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Liver transplantation for T3 lesions has higher waiting list mortality but similar survival compared to T1 and T2 lesions

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ABSTRACT

Background. Restrictive staging criteria for liver transplant (LT) patients with HCC in the U.S. have resulted in favorable long-term recurrence-free survival, but these criteria exclude a subgroup of patients who, despite tumor size beyond T2 stage, demonstrate an acceptable outcome. The aim of this study was to assess the waiting list and post-transplant mortality of patients with HCC tumors greater than Milan T2 stage. **Methods.** The U.S. OPTN standard transplant dataset was analyzed for patients with a diagnosis of HCC who were listed for liver transplantation between February 2002 and 2008. Those patients with Milan T3 stage tumors were compared to patients with T1 and T2 lesions. Multivariate survival models were developed to investigate independent predictors of death or tumor recurrence post-transplant. **Results.** 7,391 patients with HCC were identified. 351 (4.75%) had T3 lesions. Compared to non-T3 patients, total tumor burden was greater and total alpha-fetoprotein (AFP) was higher in the T3 patients. T3 patients also were more likely to receive pretransplant locoregional therapy. There were no significant differences between T3 patients and non-T3 patients in demographic variables or physiologic MELD score at the time of transplant, waiting time, or donor risk index. Waiting list mortality was increased for T3 patients compared to non-T3 and tumor progression while waiting was higher. Independent predictors of waiting list mortality included physiologic MELD score at the time of listing, total tumor burden, and serum AFP. There was significant regional variation in the utilization of exceptions for T3 patients and UNOS regions 4, 9, and 10 performed a higher percentage of their transplants in T3 patients compared to other regions. There was no difference in post transplant survival between T3 and non-T3 patients. Independent predictors of post-transplant mortality included physiologic MELD score at the time of transplant, recipient age, and donor risk index. In patients with T3 tumors, total tumor burden was not an independent predictor of post transplant survival. **Conclusions.** Patients who are listed for liver transplantation with Milan stage T3 HCC have higher waiting list mortality but have similar post-transplant survival compared to patients with T1 and T2 HCC.

Key words. Hepatocellular carcinoma. Chemoembolization. Transplantation mortality. Chemotherapy. Cancer.

INTRODUCTION

Liver transplantation (LT) is the optimal treatment of hepatocellular carcinoma (HCC) in patients with underlying liver disease as it eliminates both the cancer and the cirrhotic liver. Early experience with LT for cancer yielded disappointing results having a high rate of recurrence and an unacceptably low survival rate. This was thought to result from poor selection of candidates with advanced disease; however, there were some long term survivors.[1,2] Mazzaferro, *et al*., reported a landmark study in 1996 demonstrating an excellent post-transplant outcome which they attributed to their patient selection. As a result, the "Milan criteria" were developed including a single lesion less than or equal to 5 cm diameter, or up to three lesions all with diameter less than 3 cm.[3] Patients in this group had an excellent 4-year survival rate post-transplant of 75%, similar to patient survival rates with nonmalignant liver diseases. Following this report, experiences from other institutions showed a 5-year

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survival rate of 75% or greater for patients fulfilling these criteria.[4,5] Currently, the Milan criteria have become widely accepted for selection of LT candidates and they are incorporated into the pre-transplant evaluation process for patients with HCC in many transplant centers. Transplant candidates within Milan criteria receive standard MELD exception points in the United States.[6]

The Milan criteria have been challenged in recent years by many centers as being too conservative. Increasing experience from single center series of LT for HCC have suggested that the selection criteria may be expanded without compromising long-term outcomes.[7] Furthermore, some patients with advanced HCC can also be aggressively treated with LT following locoregional neoadjuvant therapy.[8-10] In this method, down staging of advanced HCCs that initially do not meet the Milan criteria but which fulfill the criteria following treatment and remain stable raise a particular interest. Several groups have demonstrated that tumor down staging in LT recipients has good results.[8-16] Various centers have used different treatment options and adopted inconsistent definitions of tumor down staging, typically with a small number of patients. In theory, achieving successful down staging may reflect more favorable tumor biology associated with low recurrence potential. However, not all patients in this category have acceptable post-LT outcomes,[15-16] indicating that there may be additional parameters other than tumor dimensions and stability post treatment that affect outcome. Therefore, there is a crucial need for a better understanding of the disease course after transplant for tumors outside standard criteria. To address these issues, the aim of this study was to determine wait list survival and post transplant mortality and factors of predictive of survival with tumors outside standard criteria using a large U.S. national dataset.

