test to evaluate for significance. Overall probability of survival was evaluated for potential confounding factors at the time of listing, such as demographic data, etiology of liver disease (hepatitis C versus non–hepatitis C), alpha-fetoprotein (AFP), laboratory MELD score, Child-Pugh class, tumor size, tumor number, donor type, organ allocation policy, portal vein thrombosis, meeting Milan criteria, pretransplant treatment, and UNOS regions. The cutoff for continuous variables was determined by the median value. All variables with a P value < 0.05 were then entered into an adjusted Cox proportional hazards model to evaluate for independent predictors of survival. All analyses were done with the SAS System for Windows, version 9.1 (SAS Institute, Inc., Cary, NC). P values ≤ 0.05 were considered statistically significant.

RESULTS

Patient Characteristics

During the study period, a total of 4482 patients with a diagnosis of HCC were placed on the liver transplant waiting list. The characteristics of the patients at the time of listing are listed in Table 1. The majority

TABLE 1. Clinical Features at Listing for 4482 Patients with Hepatocellular Carcinoma in the United States from January 1998 Through March 2006

Feature	n (% or as indicated)
Age, years [median (range)]	55 (18–80)
Gender, male	3547(79%)
Ethnicity	
Caucasian	2719 (61%)
Hispanic	580 (13%)
Black	369 (8%)
Asian	746 (17%)
Other	68 (1%)
Etiology of underlying disease*	
Hepatitis C	1972 (50%)
Hepatitis B	540 (14%)
Hepatitis C and alcohol	273 (7%)
Alcohol	282 (7%)
Other	856 (22%)
Blood type (O%/A%/B%/AB%)	46/35/15/4
AFP, ng/mL [median (range)]	19.0 (1–44,279)
Laboratory MELD score [median (range)]	11.0 (6–57)
Child class (A%/B%/C%)	36/45/19
Treatment prior to OLT (including active waiting patients)	1155 (23%)
RFA	433 (37%)
TACE	722 (62%)
RFA and TACE	83 (7%)
Region	
1	203 (5%)
2	418 (9%)
3	529 (12%)
4	351 (8%)
5	1168 (26%)
6	158 (3%)
7	326 (7%)
8	258 (6%)
9	649 (14%)
10	221 (5%)
11	201 (5%)
Organ allocation era†	140 (1-1928)
Pre-MELD	1433 (32%)
Post-MELD	3049 (68%)
Waiting time, days [median (range)]	64 (1–2655)
Time to dropping out in days [median (range)]††	
Patients who were transplanted	2898 (65%)
Patients who dropped out	798 (17%)
Patients who dropped out because of tumor progression	500 (63%)
Patients who dropped out because of death	298 (37%)
Patients who were removed from the list for unknown reasons	294 (7%)
Patients actively waiting	492 (10%)

Abbreviations: AFP, alpha-fetoprotein; MELD, Model for End-Stage Liver Disease; OLT, orthotopic liver transplantation, RFA, radiofrequency ablation; TACE, transarterial chemoembolization.
*The diagnosis was reported in 3923 of the 4482 patients.
†The pre-MELD era is defined as the era of those listed between 1998 and February 26, 2002; the post-MELD era is defined as the era of those listed on or after February 27, 2002.
††Patients were removed from the liver waiting list because of death or tumor progression.

of the patients were male (79%) and non-Hispanic white (61%) with a median age of 55 years (range, 18-80). Chronic HCV infection was the most common cause of underlying liver disease, being identified in 57% of the 3923 patients with a reported diagnosis. The median AFP was 19 ng/mL (range, 1-44,279), and the median laboratory MELD score was 11 (range, 6-57). Region 5 (Arizona, California, New Mexico, Nevada, and Utah) accounted for 26% of the patients listed with HCC. The majority of the patients

