Liver Transplantation for Hepatocellular Carcinoma: Long-Term Results Suggest Excellent Outcomes

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BACKGROUND: Selected 5-year survival results after liver transplantation for hepatocellular carcinoma (HCC) have been reported to be 70%. Our hypothesis was that liver transplantation is effective for long-term cancer control for HCC.

STUDY DESIGN: A 20-year retrospective review of a prospectively collected database was carried out. Demographic data and patient survival were calculated.

RESULTS: There were 1,422 liver transplantations performed between January 1990 and April 2011. Of these, 264 had HCC and 157 (59%) were pretreated with transarterial chemoembolization. Recipient age was 55.9 (±7.9) years and 208 (79%) of patients were male. The underlying disease was hepatitis C virus in 155 (58.7%), hepatitis B virus in 16 (6%), alcohol in 21 (8%), and miscellaneous in the remaining 72 cases. The mean number of tumors was 1.8 (±1.7) and the mean largest tumor diameter was 2.3 (±1.3) cm in the explanted liver. One, 5, and 10-year patient survival was 88.5%, 69.1%, and 40.5%, respectively; disease-specific survival was 99.1%, 94.4% and 87.9%; and disease-free survival was 86.0%, 64.6%, and 40.1%. One, 5, and 10-year graft survival was 87.3%, 68.0%, and 41.8%. Nine (3.4%) patients required retransplantation; 75 patients (28.4%) have died, but only 10 of 75 (13.3%) died of recurrent HCC (3.7% of all HCC patients receiving a transplant) and 6 (8%) died of recurrent viral hepatitis. An additional 9 recipients developed recurrence (total HCC recurrence, n = 19 [7%]), 4 of whom died of causes other than HCC. The remaining 5 are disease-free post-treatment (mean 5.5 years after orthotopic liver transplantation).

CONCLUSIONS: Orthotopic liver transplantation offers an effective treatment strategy for HCC in the setting of cirrhosis, even in the setting of hepatitis C virus. Hepatocellular carcinoma recurrence is uncommon in properly selected patients and disease-specific long-term survival approaches 90%. (J Am Coll Surg 2012;215:19–28. © 2012 by the American College of Surgeons)

Hepatocellular carcinoma (HCC) is on the rise in the United States as well as worldwide and resection remains the standard first-line treatment strategy. However, in many patients this is not possible because cirrhosis precludes extensive resection. In addition, resection in the face of multifocal HCC has a poor prognosis, with recurrence rates between 80% and 100% in long-term follow-up.[1] Early series of liver transplantations for HCC reported 5-year survival of 30% to 40%.[2,3] Since then, liver transplantation has become a widely accepted treatment for patients with early-stage HCC and more selectively for downstaged patients with more advanced disease.[4,5] Patients eligible for liver transplantation in the United States include those within the Milan criteria[4] (ie, 1 tumor ≤5 cm or up to 3 tumors, with the largest ≤3 cm), currently defined on contrasted enhanced cross-sectional imaging. These patients receive 22 Model for End-Stage Liver Disease (MELD) exception points for transplantation priority.[6] Because of wait time variability throughout the United States, in some regions patients can wait from 6 months to 1 year, despite the 10% increase in MELD every 3 months on the waiting list.[6] Locoregional tumor therapies such as

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Abbreviations and Acronyms

HBV = hepatitis B virus
HCC = hepatocellular carcinoma
HCV = hepatitis C virus
MELD = Model for End-Stage Liver Disease
NASH = nonalcoholic steatohepatitis
RFA = radiofrequency ablation
TACE = transarterial chemoembolization

transarterial chemoembolization (TACE) or radiofrequency ablation (RFA) are commonly used as a bridge to transplantation or to down-stage potential candidates.[7,8] Reports have shown that down-staged patients have survival similar to stage II recipients.[8] The aim of the current report is to review our center's 20-year experience with liver transplantation for HCC and to assess the long-term results of transplantation for this malignancy.

METHODS

This study was compiled after approval from our institutional review board and used a prospectively collected clinical database of our liver transplantation patients. For all liver transplant recipients, patient demographics, clinical details, outcomes, and recurrence data were obtained. Disease-specific and disease-free survival along with patient and graft survival rates were calculated and compared with survival rates of non-HCC patients who underwent liver transplantation between January 1, 1990 and April 30, 2011. We also examined differences in wait time, stage of HCC, and survivals in the pre-MELD allocation era (before February 2002) and the MELD era.

Diagnosis

In the 1990s, HCC was most commonly diagnosed on the basis of cross-sectional imaging with CT, with or without biopsy. However, with the advancement of cross-sectional imaging in the last decade, HCC is usually diagnosed without biopsy, with gadolinium-enhanced MRI or triphasic CT. Before transplant listing, every patient had a complete evaluation and presentation at multidisciplinary transplantation conference. At our center, patients who have been down-staged from outside of Milan criteria were considered for exception points after regional review board approval. Patients listed with HCC had interval imaging studies (usually with chest CT and abdominal MRI or CT) every 3 months to assess for new or progressive disease. During the evaluation, a bone scan is performed to rule out evidence of metastatic disease. Positron emission tomography scanning is not routinely performed.