METHODS

The United States Organ Procurement and Transplantation Network database was analyzed for patients listed for liver transplantation with hepatocellular carcinoma between February 2002 and January 2009. This analysis includes all patients with an HCC reported to United Network for Organ Sharing (UNOS) and eventually listed for liver transplantation. Not all patients included in this study necessarily received a MELD exception for HCC. For instance, some patients might have been listed with a primary indication of hepatitis C and had a MELD score high enough to enable liver transplantation without MELD exception points for HCC. In the U.S., UNOS uses a modified version of the Milan criteria[3] to establish transplantation priority for patients with HCC.[17] Patients were considered to be stage T3 if they had one lesion greater than 5 cm, or 2-3 nodules, at least one greater than 3 cm in size. Pre-transplant tumor staging is based on radiographic tumor appearance, not explant findings. The decision to assign transplant priority to patients with T3 lesions is decided at the regional level in the U.S. and is determined by a review board of transplant physicians and surgeons.

In this analysis, patients with T3 lesions were compared to patients with non-T3 lesions. Non-hepatocellular carcinoma liver tumors were excluded (cholangiocarcinoma, hepatoblastoma, metastatic carcinoma). Patients were also categorized by total number of lesions and by cumulative total tumor size. Locoregional interventions performed on patients with HCC are also routinely reported to UNOS as part of the listing process in patients with HCC. For this analysis, the types of locoregional intervention performed were categorized into the following:

- None.
- Transarterial chemoembolization (TACE) or radioactive bead embolization.
- Radiofrequency ablation (RFA) or cryoablation.

Tumor size estimates were based on measurements prior to locoregional therapies.

Patient demographics and other patient characteristics were compared between groups. Univariate and multivariate waiting list and post-transplant survival models were developed to investigate independent predictors of waiting list or post-transplant death. Waiting list removals for "death", "condition deteriorated" or "too sick to transplant" were considered waiting list deaths. Reason for post-transplant mortality was generally not available in the dataset, although recipient status is routinely verified through the U.S. Social Security National Death Registry. Categorical variables were analyzed using the chi-square or Fisher's exact test where appropriate. Continuous variables were analyzed using analysis of variance, independent sample t-test or Wilcoxon sign rank test as appropriate. Univariate survival modeling was performed using the Kaplan-Meier technique and the log-rank test with censoring at death, transplant, or last follow-up. Multivariate adjusted survival models were constructed using the Cox proportional hazards techni-

que with censoring at death or last follow-up. Candidate variables were included in the multivariate survival models if they were statistically significant to a level of 0.20 in the univariate analysis or have been shown in other published models or clinical experience to be significant predictors of survival. No data imputation was performed. All statistical testing was two sided with the level of statistical significance for type one error set at p less than or equal to 0.05. All dataset manipulation and statistical analysis was performed using SAS (Cary, NC, version 9.1.3). No institutional review board approval was needed for the use of this deidentified dataset.

RESULTS

7,391 patients with HCC were identified. 351 (4.75%) had T3 lesions. As expected, patients were predominantly male and Caucasian. There were no differences between patients with T3 lesions and those with non-T3 lesions in mean age (56.7 in T3 patients *vs.* 56.0 years in non-T3 patients, p = 0.228), gender (81.5% male *vs.* 77.1%, p = 0.057), race (65.8% Caucasian *vs.* 61.6%, p = 0.113), MELD score at transplant (14.0 *vs.* 13.7, p = 0.503), HCV infection (21.4% *vs.* 25.8%, p = 0.063), or time spent on the transplant waiting list (199 days *vs.* 195, p = 0.720). Mean donor age was marginally higher in the T3 patients (44.8 years *vs.* 41.8, p = 0.007) but the overall donor quality as assessed by the donor risk index (DRI)[18] was similar between groups (1.85 *vs.* 1.81, p = 0.104). See table 1 for details.