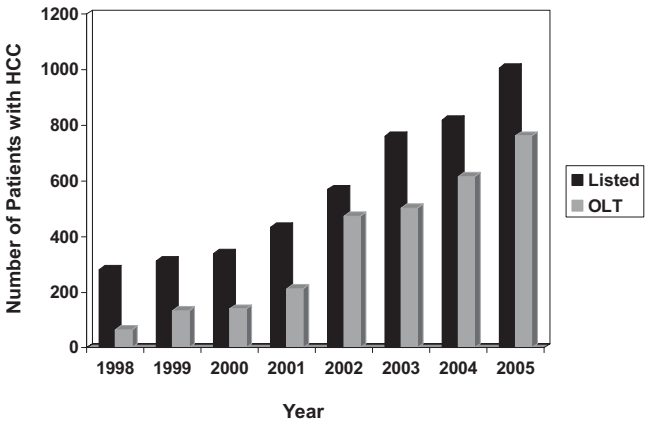

Figure 1. The number of candidates listed for liver transplantation (black) and the number of patients who actually underwent liver transplantation (gray) with a diagnosis of hepatocellular carcinoma from 1998 to 2005 are demonstrated. There was an increase in the number of candidates with HCC who were listed and transplanted after the implementation of the Model for End-Stage Liver Disease organ allocation system in 2002. Abbreviations: HCC, hepatocellular carcinoma; OLT, orthotopic liver transplantation.

(68%) were listed in the post-MELD era. The number of patients who underwent HCC treatment while awaiting OLT was 1155 (26%), with transarterial chemoembolization being the most common treatment.

Of the 4482 patients listed, 65% (n = 2898) underwent liver transplantation, 10% (n = 492) were actively waiting as of January 2006, 18% (n = 798) dropped out because of tumor progression (n = 500) and/or death (n = 298), and 7% (n = 294) were removed from the waiting list for unknown reasons that were not detailed within the OPTN database. Figure 1 depicts the number of patients with HCC on the waiting list and those undergoing OLT per year. As a result of the MELD allocation policy, there was approximately a 2-fold increase in the number of patients transplanted for HCC in 2002, and this number continued to increase through 2006. Clinical, demographic, and laboratory data for patients listed in the pre-MELD and post-MELD eras are listed in Table 2. In addition, patients listed in the pre-MELD era were noted to have decreased survival at 1 and 3 years after listing in comparison with those listed in the post-MELD era (72.1% and 59.1% versus 76.9% and 64.1%, $P = 0.007$; Fig. 2).

Tumor Characteristics

Tumor information at the time of listing was available for 3136 of the 4482 (70%) candidates (Table 3). The median maximum tumor diameter was 2.5 cm (range, 0.5-15 cm), 2226 (71%) patients had a solitary tumor, and 282 (9%) had ≥3 nodules. Only 2% (n = 72) were reported to have portal vein thrombosis by radiological imaging at the time of listing. Of the patients with available tumor information, 2790 (89%) met the Milan criteria, with the majority (85%) being at the T2 stage. A total of 346 (11%) HCC patients exceeded the Milan criteria, with the proportion exceeding the Milan criteria increasing steadily since 1998 (Fig. 3).

Dropout from the Liver Waiting List

The overall median time on the OLT waiting list was 64 days (range, 1-2655), and the median time to dropping out from the transplant waiting list because of death or tumor progression was 140 days (range, 1-1928). Considerable variability was noted for removal rates from the liver transplant waiting list based on the UNOS region (Table 4). For all candidates with HCC, the 1- and 3-year probability of dropping out because of tumor progression and/or death was 12% and 20%, respectively, as shown in Fig. 4. Compared to those with tumors meeting the Milan criteria, candidates with tumors exceeding the Milan criteria were significantly more likely to be removed from the waiting list for tumor progression and/or death ($P < 0.0001$).

Significant predictors of removal from the liver waiting list based on univariate analysis are listed in Table 5. The factors that predicted dropout were age > 55 years, blood type, nonviral etiology of liver disease, AFP > 20 ng/mL, laboratory MELD score > 10, Child classes B and C, the diameter of the largest tumor being greater than 2.5 cm, presence of portal vein thrombosis, being listed in the pre-MELD organ allocation era, and being listed in region 9. Univariate factors predicting a decreased risk for waiting list removal included meeting the Milan criteria and being listed within region 3. The independent predictors of dropout (Table 5), based on multivariate analysis, included nonviral etiology of liver disease [hazard ratio (HR), 1.1; 95% confidence interval (CI), 1.001-1.16], Child class B (HR, 1.7; 95% CI, 1.16-2.62), Child class C (HR, 4.4; 95% CI, 2.79-6.85), AFP > 20 ng/mL (HR, 1.6; 95% CI, 1.2-2.3), and being listed in the pre-MELD era (HR, 1.6; 95% CI, 1.29-2.89). The only independent predictor of being transplanted or remaining on the list rather than dropping out was having a tumor meeting the Milan criteria (0.37; 95% CI, 0.23-0.59).