Locoregional therapy

Before 1998, TACE was not routinely performed at our center. Since 1998, TACE has been performed in patients with cross-sectional imaging diagnostic of HCC, with a bilirubin <2 mg/dL and well-compensated cirrhosis. A bilirubin up to 4 mg/dL was considered in selective cases. A mixture of chemotherapy (mitomycin and cisplatin) and ethiodized oil, followed by embolization with absorbable gelatin sponge was used most commonly for TACE. MRI follow-up was performed 6 weeks after TACE to assess for completeness of the ablation. If a complete response (no remaining tumor enhancement) was observed, interval surveillance was scheduled at 3 months. If there was evidence of residual disease, repeat TACE was performed. For tumors outside of Milan boundaries, the patient received repeated TACE in an attempt to down-stage to "within Milan." Radiofrequency ablation was performed in a smaller number of patients, as TACE is our preferred locoregional therapy. In cases where RFA was used, this was performed percutaneously and the antenna was introduced into the tumor under image guidance. Ablation was performed according to manufacturers' standard recommendations.

Transplantation technique

Standard piggy-back technique with caval preservation without the use of veno–venous bypass has been used since 1995 at our center. Our standard immunosuppression is a 3-drug regimen with tacrolimus, mycophenolic acid, and a short steroid taper. The explant was assessed in pathology and incidental HCC was defined when the diagnosis of HCC was not made on preoperative imaging. Post-transplantation surveillance every 6 months for 5 years with α-fetoprotein and MRI was the routine. Recurrence of HCC was treated depending on the location (see Results).

Statistical analysis

Overall patient survival and disease-specific and recurrence-free survival were traced using Kaplan-Meier curves. Curves were compared using log-rank test. For all comparisons, differences were considered statistically significant whenever p value was <0.05. Categorical variables were compared using Fisher's exact test. Student's *t*-test was used to compare continuous variables. Unless otherwise specified, results are expressed as mean $\pm$ SD or median with range.

RESULTS

There were 1,422 liver transplantations (1,227 adult and 195 pediatric) performed between January 1, 1990 and April 30, 2011. Two hundred and sixty-four patients had HCC (18.5%) and in 32 (12%) of those recipients, the

Figure 1. The number of transplantations for hepatocellular carcinoma from 1990 to 2011. Transplantations for hepatocellular carcinoma have increased significantly since 1990 (*annualized for 2011; $p < 0.0001$). Black line, total adult transplantationss; gray line, hepatocellular carcinoma transplantations as percent of total transplantationss.

HCC was an incidental finding on explant. The number of transplantations for known HCC has increased since 1990. In the pre-MELD era, 39 of 530 (7.4%) transplantations were performed for HCC compared with 225 of 697 (32.3%) in the MELD allocation era ($p < 0.0001$; Fig. 1). Thirty-four transplantations for nonincidental HCC were performed (34 of 530 [6.4%]) in the pre-MELD era vs 198 of 697 (28.4%) in the MELD era ($p < 0.0001$).

Demographics

Mean recipient age was 55.9 (±7.9) years and 79% (n = 208) of patients were male. Seventy-nine percent (n = 209) were Caucasians, 12% (n = 31) were African Americans, and the remainder (n = 24) were of varied ethnicity. The underlying cause of cirrhosis was hepatitis C virus (HCV) in 155 (58.7%), hepatitis B virus (HBV) in 16 (6%), alcohol in 21 (8%), and nonalcoholic steatohepatitis (NASH) in 17 (6.4%). Thirty-six percent of all HCV transplantations had HCC, and 13.6% of the non-HCV transplantations had HCC ($p < 0.0001$). On univariate analysis, HCC was more common in older male recipients with cirrhosis from HCV, HBV, or NASH (Table 1). Mean laboratory MELD at transplantation was 16 (±8) and mean MELD with exception at transplantation was 23 (±5; $p = 0.0001$). Median follow-up was 5 years.

Hepatocellular carcinoma details

One hundred fifty-eight (59%) patients were pretreated with TACE. Mean number of tumors was 1.8 (±1.7) and the mean largest tumor diameter on explant was 2.3 (±1.3) cm (including all stages and incidentals). Mean radiologic tumor size was 3.2 (±1.5) cm overall, 2.8 (±0.9) cm in stage II recipients and 4.7 (±2.1) cm in stage III and IV recipients. Mean radiologic number of tumors was 1.7 (±1.1) overall, 1.4 (±0.7) for stage II recipients, and 2.7 (±1.6) for stage III and IV recipients. Two patients had a previous liver resection for HCC and recurrence developed, and 1 received a liver transplant for HCV 13 years earlier and, on follow-up, cirrhosis and HCC had developed in the transplanted liver. Percutaneous RFA was performed in 7 patients (2.7%). Post-TACE (or RFA) ≥90% treatment effect was seen on explant in 60% recipients who had received pretreatment. Review of explanted livers confirmed HCC in all but 5 patients, 1 had an incidental 1-cm cholangiocarcinoma and 4 patients had mixed features of HCC and cholangiocarcinoma. Tumor differentiation was challenging to assess in many cases because of treatment-induced necrosis, but of those with some viable tumor, 77 (51.3%) were well differentiated, 60 (40%) were moderately differentiated, and 13 (8.7%) were poorly differentiated. HCC was discovered incidentally on explant in 8 (20.5% of HCC) recipients in the pre-MELD era compared with 24 (10.7% of HCC) in the post-MELD time period ($p = 0.1$).