Because of the definition of the groups, there were significant differences in the characteristics of the tumors between groups. The total tumor burden (6.91 cm in T3 patients *vs.* 3.10 in non-T3 patients, p <0.0001), mean number of lesions (2.23 *vs.* 1.36, p <0.0001), serum AFP (864 ng/mL *vs.* 340, p = 0.0003), and percentage of patients undergoing no pre-transplant tumor locoregional intervention (39.0% *vs.* 64.9%, p <0.0001) were all significantly different between T3 patients and non-T3 patients (Table 1). Amongst the UNOS regions, there was significant variation in listing practices for candidates with T3 lesions. Regions 9 (New York, n = 79, 22.5%), 5 (California, Nevada, Utah, Arizona, and New Mexico, n = 76, 21.7%), and 4 (Texas and Oklahoma, n = 72, 20.5%) listed more than 60% of all candidates with T3 tumors. T3 candidates accounted for 12.2% of all regional candidates with HCC within Region 4, 7.2% in Region 9, and 7.1% in Region 10 (Michigan, Indiana, and Ohio). These regions were significantly different compared to all other regions (p <0.0001).

Waiting list mortality was increased for T3 patients compared to non-T3 (18.5 *vs.* 11.3%, p <0.0001). Figure 1 shows the unadjusted Kaplan-Meier waiting list survival for the population. Ninety-day survival for candidates with T3 tumors was 94.2% compared to 96.7% for non-T3 candidates (p = 0.0006). This survival disadvantage continued at one year with 71.3% for T3 candidates and 74.6% for non-T3 patients (p = 0.0006). In the multivariate survival model, independent predictors for increa-

Table 1. Patient population and tumor characteristics. Continuous variables are expressed as means and 95% confidence intervals. Categorical variables are expressed as number and percent.

Variable	T3 Patients (n = 351)	Non-T3 Patients (n = 7,040)	p-value
Recipient age (years)	56.7 (55.7-57.7)	56.0 (55.9-56.3)	0.228
Recipient male	286 (81.5)	5430 (77.1)	0.057
Recipient Caucasian	231 (65.8)	4337 (61.6)	0.113
MELD score at transplant	14.0 (13.3-14.7)	13.7 (13.6-13.9)	0.503
Hepatitis C infection	75 (21.4)	1816 (25.8)	0.063
Waiting time (days)	199 (172-226)	195 (189-201)	0.720
Donor age (years)	44.8 (42.7-47.0)	41.8 (41.3-42.5)	0.007
Donor risk index*	1.85 (1.80-1.91)	1.81 (1.80-1.82)	0.104
Total tumor burden (cm)	6.91 (6.78-7.05)	3.10 (3.07-3.13)	<0.0001
Number of lesions	2.23 (2.17-2.30)	1.36 (1.35-1.38)	<0.0001
Serum alpha-fetoprotein (ng/mL)	864 (588-1140)	340 (278-401)	0.0003
Pre-op chemoembolization	159 (45.3)	1699 (24.1)	<0.0001
Pre-op percutaneous ablation	73 (20.8)	914 (13.0)	<0.0001
No pre-op intervention	137 (39.0)	4568 (64.9)	<0.0001

* As defined by Feng, *et al.* See text.

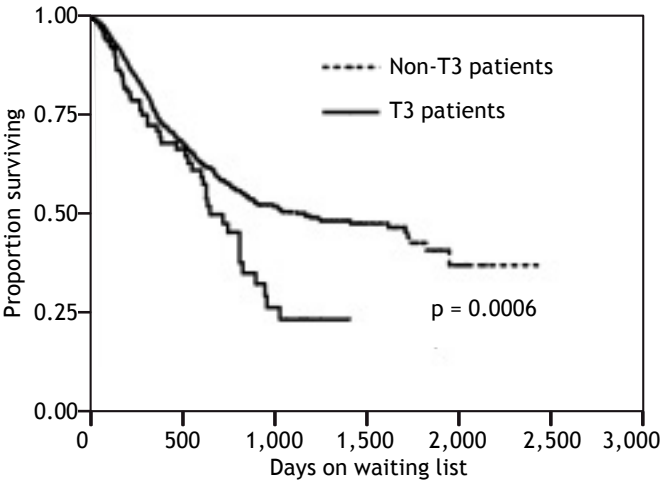

Figure 1. Waiting list survival for patients with T3 hepatocellular carcinoma compared to those with non-T3 lesions.