Survival

Intent To Treat

The median duration of follow-up from listing was 29 months (1-58 months). The overall 1-, 3-, and 5-year intent-to-treat survival for the 4482 patients listed was 81%, 65%, and 51%, respectively (Fig. 5). The intent-to-treat survival was further evaluated for the 3136 patients for whom tumor data were available according to whether patients met or exceeded the Milan criteria (Fig. 6). On an intent-to-treat basis, candidates listed with tumors within the Milan criteria demonstrated a significant survival advantage in comparison with subjects exceeding the Milan criteria (P value < 0.001).

An unadjusted univariate analysis of predictors of survival included age < 55 years, HCV as the etiology of the underlying liver disease, lower Child class, lack of portal vein thrombosis, receiving a deceased donor organ (versus a living donor), being listed in the pre-

TABLE 2. Clinical, Demographic, and Laboratory Data for Patients Listed in the Pre-MELD and Post-MELD Eras

Variable	Pre-MELD (n = 1433)	Post-MELD (n = 3049)	*P* Value
Age, years	54 ± 9.0	56 ± 8.2	<0.0001
Gender			0.0002
Male	1093 (77.5%)	2426 (80.2%)	
Female	340 (22.5%)	624 (19.8%)	
Ethnicity			
Caucasian	844 (60.7%)	1832 (60.9%)	
Hispanic	190 (13%)	397 (12.9%)	
Black	103 (6.6%)	285 (9.1%)	0.0299
Asian	260 (18.1%)	478 (15.6%)	
Other	235 (1.6%)	46 (1.5%)	
Etiology of underlying disease*			
Hepatitis C	419 (49.5%)	1561 (51.2%)	0.0392
Hepatitis B	113 (13.3%)	415 (13.6%)	
Hepatitis C and alcohol	53 (6.2%)	220 (7.1%)	
Alcohol	53 (6.2%)	230 (7.4%)	
Other	208 (24.8%)	621 (20.6%)	
AFP, ng/mL	164.9 ± 489	393.4 ± 2017	0.0706
Child class†			
A	88 (6.4%)	1083 (36.2%)	0.0195
B	156 (11.4%)	1329 (44.5%)	
C	50 (3.6%)	567 (19%)	
Maximum tumor diameter (cm)‡	2.5 ± 1.1	3.1 ± 1.1	<0.0001
Tumor nodule number‡	1.4 ± 0.6	2.1 ± 0.7	<0.0001
1	129 (9.4%)	1625 (54.4%)	0.5621
2	46 (3.4%)	460 (15.4%)	
≥3	13 (0.9%)	212 (7.1%)	
Portal vein thrombosis‡	22 (1.6%)	85 (3.7%)	<0.0001
Met the Milan criteria	1126 (88%)	2154 (72%)	0.002
Pre-OLT treatment	19 (10%)	1035 (45%)	<0.0001
Median waiting time to transplant, days (range)	138 (1–2655)	46 (1–1237)	<0.0001
OLT rate	802/1433 (56%)	2173/3049 (71.3%)	<0.0001
Dropout due to death or disease progression	391 (28.5%)	300 (10.0%)	<0.0001

NOTE: Values are presented as mean ± standard deviation.
Abbreviations: AFP, alpha-fetoprotein; MELD, Model for End-Stage Liver Disease; OLT, orthotopic liver transplantation.
*Data were available for only 846 patients pre-MELD.
†The Child class was available for 3273 patients with MELD information.
‡Tumor data were available for 2485 patients.

MELD era (versus the post-MELD era), UNOS region, having a tumor within the Milan criteria, and undergoing OLT (Table 6). To identify independent risk factors for survival on an intention-to treat basis for all liver transplant candidates with HCC, a multivariate analysis was performed that was adjusted for age, gender, UNOS region, organ allocation system, and length of follow-up. As shown in Table 7, the independent predictors of survival were age < 55, Child class, having a tumor within the Milan criteria, and undergoing OLT.