Overall survival

During the 20-year period, 1-, 5-, 10-, and 20-year patient survival in the recipients with HCC, when compared with recipients of transplants for other reasons, approached significance (88.5%, 69.1%, 44.5%, and 27.6% vs 86.3%, 74.6%, 61.4%, and 29.8%, respectively; $p = 0.055$; Fig. 2A). In the pre-MELD era, however, there was a significant survival advantage seen in non-HCC recipients with 1, 5, 10, and 20-year survival of 86.3%, 72.7%, 59.7%, and 28.9% vs 72.5%, 52.3%, 35.7%, and 19.4% in HCC transplant recipients in the same era ($p = 0.001$; Fig. 2B). On the other hand, in the MELD era, there appeared to be no survival difference between the 2 groups (1, 5, and 9-year MELD era survival with HCC, 91.9%, 71.3%, and 52.2% vs non-HCC MELD era 88.1%, 79.1%, and 71.5%, respectively; $p = 0.16$). Overall 1, 5, 10, and 20-year disease-specific survival was 99.1%, 94.4%, and 87.9% and 87.9%, respectively (Fig. 3) and disease-free survival was 86.0%, 64.6%, and 40.1% and 27.5%, respectively (Fig. 4).

Nine (3%) patients required retransplantation (3 for primary non-function, 2 for hepatic artery thrombosis, 2 for chronic rejection, and 2 for longstanding recurrent HCV).

Table 1. Univariate Analysis Comparing Transplant Recipients With and Without Hepatocellular Carcinoma

Parameter	HCC OLT	Non-HCC OLT	p Value
Total, n	264	1,158	
Adults only, n	264	961	
Age, y, median (range)	56 (22−75)	51 (18−75)	<0.0001
Age, y, mean (SD)	55.9 (7.9)	50.2 (11.1)	
Male sex, n (%)	208 (78.8)	551 (57.3)	<0.0001
Caucasians, n (%)	209 (79.2)	830 (86.4)	0.004
African Americans, n (%)	31 (11.7)	89 (9.3)	0.24
HCV cirrhosis, n (%)	155 (58.7)	269 (28.0)	<0.0001
HBV cirrhosis, n (%)	16 (6)	29 (3.0)	0.02
ETOH cirrhosis, n (%)	21 (8)	122 (12.7)	0.12
NASH, n (%)	17 (6.4)	24 (2.5)	0.003
Laboratory MELD (HCC MELD era only), median (range)	14 (6−48)	23 (6−54)	
Laboratory MELD (HCC MELD era only), mean (SD)	16 (8)	24 (9)	<0.0001
MELD with exception points (HCC cases throughout MELD era), median (range)	22 (6−42)	23 (6−54)	
MELD with exception points (HCC cases throughout MELD era), mean (SD)	23 (5)	24 (9)	<0.0001

ETOH, alcohol-related; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MELD, Model for End Stage Liver Disease; NASH, nonalcoholic steatohepatitis; OLT, orthotopic liver transplantation.

Seventy-five patients (28.4%) have died but, of those, only 10 (13.3%) died from recurrent HCC. Four additional patients with recurrent HCC died from non-HCC causes. Six (8%) died from recurrent viral hepatitis C. Of the remaining 55, eight died from transplant-related causes (1 acute hemorrhage, 4 unspecified graft failures, 1 rejection, 1 primary non-function and 1 hepatic artery thrombosis), 8 from other cancers, 21 from medical causes, 7 from sepsis, 1 suicide, 2 accidental, and in the remaining 8 the cause of death is unknown.

Survival with hepatocellular carcinoma in the pre–Model for End-Stage Liver Disease and Model for End-Stage Liver Disease eras

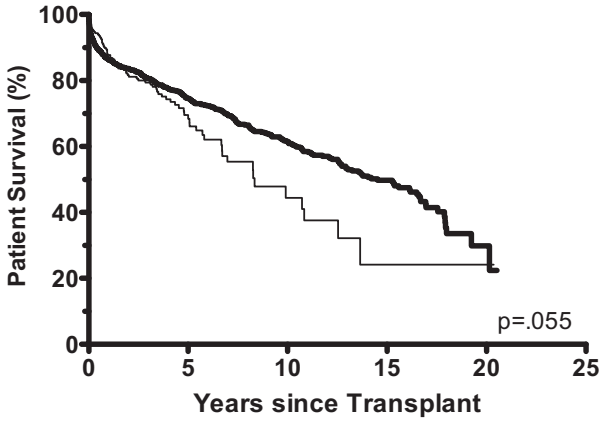
Survival comparison between the pre-MELD and MELD eras in all recipients with HCC was also performed. Because no patient has yet reached 10 years of follow-up in the MELD era, we compared survival rates at 1, 5, and 9 years. For HCC transplant recipients, 1, 5, and 9-year overall patient survival was significantly lower in pre-MELD era compared with MELD era (72.5%, 52.3%, and 38.5% vs 91.9%, 71.3%, and 52.2%; $p = 0.01$; Fig. 5). A similar statistically significant difference was also seen in 1, 5, and 9-year disease-specific survival rates (90%, 84.6%, and 75.2% in pre-MELD era compared with 100%, 95%, and 95% in the MELD era; $p = 0.0009$; Fig. 6). Interestingly, 20-year survival for the pre-MELD era HCC transplants is still almost 20% and the disease-specific survival is 75% in this group. Recipient wait time from listing to transplantation was also evaluated and compared between the pre-MELD and MELD eras. Waiting time was considerably longer in the pre-MELD era (median 299.5 days; range 37 to 765; mean 353.2 ± 230 days) compared with the MELD era (median 39 days; range 4 to 906; mean 132.5 ± 222 days; $p = 0.0001$; Fig. 7). After MELD implementation for HCC exception in 2002, waiting time dramatically fell, but has risen steadily during the last 9 years.