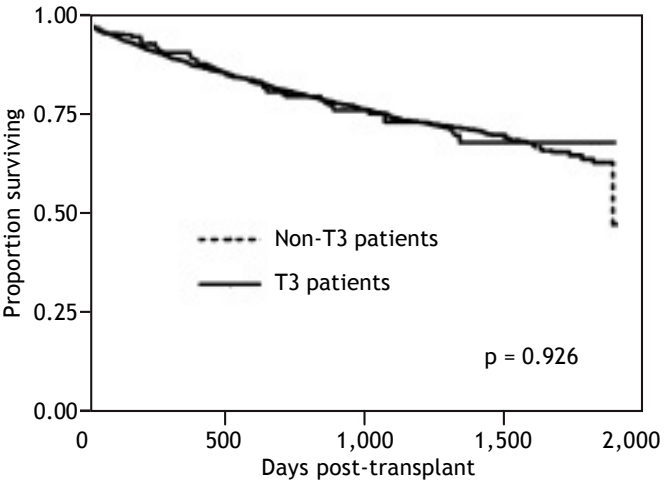

Figure 2. Post liver transplant survival for patients with T3 hepatocellular carcinoma compared to those with non-T3 lesions.

Table 2. Independent predictors of adjusted waiting list and adjusted post-transplant mortality.

Variable	Hazard Ratio	Interval	95% Confidence p-value
Waiting List Mortality			
MELD score at listing	1.126	1.108 - 1.144	<0.0001
Any pre-op tumor intervention	0.904	0.774 - 1.056	0.203
Total tumor burden (cm)	1.113	1.069 - 1.158	<0.0001
Serum alpha-fetoprotein (ng/mL)	1.001	1.000 - 1.002	<0.0001
Post-Transplant Mortality			
Recipient age (years)	1.012	1.004 - 1.019	0.002
Hepatitis C infection	1.040	0.924 - 1.171	0.512
MELD score at transplant	1.024	1.016 - 1.033	<0.0001
Any pre-op tumor intervention	0.981	0.873 - 1.103	0.751
Total tumor burden	1.022	0.983 - 1.063	0.277
Donor risk index*	1.473	1.301 - 1.668	<0.0001

* As defined by Feng, *et al.* See text.

sed waiting list mortality included MELD score at listing (HR 1.126, 95% CI 1.108-1.144, p <0.00001), total tumor burden (HR 1.113 per cm of tumor, 1.069-1.158, p <0.0001), serum AFP (HR 1.001 per unit change in AFP, 1.000-1.002, p <0.0001). See table 2 for details.

Despite the differences in waiting list mortality, there was no difference in post transplant survival between T3 and non-T3 patients (p = 0.926). Figure 2 shows the unadjusted survival curves for the T3 patients *vs.* the non-T3 patients. Independent predictors of post-transplant mortality (Table 2) included physiologic MELD score at the time of transplant (HR 1.024, 1.016-1.033, p <0.0001), recipient age (HR 1.012 per year, 1.004-1.019, p = 0.002), and donor risk index (HR 1.473, 1.301-1.668, p <0.0001. Total pretransplant tumor burden was not an independent predictor of post transplant survival (p = 0.277).

DISCUSSION

With recent advances in therapeutic options and surveillance for HCC, more patients with large HCC have come to be evaluated for transplantation. Data suggest that there is a select group of patients with advanced stage HCC that do well with liver transplantation. There is also evidence that some tumors which are initially outside of standard transplant criteria may be successfully down staged pre-operatively and have similar outcomes.[7-13,19,20] The challenge is to determine if expanded criteria and down

staging offers a similar long-term survival to those candidates with smaller tumors in this era of organ shortage. In light of the success in tumor down staging demonstrated by UCSF,[7,9,10,13] many centers have pushed forward with this type of protocol asking for MELD exception points on candidates outside standard accepted Milan criteria who show stability after locoregional down staging.[9-13] Currently, review boards consider these situations on a case by case basis. Those tumors that can be down staged into Milan T2 criteria and have documented stability for three months are typically given the same exception points that standard T2 tumors receive. Tumors outside the standard criteria may also receive exception points or, in some cases, be transplanted based upon native MELD score.