Post-Transplant

When we took into account only the 2898 patients who underwent OLT, the 1- and 5-year post-OLT survival was 88% and 62%, respectively, and this was significantly better than the 1- and 5-year survival among those not transplanted (30% and 3%, respectively; $P < 0.0001$). The 1-, 3-, and 5-year survival was 89%, 75% and 65%, respectively, for those that met the Milan

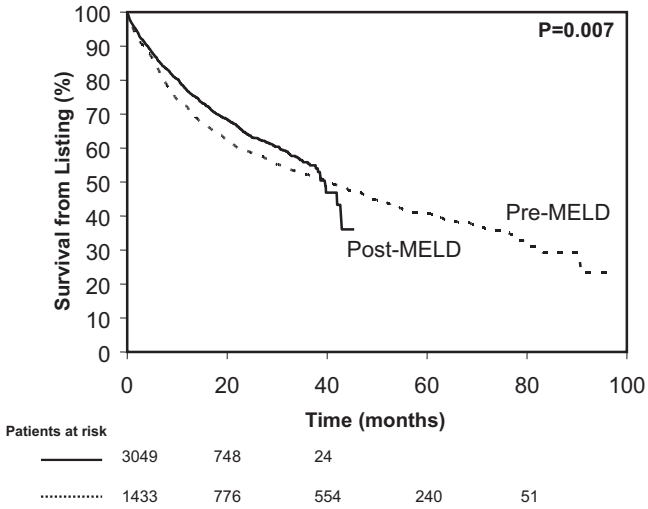

Figure 2. Unadjusted comparison of intent-to-treat survival for patients listed with hepatocellular carcinoma in either the Pre-MELD or Post-MELD eras.

TABLE 3. Tumor Information at the Time of Listing for Liver Candidates with Hepatocellular Carcinoma

Maximum tumor diameter, cm [median (range)]	2.5 (0.5–15)
Number of tumor nodules [median (range)]	1.0 (1–5)
1	2226 (71%)
2	628 (20%)
≥3	282 (9%)
TNM staging	
T1	125 (4%)
T2	2665 (85%)
T3	219 (7%)
T4	127 (4%)
Portal vein thrombosis	72 (2%)
Met the Milan criteria	2790 (89%)

NOTE: Data were available for 3136 of the 4482 (70%) candidates.
Abbreviation: TNM, Tumor-Node-Metastasis.

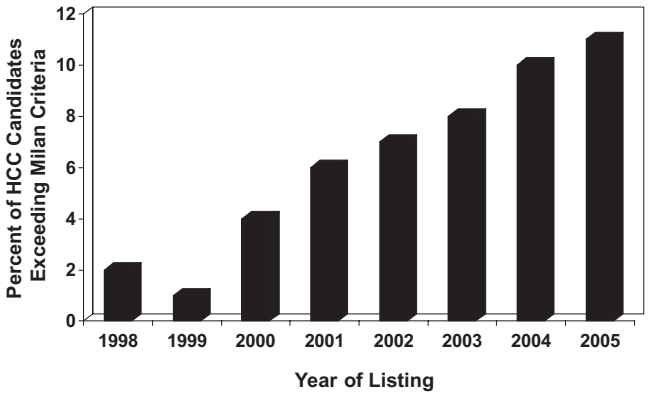

Figure 3. The percentage of patients listed for HCC from 1998 to 2005 that exceeded the Milan criteria is demonstrated. Tumor information was determined at the time of listing. Abbreviation: HCC, hepatocellular carcinoma.

TABLE 4. Rate of Removal from the Liver Transplant Waiting List for Tumor Progression or Death According to the UNOS Region

UNOS Region	Waiting List Dropout Rate (%)*
1	12.2
2	18.3
3	11.9
4	9.3
5	26.6
6	6.8
7	17.0
8	12.2
9	28.7
10	12.4
11	16.7

Abbreviation: UNOS, United Network for Organ Sharing.
*Removal from the liver waiting list for either tumor progression or death.

criteria versus 82%, 65%, and 38%, respectively, for those that exceeded the Milan criteria ($P < 0.0001$).