Survival with hepatocellular carcinoma and hepatitis C virus

Significantly more patients were received transplants for HCV in the MELD era (301 [43.2%]) compared with (135 [25.5%]) the pre-MELD era ($p < 0.0001$). Overall, survival of HCV patients was worse compared with patients receiving transplants for other reasons ($p = 0.01$; Fig. 8). However, in the MELD era, comparison of patients with hepatitis C and HCC to patients without hepatitis C and cancer, no survival difference was seen ($p = 0.37$; Fig. 9). Of the 155 patients with HCV and HCC, 6 died from recurrent HCV infection (3.9%), and of the overall cohort, 10 of 264 (3.8%) patients died of recurrent HCC ($p = NS$), so our patients with HCV and HCC are not dying from recurrent HCV.

Recurrence

Nineteen of 264 recipients (7.1%) had an HCC recurrence overall. Five of them are currently alive and disease free, with a median survival of 5.5 years (range 1.9 to 8.7 years). Ten (3.8%) died from HCC and 4 from other causes (Table 2). Six of 39 (15.4%) of the HCC-related deaths were in the pre-MELD era and 4 of 225 (1.8%) were in the MELD



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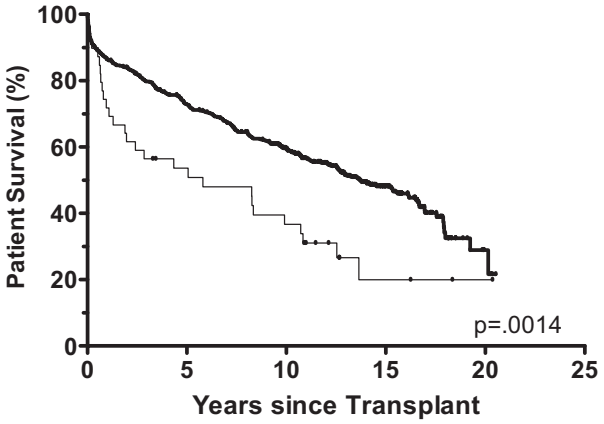

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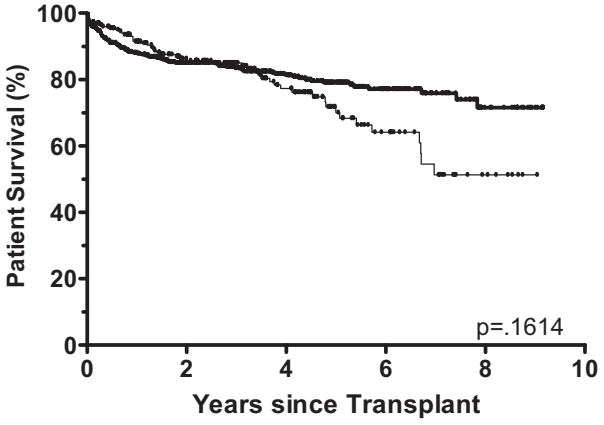

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Figure 2. (A) Overall, (B) pre–Model for End-Stage Liver Disease (MELD), and (C) MELD era patient survival comparing recipients of transplants for cirrhosis with hepatocellular carcinoma compared with transplantations for other indications during the study period (p = 0.06, p = 0.01, and p = 0.16, respectively). Thick line, nonhepatocellular carcinoma orthotopic liver transplantation; thin line, hepatocellular carcinoma orthotopic liver transplantation.

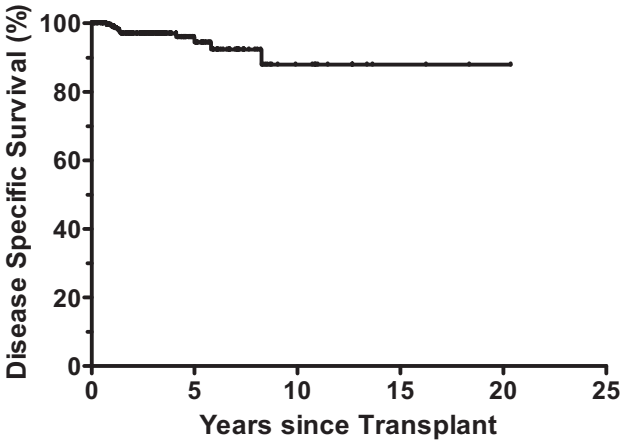


Figure 3. Graph showing overall disease-specific survival in recipients of transplants for hepatocellular carcinoma.

era (p = 0.0005). Similarly, HCC recurrence was more common in the pre-MELD era, 8 of 39 (20.5%) vs 11 of 225 (4.9%) in MELD-era (p = 0.006). From the pre-MELD era, 6 of 8 (75%) recurrences were stage III/IV, and 9 of 11 (81.8%) recurrences in the MELD era had stage II disease pretransplantation. Ten of the 19 recurrences were single metastatic deposits amenable to treatment and only 2 of these patients died from HCC. Mean time from transplantation to recurrence was 1.7 years and, in those who died from HCC, the time from transplantation to death from disease was 2.5 years. Median survival in patients in whom recurrence developed was 1.4 years overall.