In this analysis, patients with T3 lesions were compared to patients with non-T3 lesions and found to have similar outcomes after transplantation. It is somewhat challenging to determine which patients underwent a down staging treatment prior to transplant or not due to the nature of this database analysis. However patients who survived to transplant did as well regardless of tumor stage at listing. Whether or not pre-transplant locoregional therapy is beneficial is still controversial. Some have argued that pre-operative locoregional down staging have not demonstrated a significant effect on survival which is dramatically demonstrated in those waiting greater than 6 months for transplantation.[21] Recently Northup, *et al*., presented data demonstrating an increased list removal rate with locoregional therapy in patients with T1 lesions compared to T2 lesions.[22] There was not a significant survival advantage to locoregional therapy in patients with T2 lesions post transplant. Moreover, at a national consensus conference on liver allocation for patients with HCC, a work group reviewed locoregional therapy and concluded that devices and image guidance techniques are constantly improving and the true complete ablation rate will likely improve with advancing technologies.[23] Despite this, locoregional therapy should currently be viewed as a bridge to rather than a replacement for transplantation.

Locoregional interventions performed on patients with HCC are also routinely reported to UNOS as part of the listing process in patients with HCC. Non-T3 patients were more likely to not have pre-transplant locoregional therapy as compared to T3 patients (64.9% *vs.* 39.0%). Furthermore, it was interesting to discover that only 65% of patients with T3 tumors had pre-transplant locoregional intervention. Despite the favorable tumor biology expected in successfully down staged patients, previously published data have yielded inconsistent results in relation to post-transplant outcomes.[10-16] This highlights the need for improved understanding of the long-term clinical course of down staged HCC. Identifying prognostic factors would establish the basis for which we elect LT for selected down staged patients.

Regional variation is difficult to account for within this database analysis. Regions that tend to transplant at higher MELD scores also had a higher incidence of T3 tumors. Again, it could be postulated that these cases were transplanted on standard MELD score *vs.* exception. Regions 9 (New York, n = 79, 22.5%), 5 (California, Nevada, Utah, Arizona, and New Mexico, n = 76, 21.7%), and 4 (Texas and Oklahoma, n = 72, 20.5%) listed more than 60% of all candidates with T3 tumors. T3 candidates accounted for 12.2% of all regional candidates with HCC within Region 4, 7.2% in Region 9, and 7.1% in Region 10 (Michigan, Indiana, and Ohio). These regions were significantly different that all other regions ($p < 0.0001$). The regional variation in transplant practice in the U.S. is of great debate as supply and demand are not equally distributed throughout the country. The current allocation system is being evaluated for alterations to allow for more equitable organ distribution more equitable based on population and geography.

Waiting list mortality or removal from the waiting list was expected to be higher in the T3 patients. Waiting list removals for "death", "condition deteriorated" or "too sick to transplant" were considered as waiting list deaths in the analysis. Waiting list mortality was increased for T3 patients compared to non-T3. This waiting list death and removal accounted for a significant decrease in overall survival at 90 days and one year from the time of listing. However, those patients that survived to transplant had no survival difference between T3 and non-T3 patients. In the multivariate wait list survival model, independent predictors for increased probability of wait list removal included MELD score at listing, total tumor burden and serum AFP. These results suggest sicker patients, and those with larger and more aggressive tumors, have a higher rate of waiting list removal. AFP continues to be a significant predictor of poor outcome in tumor patients.

There are inherent weaknesses of large data set analyses such as incomplete reporting to UNOS, unclear cause of death in the dataset and incomplete

reporting of recurrent tumors post-transplant, relatively short follow-up period, and no justifiable accounting for tumor patients that are never listed. There is also a lack of granularity to show details about explant pathology or the total denominator of HCC patients undergoing transplant and these weakness in the OPTN database have been discussed elsewhere.[24] Finally, mortality is a poor endpoint for many disease processes as the true cause of mortality is multifactorial in most cases. Other factors such as local standard of care, regional surgical variation, and unnamed factors are likely to contribute greatly to overall survival. Despite these obvious weaknesses, this study offers the largest sample size of well defined T3 HCC patients with extended follow-up published to date.