DISCUSSION

Before the use of the Milan criteria, OLT for HCC was associated with disappointing results, including a 5-year survival rate of 36% or less and a tumor recurrence rate of up to 54%.[5,9] In 1996, Mazzaferro and colleagues[6] published the Milan criteria, which allowed the identification of a group of patients with HCC that had a low likelihood of developing recurrent tumors and an acceptable survival rate after OLT. Other studies have demonstrated that the best long-term results and the lowest recurrence rates are achieved when those undergoing liver transplantation have early-stage HCC (ie, stage T2).[6,8,10-12] Therefore, the Milan criteria have been adopted by many countries, including the United States, in an attempt to maximize the efficacy of a therapy that is significantly limited by donor availability. Researchers have attempted to expand the Milan criteria while still aiming for acceptable results.[8,13-18] While numerous single-center studies have been reported on liver transplantation and HCC, the present study uses a national database to evaluate survival and dropout on an intention-to-treat basis.

The present retrospective study utilized registry data from UNOS/OPTN to analyze the outcome of candidates listed for HCC over an 8-year period. Almost two-thirds of the study population were transplanted within the MELD organ allocation era, and the majority (89%) met the Milan criteria at listing. The median waiting time was 64 days with a 12% dropout rate at 1 year. While the survival rate at 5 years post-transplant for those with tumors within the Milan criteria was 61%, for recipients with tumors exceeding these criteria, the 5-year posttransplant survival rate was significantly less at 32%. In addition, a multivariable analysis controlling for confounding factors demonstrated that pa-

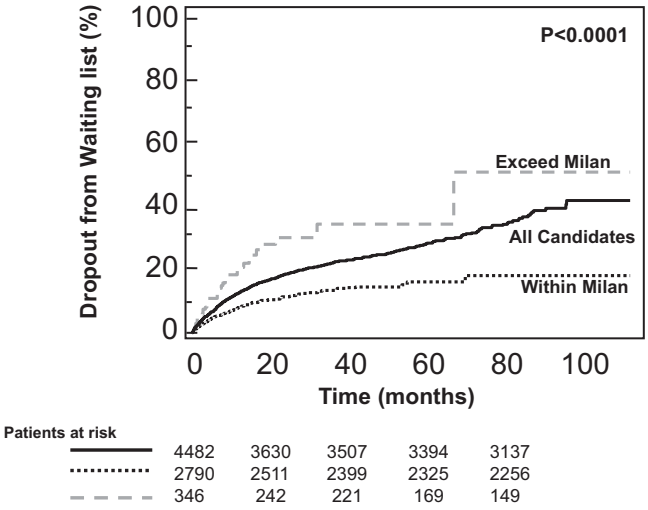

Figure 4. Probability of removal from the transplant waiting list for tumor progression and/or death for all candidates (black solid line; n = 4480) listed with a diagnosis of hepatocellular carcinoma from 1998 to 2005. Probability of removal from the waiting list is also demonstrated for candidates with tumors meeting (black dotted line; n = 2790) or exceeding the Milan criteria (dashed gray line; n = 346). Compared to those with tumors meeting the Milan criteria, candidates with tumors exceeding the Milan criteria were significantly more likely to be removed from the waiting list for tumor progression and/or death (*P* < 0.0001). Dropout is defined as removal from the liver waiting list for either tumor progression or death.

TABLE 5. Univariate and Multivariate Analyses for Predictors of Waiting List Dropout for Liver Candidates with Hepatocellular Carcinoma

Parameter	HR (95% CI)	*P* Value
Univariate analysis		
Age > 55 years	1.4 (1.1–2.3	0.0135
Blood type (O versus others)	1.1 (1.01–1.4)	0.014
Nonviral etiology	1.9 (1.3–2.6)	<0.0001
AFP > 20 ng/mL	1.1 (1. 5–1.9)	0.0003
MELD score > 10	1.2 (1.02–2.1)	0.0123
Child class B/C	3.9 (2.1–4.3)	<0.0001
Largest tumor > 2.5 cm	1.5 (1.1–2.8)	<0.0001
Portal vein thrombus	1.7 (1.1–3.3)	0.0021
Met the Milan criteria	0.32 (0.23–0.65)	<0.0001
Pre–MELD allocation*	1.8 (1.2–2.4)	<0.0001
Region		0.0001
9	1.7 (1.3–1.9)	
3	0.81 (0.43–0.72)	
Multivariate analysis		
Nonviral etiology	1.1 (1.001–1.16)	<0.0001
Child class B	1.7 (1.16–2.62)	0.007
Child class C	4.4 (2.79–6.85)	<0.001
AFP > 20 ng/mL	1.6 (1.2–2.3)	0.0002
Pre–MELD allocation*	1.6 (1.29–2.89)	0.003
Met the Milan criteria	0.37 (0.23–0.59)	<0.001