Treatment pre–liver transplantation

Of the 264 recipients with known HCC before transplantation, 163 (70.3%) were treated before transplantation. Of those treated, most (n = 151 [92.6%]) were treated in the MELD era. Twenty-eight patients (71.8 %) in the pre-MELD era did not receive pretreatment. Comparing pretreated recipients by stage, there was no difference in overall patient (74%, 67%, 95%, and 75% stage I, II, III, and IV, respectively, at 5 years; p = 0.6), disease-free (74%, 59%, 95%, 75% stage I, II, III, and IV, respectively, at 5 years; p = 0.4), or disease-specific survival (100%, 94%, 100%, 85.7% stage I, II, III, and IV, respectively, at 5 years; p = 0.3; Fig. 10). Of the MELD era pretreated patients, 21% were down-staged from stage III or IV (17% of stage III cases and 7% of stage IV cases, respectively) and had MELD exception points granted after regional board review. In the pre-MELD era, 30% of patients with stage III and IV disease were not treated pretransplantation compared with 8% in the MELD era (p = 0.005). Pretreated recipients had an overall median survival of 8.3 years and disease-free survival of 7 years.

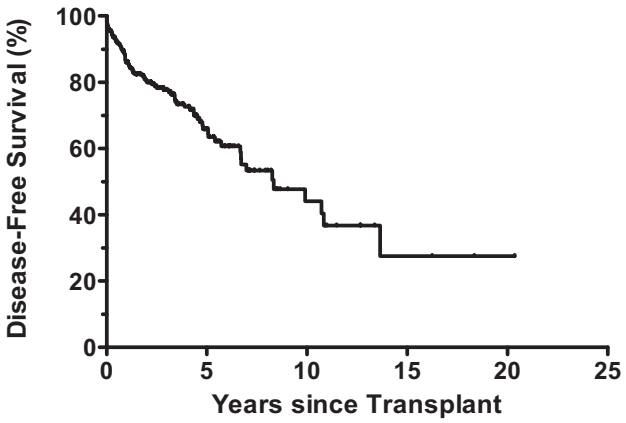


Figure 4. Graph showing overall disease-free survival in recipients of transplants for hepatocellular carcinoma.

Figure 5. Comparison of patient survival between the pre and Model for End-Stage Liver Disease (MELD) era (ie, pre and post-February 2002; p = 0.01). Thick line, pre-MELD era; thin line, MELD era.

DISCUSSION

In this report, we examine our 20-year experience with liver transplantation for HCC associated with chronic liver disease. This therapy resulted in overall patient survival rates of 88.5%, 69%, and 40.5% at 1, 5, and 10 years, respectively, with disease-specific survival of 99%, 94%, and 88% at similar time points. Importantly, results for liver transplantation for HCC since the introduction of MELD allocation in 2002 have continued to improve with current 1, 5, and 9-year survival rates of 92%, 71%, and 52%, and disease-specific survival of 100%, 95%, and 95%, and associated tumor recurrence rates of <10%. As a therapeutic modality for a very difficult to treat malignancy, transplantation seems to offer a highly effective strategy in properly selected patients.

Historically, hepatic malignancy was originally thought to represent an ideal indication for liver transplantation because this allowed for removal of advanced-stage cancers and eliminated sites of potential recurrence in the remnant liver.[9,10] However, early results were very poor with high tumor recurrence rates (60% to 70%), and poor survival. For this reason, a moratorium on transplantation for malignancy was suggested in 1989,[11,12] although some centers continued to perform limited cases of transplantation for HCC. In 1996, the Milan trial was reported,[4] demonstrating excellent results with transplantation for HCC, but only for early-stage cases. Since that time, transplantation for HCC has steadily increased and is now considered standard therapy for early-stage cases in the setting of decompensated cirrhosis in the United States and many parts of the world. This is reflected in the number of transplantations for malignancy in our cohort where, in the pre-MELD era, 7.4% of transplantations were performed for HCC vs 32.3% in the MELD era. Because of concern for prolonged wait-list times with risk of drop-out from disease progression,[4] the United Network for Organ Sharing introduced special MELD exception point allocation for recipients with early-stage disease in 2002 and, with subsequent modifications, the current allocation is 22 MELD exception points for stage II disease.

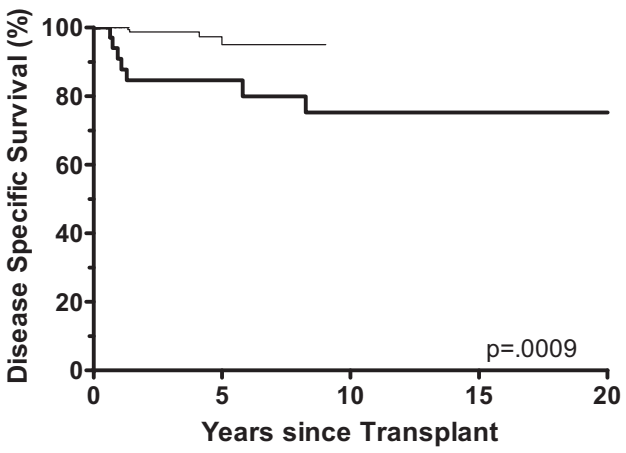
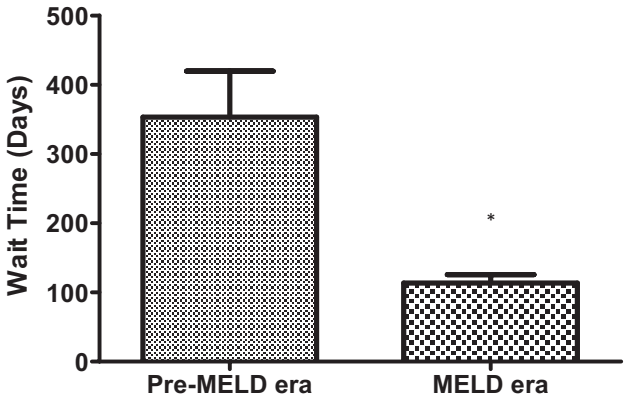