The survival model post transplant was strikingly different from the pre-transplant model. It revealed that the MELD score at the time of transplant was an independent predictor of post-transplant mortality as was recipient age and donor risk index. These findings confirm previously published single center studies. Interestingly, total pretransplant tumor burden was not an independent predictor of post transplant survival. This suggests that patients who have tumors outside of the UNOS (Milan) T2 criteria who successfully navigate the transplant process have similar survival to candidates with lower tumor burden pre-transplant. Our results support the assertion that transplant centers and the various regional review board methods allow select patients outside standard criteria to be transplanted with good results. Whether these patients are transplanted on their MELD score, through regional review board exception points, or tumor down staging protocols, these data demonstrated that there is a role for expanding the listing criteria with demonstrated good outcomes. Unfortunately defining the expanded criteria is difficult for T3 and greater lesions with the present data. Further work is needed to develop improved and more specific pre-transplant predictive models for aggressive tumors such as serum markers, tumor genetic profiles, and improved radiographic analysis in order to establish if there a role for pre- and post-transplant chemoprophylaxis for high risk tumors given the advent of new chemotherapeutic agents. The current data demonstrates further the need for a down staging waiting period in patients who have tumors outside standard criteria in order to identify aggressive tumors until better methods of assessing tumor activity are available.

CONCLUSION

Analysis of the US MELD-era data shows that patients who are listed for liver transplantation with Milan stage T3 HCC have increased waiting list mortality but have similar post-transplant survival rates compared to patients with stages T1 and T2 lesions and provides further evidence that criteria for transplantation for HCC should be liberalized, probably through the use of down staging waiting periods and improved detection methods of aggressive tumors.

ABBREVIATIONS:

- **AFP:** Alpha fetoprotein.
- **HCC:** Hepatocellular carcinoma.
- **HCV:** Hepatitis C virus.
- **OPTN:** Organ Procurement and Transplantation Network.
- **RFA:** Radiofrequency ablation.
- **TACE:** Transarterial chemoembolization.
- **UNOS:** United Network for Organ Sharing.

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REFERENCES

1. Iwatsuki S, Starzl TE, Sheahan DG, Yokoyama I, Demetris AJ, Todo S, Tzakis AG, et al. Hepatic resection versus transplantation for hepatocellular carcinoma. *Ann Surg* 1991; 214: 221-8, 228-9.
2. Ringe B, Pichlmayr R, Wittekind C, Tusch G. Surgical treatment of hepatocellular carcinoma: experience with liver resection and transplantation in 198 patients. *World J Surg* 1991; 15: 270-85.
3. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, Montalto F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996; 334: 693-9.
4. Llovet JM, Fuster J, Bruix J. Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: resection versus transplantation. *Hepatology* 1999; 30: 1434-40.
5. Regalia E, Coppa J, Pulvirenti A, Romito R, Schiavo M, Burgoa L, Mazzaferro V. Liver transplantation for small hepa-