Abbreviations: AFP, alpha-fetoprotein; CI, confidence interval; HR, hazard ratio; MELD, Model for End-Stage Liver Disease.
*The pre-MELD era is defined as the era of those listed between 1998 and February 26, 2002.

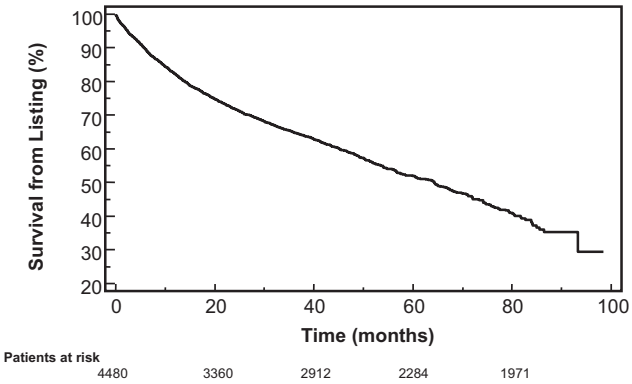

Figure 5. Overall intent-to-treat survival of 4480 patients listed for hepatocellular carcinoma.

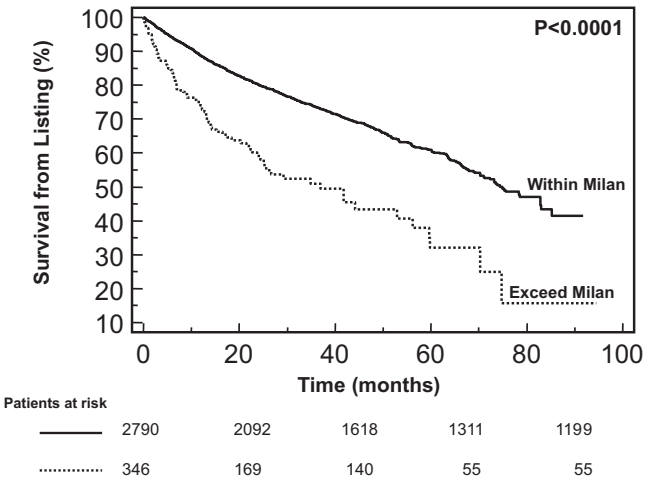

Figure 6. Overall intent-to-treat survival of patients listed for hepatocellular carcinoma according to the utilized criteria. There was a significant difference in survival among those that met the Milan criteria (black line) compared to those who exceeded the Milan criteria (black dotted line). The *P* value was <0.0001.

tients transplanted with tumors within the Milan criteria had a significantly decreased relative risk of death in comparison with those transplanted beyond the Milan criteria (HR, 0.49; $P = 0.0002$). Our data show that for those listed for HCC, undergoing OLT is an independent predictor of survival, but the best survival rates are achieved in HCC patients that meet the Milan criteria. These data need to be interpreted carefully. In the current liver allocation system, candidates with tumors exceeding the Milan criteria are not given preferential MELD exceptions and, as a result, may not have equal access to liver transplantation in comparison with those with tumors within the Milan criteria.