Figure 6. Comparison of disease-specific survival between the pre- and Model for End-Stage Liver Disease (MELD) era (p = 0.0009). Thick line, pre-MELD era; thin line, MELD era.

In the current report, similar to previous studies,[13] we found an increased incidence of HCC in older males with HCV, HBV, or NASH. A recent review suggests that the 5-year cumulative risk for HCC in patients with cirrhosis ranges between 5% and 30% overall and among those infected with HCV it is 15 to 20-fold higher.[14,15] End-stage liver disease from NASH is becoming more common and, as in our cohort, the risk of HCC is higher in these patients also.[16-18] As has been reported previously, the wait time in the pre-MELD era was considerably longer and, as a result,



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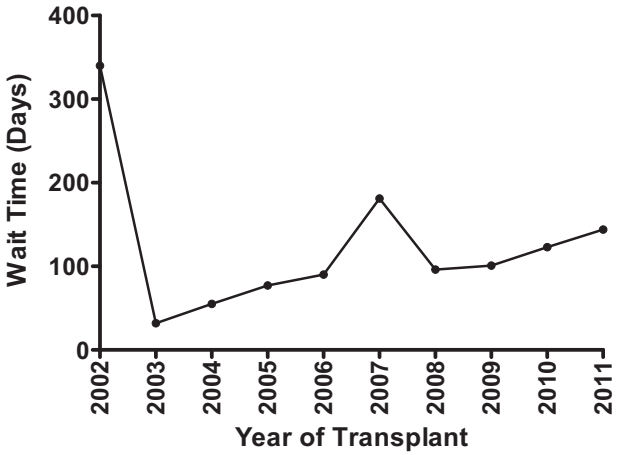

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Figure 7. (A) Comparison of wait time from listing to transplantation for pre and Model for End-Stage Liver Disease (MELD) era. (B) Wait time for transplantation in the MELD era by year (p = 0.0001).

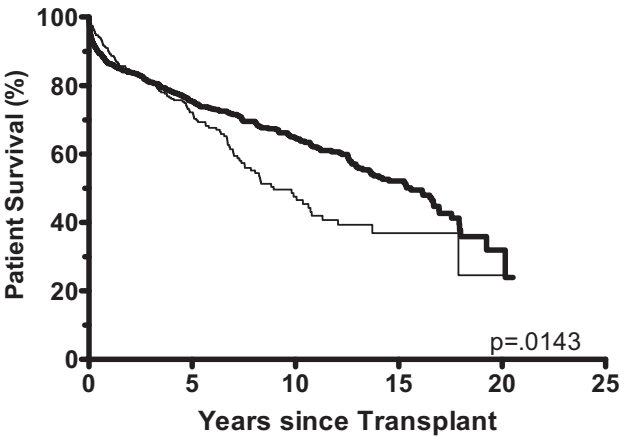

Figure 8. Overall survival in patients with hepatitis C and non–hepatitis C (p = 0.01). Thick line, non–hepatitis C orthotopic liver transplantation; thin line, hepatitis C orthotopic liver transplantation.

more patients dropped off the waiting list because of progression of disease[13,19] and changing the MELD allocation dramatically reduced wait times.[20,21] Wait time was shortened at our center by 62% after 2002, from on average of almost 12 months to 4 months. Currently, 16,246 recipients are on the waiting list in the United States for a liver transplant and 734 (4.5%) are listed with a diagnosis of HCC, according to the Scientific Registry of Transplant Recipients.[22] As the number of patients on the wait list continues to increase, the donor pool is increasing at a slower pace, so overall the waiting time for all recipients is rising every year, although it is still considerably less than for HCC in the pre-MELD era.[22] The amount of allocation priority given for HCC remains a matter of debate within the transplantation community.

In the current report, overall survival in HCC recipients compared with those without HCC receiving transplants approached significance (Fig. 2A; p = 0.055). To remove potential bias because of allocation differences, we also examined survival in the pre-MELD and MELD era (Fig. 2B and C). Having HCC was associated with a considerable survival disadvantage in the pre-MELD era compared with recipients of transplants for non-HCC indications during the same time period. In addition, survival with transplantation for HCC pre-MELD was considerably worse than transplantation for HCC in the MELD era, for several possible reasons (Fig. 5). Only 12 (29%) patients received regional therapy at our center pretransplantation before 2002, compared with 151 (92.6%) since that time. It is possible that this was associated with the higher rate of HCC recurrence and death in the pre-MELD compared with MELD era. Today, we treat HCC recurrence in our patients and have been able to achieve a 50% 5-year survival after single-site recurrence with this approach, which includes resection, ablation, or radiation. In many cases pre-MELD, particularly before 1995, no treatment was offered to patients with recurrence.