tocellular carcinoma in cirrhosis: analysis of our experience. *Transplant Proc* 2001; 33: 1442-4.
6. Befeler AS, Hayashi PH, Di Bisceglie AM. Liver transplantation for hepatocellular carcinoma. *Gastroenterology* 2005; 128: 1752-64.
7. Yao FY, Ferrell L, Bass NM, Watson JJ, Bacchetti P, Venook A, Ascher NL, et. al. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. *Hepatology* 2001; 33: 1394-403.
8. Otto G, Herber S, Heise M, Lohse AW, Monch C, Bittinger F, Hoppe-Lotichius M, et al. Response to transarterial chemoembolization as a biological selection criterion for liver transplantation in hepatocellular carcinoma. *Liver Transpl* 2006; 12: 1260-7.
9. Yao FY. Expanded criteria for hepatocellular carcinoma: down-staging with a view to liver transplantation-yes. *Semin Liver Dis* 2006; 26: 239-47.
10. Yao FY, Kerlan RK Jr., Hirose R, Davern TJ 3rd, Bass NM, Feng S, Peters M, et al. Excellent outcome following down-staging of hepatocellular carcinoma prior to liver transplantation: an intention-to-treat analysis. *Hepatology* 2008; 48: 819-27.
11. Chapman WC, Majella DMB, Stuart JE, Vachharajani N, Crippin JS, Anderson CD, Lowell JA, et al. Outcomes of neoadjuvant transarterial chemoembolization to downstage hepatocellular carcinoma before liver transplantation. *Ann Surg* 2008; 248: 617-25.
12. Lu DS, Yu NC, Raman SS, Lassman C, Tong MJ, Britten C, Durazo F, et al. Percutaneous radiofrequency ablation of hepatocellular carcinoma as a bridge to liver transplantation. *Hepatology* 2005; 41: 1130-7.
13. Yao FY, Hirose R, LaBerge JM, Davern TJ 3rd, Bass NM, Kerlan RK Jr., Merriman R, et al. A prospective study on downstaging of hepatocellular carcinoma prior to liver transplantation. *Liver Transpl* 2005; 11: 1505-14.
14. Majno PE, Adam R, Bismuth H, Castaing D, Ariche A, Krissat J, Perrin H, et al. Influence of preoperative transarterial lipiodol chemoembolization on resection and transplantation for hepatocellular carcinoma in patients with cirrhosis. *Ann Surg* 1997; 226: 688-701, 701-3.
15. Millonig G, Graziadei IW, Freund MC, Jaschke W, Stadlmann S, Ladurner R, Margreiter R, et al. Response to preoperative chemoembolization correlates with outcome after liver transplantation in patients with hepatocellular carcinoma. *Liver Transpl* 2007; 13: 272-9.
16. Roayaie S, Frischer JS, Emre SH, Fishbein TM, Sheiner PA, Sung M, Miller CM, et al. Long-term results with multimodal adjuvant therapy and liver transplantation for the treatment of hepatocellular carcinomas larger than 5 centimeters. *Ann Surg* 2002; 235: 533-9.
17. Wiesner RH, McDiarmid SV, Kamath PS, Edwards EB, Malinchoc M, Kremers WK, Krom RA, et al. MELD and PELD: application of survival models to liver allocation. *Liver Transpl* 2001; 7: 567-80.
18. Feng S, Goodrich NP, Bragg-Gresham JL, Dykstra DM, Punch JD, DebRoy MA, Greenstein SM, et al. Characteristics associated with liver graft failure: the concept of a donor risk index. *Am J Transplant* 2006; 6: 783-90.
19. Duffy JP, Vardanian A, Benjamin E, Watson M, Farmer DG, Ghobrial RM, Lipshutz G, et al. Liver transplantation criteria for hepatocellular carcinoma should be expanded: a 22-year experience with 467 patients at UCLA. *Ann Surg* 2007; 246: 502-9, 509-11.
20. Mazzaferro V, Llovet JM, Miceli R, Bhoori S, Schiavo M, Mariani L, Camerini T. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. *Lancet Oncol* 2009; 10: 35-43.
21. Porrett PM, Peterman H, Rosen M, Sonnad S, Soulen M, Markmann JF, Shaked A, et al. Lack of benefit of pretransplant locoregional hepatic therapy for hepatocellular cancer in the current MELD era. *Liver Transpl* 2006; 12: 665-73.
22. Northup PG, Argo CK, Shah N, Schmitt TL. Locoregional Therapy of T1 Hepatocellular Carcinomas is Associated with Increased Transplant Wait List Mortality and Offers No Additional Post-Transplant Survival [Abstract]. *Hepatology* 2009; 50: 306A.
23. Pomfret EA, Washburn K, Wald C, Nalesnik MA, Douglas D, Russo M, Roberts J, et al. Report of a national conference on liver allocation in patients with hepatocellular carcinoma in the United States. *Liver Transpl;* 16: 262-78.
24. Freeman RB. Transplant data collection: you get what you pay for. *Am J Transplant*; 10: 1503-4.