There are several limitations of the current retrospective study using the UNOS/OPTN national registry database. Since the database does not capture tumor recurrences, we were not able to evaluate this important endpoint. Furthermore, preoperative imaging techniques and interpretation may not be comparable from

TABLE 6. Unadjusted Analysis of Baseline Predictors of Survival in Patients with Hepatocellular Carcinoma Listed for Liver Transplantation

	Number of Patients	Median Survival (Months)	*P* Value
Age, years			
<55	2244	52.6	**0.0002**
≥55	2078	39.2	
Gender			
Male	3547	43.8	0.1979
Female	935	47.2	
Ethnicity			
Non-Hispanic white	2719	45.7	0.7378
Others	1763	39.8	
Etiology			
Hepatitis C	2245	55.4	**<0.0001**
Non–hepatitis C	1678	34.4	
Child class			
A	1613	—	**<0.0001**
B	2016	38.2	
C	852	24.1	
Portal vein thrombosis			
Yes	72	26.2	**0.0050**
No	4251	44.2	
Donor type*			
Deceased	2774	78.3	**0.0383**
Live	140	53.1	
Lab MELD score			
<10	2419	38.7	0.4072
≥10	1903	44.1	
Treatment pre-OLT†			
Yes	1155	—	0.1030
No	2434	48.6	
Organ allocation policy‡			
Pre-MELD	1433	40.5	**0.003**
Post-MELD	3049	37.8	
UNOS region			
1	198	44.3	
2	395	41.9	
3	518	48.8	
4	345	—	
5	1106	38.9	**<0.0001**
6	153	—	
7	310	44.1	
8	254	63.5	
9	625	26.9	
10	220	42.4	
11	198	45.9	
Number of nodules§			
1	2226	52.6	0.5615
>1	910	52.0	
Maximal tumor diameter (cm)			
<2.5	2320	43.9	0.9708
≥2.5	816	41.5	
Met the Milan criteria			
Yes	2790	—	**<0.0001**
No	346	41.1	
AFP, ng/mL‖			
<20	3452	44.1	0.6309
≥20	870	50.4	
Liver transplantation			
Yes	2898	77.9	**<0.0001**
No	1584	10.5	

NOTE: A dash (—) indicates that the median survival could not be calculated because the last cumulative survival was greater than 50%.
Abbreviations: AFP, alpha-fetal protein; MELD, Model for End-Stage Liver Disease; OLT, orthotopic liver transplantation; UNOS, United Network for Organ Sharing.
*Data were available for 2914 patients.
†Treatment pre-OLT is defined as the treatment of a tumor prior to transplantation, including radiofrequency ablation and transarterial chemoembolization.
‡The pre-MELD era is defined as the era of those listed between 1998 and February 26, 2002; the post-MELD era is defined as the era of those listed on or after February 27, 2002.
§Tumor data were available for 3136 patients.
‖Data were available for 4322 patients.

TABLE 7. Covariate-Adjusted Mortality HRs for All Patients Listed for Liver Transplantation with Hepatocellular Carcinoma

Variable	HR	95% CI	*P*
Age < 55 years old	0.76	0.64–0.88	0.0001
Child class B	1.40	1.28–1.64	0.003
Child class C	2.20	1.96–2.56	0.001
Tumor meeting the Milan criteria	0.49	0.45–0.54	0.0002
Liver transplantation	0.23	0.21–0.25	<0.0001

NOTE: HRs were adjusted for age, gender, United Network for Organ Sharing region, organ allocation system, and length of follow-up.
Abbreviations: CI, confidence interval; HR, hazard ratio.

one center to another. There is also substantial variability in transplant center candidate selection policies and donor availability that could not be controlled for in our retrospective analysis. Furthermore, the effects of down-staging with neoadjuvant treatment are also difficult to evaluate from the UNOS/OPTN database. Finally, HCC staging data were available for only 70% of the HCC OLT candidates during this study period, and this introduced potential selection bias. However, the intent of this study was to evaluate outcomes among HCC patients on the waiting list in an intention-to-treat manner by using information available on over 4000 patients from multiple centers. Of note, this study was not meant to be a comparison of HCC patients within or beyond the Milan criteria because the current organ allocation system assigns different priorities, making a meaningful comparison difficult if not impossible. While these limitations exist, the present study shows an important national view of the overall efficacy of OLT for HCC as it pertains to patient survival in an intent-to-treat analysis, accounting for dropouts.

In conclusion, the present study demonstrates that the current criteria for liver transplantation of patients with HCC have an acceptable 5-year survival while minimizing the rate of removal from the waiting list for either tumor progression or death. Expansion of the radiographic criteria for transplanting HCC requires careful consideration in light of the higher potential risk of tumor recurrence with lower patient survival[19] and the impact on the many other non-HCC patients with liver failure.[20]

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