Mazzaferro and colleagues' landmark article[4] demonstrating increased survival after transplantation for stage II or lower has been confirmed during the past decade. A report from University of California, Los Angeles of 467 patients demonstrated 5-year survival of 74%, considerably better than their pre-MELD era survival of 47%.[23] The Baylor group reported similar improvements in outcomes, with a 5-year overall survival improvement from 28.6% in 1987 to 1992 to 42.3% in 1992 to 1997, and after 1997, 5-year survival improved to 76% for HCC patients and was similar to survival in nonmalignant indications. Tumor recurrence rates dropped from 52.9% (1987 to 1992) to 8.4% (2002 to 2007).[13]

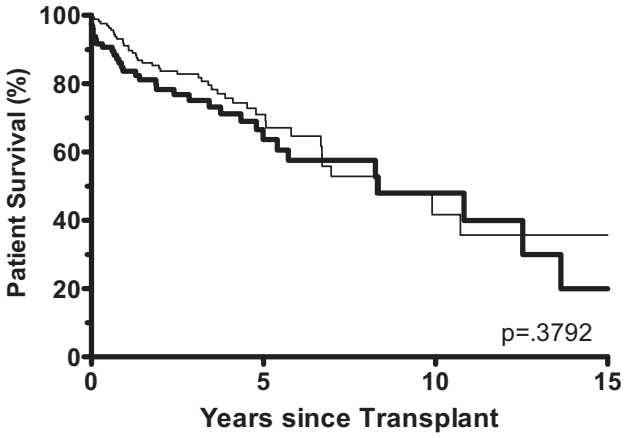

Figure 9. Survival graphs for patients with hepatocellular carcinoma (HCC) and hepatitis C and HCC without hepatitis C ($p = 0.37$). Thick line, HCC in non–hepatitis C; thin line, HCC in hepatitis C.

In the current series, 20-year survival rate in the pre-MELD era is 20%, with a disease-specific survival rate of 75%, suggesting that the majority of patients who receive transplants for HCC die from problems unrelated to malignancy. In an analysis of the United Network for Organ Sharing/Organ Procurement and Transplantation Network database, a 12% 1-year and 20% 3-year risk of dropping off the wait list due to tumor progression or death were reported.[24] Using pretransplantation chemoembolization, the Mayo Clinic demonstrated a cumulative probability of drop out on the waiting list of 15% at 6 months and 25% at 1 year.[25] Mazzaferro and colleagues[26] treated 60 tumors in 50 patients with pretransplantation RFA. After a median waiting time of 9.5 months, there were no patients dropped due to tumor progression and the 1 and 3-year overall survival rates were 95% and 83%, respectively. TACE, as a bridge to transplantation, is well described for HCC,[27-29] and appears to be effective, at least for a period of up to 6 to 9 months.

We previously reported 100 patients with HCC who underwent transplantation, with 46 receiving pretransplantation locoregional therapy. Those who had pretransplantation therapy had significantly better 5-year survival (82.4% vs 51.8%; $p = 0.01$).[30] When stratified by tumor stage, the treatment benefit was seen only in those with T2 to T4 tumors. Patients with T1 tumors experienced excellent outcomes with or without neoadjuvant locoregional therapy. Based on pre-MELD no pretreatment poor outcomes, this suggests some advantage of neoadjuvant locoregional therapy. Yao and colleagues demonstrated a beneficial effect of locoregional therapy in transplant disease-free survival for patients with stage II and III HCC.[7] Another study pretreating HCC outside Milan but within Univer-

Table 2. Details of Hepatocellular Carcinoma Recurrence in Recipients after Transplantation

HCC recurrence	Patient no.	HCC stage OLT	Management of recurrence	Survival, %	Time from transplantation to recurrence, y	Time from transplantation to death, y	Survival time of patients living, y	Cause of death
Chest wall	1	II	Resection	100	4.4	—	4.5	Alive
Liver	2	II	RFA	100	1.1	—	7.5	Alive
		II	RFA		0.858	—	1.9	Alive
Lung	2	II	1 Resected	50	4.1	—	8.7	Alive
		II	1 Extensive disease		0.5	0.6	—	HCC
Retroperitoneal tissue	3	II	1 Radiation	33.3	0.5	—	5.5	Alive
		III	2 Excision		(0.3, 0.4)	0.6	—	HAT-related liver failure;
		IVA2				1.1		HCC
Adrenal	2	II	Resection	100	4.6	8.3	—	HCC
		IVA1			1.1	3.7	—	Sepsis
Liver and adrenal	1	II	Refused treatment	0	1.0	1.3	—	HCC
Vertebrae	1	II	Resection	100	0.3	1.5	—	HCV infection
Multiple abdominal sites	3	I	Chemotherapy	0	3.4	5.0	—	HCC
		II			1.4	1.4	—	HCC
		II			0.9	1.2	—	Primary lung cancer
Multiple sites	4	IVA2, IVA2, III, II	No treatment	0	Unknown	0.7−1.3		HCC

HAT, hepatic artery thrombosis; HCC, hepatocellular carcinoma; HCV, hepatitis C; RFA, radiofrequency ablation.

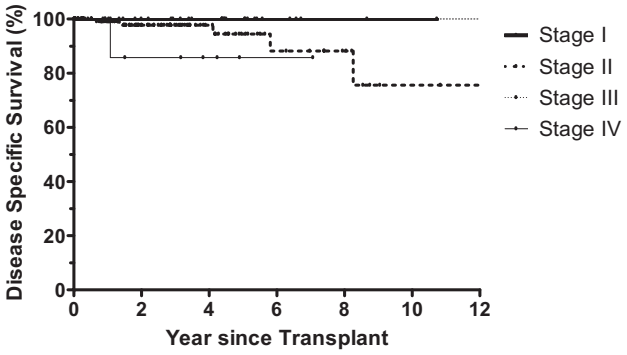

Figure 10. Disease-specific survival by stage in recipients who were pretreated and/or down-staged ($p = 0.3$).

sity of California, San Francisco criteria (single lesion ≤6.5 cm multiple lesions ≤3 cm, largest tumor diameter if multiple ≤4.5 cm, total tumor diameter if multiple ≤8 cm), followed by 3 months surveillance reported successful down-staging in 70.5%.[31] One and 4-year overall survival after transplantation was 96.2% and 92.1%, respectively, and no tumor recurrence was seen at a median follow-up of 25 months. We previously reported the successful down-staging of 23.7% of all stage III and IV patients having TACE and found no difference in survival in those going on to transplantation between stages I and IV.[8] In the current report, 15% of recipients started with stage III disease and 7% started with stage IV, but there was no difference in overall patient, disease-specific, or disease-free survival between stages, suggesting that pretreatment and down-staging effectively puts the patient in the same category as those patients starting in stage II. Although it is possible that we are selecting favorable tumor biology with a minimum 3 to 6-month surveillance period in down-staged patients before transplantation, it seems clear that more advanced-stage patients treated with such a strategy have excellent results, similar to those who receive transplants for non-HCC indications.

CONCLUSIONS

During a 20-year period, the transplantation rate for HCC has dramatically increased since the decade before HCC MELD allocation. Survival is improved, wait time is shorter, and HCC recurrence is less in the MELD era. Survival with HCC, even in patients with stage III and IV disease, is similar to non-HCC orthotopic liver transplantation, and when the rare recurrences occur, aggressive treatment can lead to prolonged disease-free and overall survival.

Author Contributions

Study conception and design: Doyle, Vachharajani, Chapman

Acquisition of data: Maynard, Vachharajani

Analysis and interpretation of data: Doyle, Vachharajani, Lowell, Chapman

Drafting of manuscript: Doyle, Shenoy, Anderson, Wellen, Chapman

Critical revision: Doyle, Vachharajani, Maynard, Shenoy, Anderson, Wellen, Lowell, Chapman

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Discussion

INVITED DISCUSSANT: DR ALAN HEMMING (San Diego, CA): Drs Doyle, Chapman, and colleagues look at 20 years of experience with transplantation for hepatocellular carcinoma (HCC) that covers a time period during which major changes in management have occurred for this disease, which is rapidly increasing in frequency in North America. As the authors point out, early in the study, from 1990 to 1996 (or pre Milan), there was essentially a moratorium on liver transplantation for HCC; currently HCC in the setting of a cirrhotic liver has become one of the most common indications for liver transplantation. Improvements in results have been in large part due to the improved ability to select patients with early disease (within Milan criteria) who benefit from transplantation and improved access and timing of transplantation for patients with HCC in the form of Model for End-stage Liver Disease (MELD) exception policy. Drs Doyle and Chapman have confirmed in their study that liver transplantation for HCC, as currently practiced, is not only successful in general but is astonishingly successful when viewed from the oncologic point of view. Although overall 5- and 20-year survivals were 69% and 27%, respectively, the disease-specific survival at 20 years was 88%. So as a cancer operation, liver transplantation is spectacularly successful for what has generally been considered a malignancy with dismal outcomes. The authors are to be congratulated for their excellent results.

I have several questions: First, you note that in the pre-MELD era there was a significantly worse survival in patients receiving transplantation for HCC as compared with those having transplantation for other reasons, and that this difference was not seen in the post-MELD era. The pre-MELD era in this study includes patients from 1990 to 1996, which was pre-Milan criteria, as well as patients from 1996 to 2002, when Milan criteria were presumably being used. Were many patients transplanted in 1990 to 1996 with HCC, and if so, were they within Milan criteria or outside of criteria, which might worsen results, or do you think that the institution of the MELD scoring system and exception points for HCC is the main reason for improvement?

Second, hepatitis C patients tend to do a little worse long-term with liver transplantation because of recurrent hepatitis C in the graft. Did your patients with hepatitis C and HCC do worse than other groups or even worse than patients transplanted for hepatitis C alone? Was it possible to do a multivariate analysis on some of the other factors thought to influence outcomes?

Finally, the best reports of liver resection for HCC report 5-year overall survival figures of about 50%. Although I realize that many times when we are comparing transplantation to resection we are comparing groups with different patient and tumor characteristics. Do you think that the excellent long-term oncologic results that you have demonstrated influence you as to what treatment you would choose for a 50-year-old patient with hepatitis C and well compensated cirrhosis, who could equally be offered liver transplantation or liver resection?

DR MAJELLA DOYLE (St Louis, MO): Between 1990 and 1996 there were only 14 transplants performed for HCC, probably due to the moratorium. Fifty percent of these recipients had stage III and IV