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Comparison of Liver Transplant–Related Survival Benefit in Patients With Versus Without Hepatocellular Carcinoma in the United States

Kristin Berry[1] and George N. Ioannou[1,2]

[1]Research and Development, Veterans Affairs Puget Sound Health Care System, Seattle, Washington and [2]Division of Gastroenterology, Department of Medicine, Veterans Affairs Puget Sound Health Care System and University of Washington, Seattle, Washington

This article has an accompanying continuing medical education activity on page e15. Learning Objective: Upon completion of this activity, successful learners will be able to (a) apply the most recent professional guidelines on screening for HCC, (b) discuss the diagnosis of HCC based on current guidelines, and (c) identify appropriate treatments for HCC based on current guidelines.

See editorial on page 531.

BACKGROUND & AIMS: Patients with T2 hepatocellular carcinoma (HCC) can obtain an exception that allows them to undergo liver transplantation with much lower actual Model for End-Stage Liver Disease (MELD) scores than patients without HCC. We compared patients who received liver transplants, with and without HCC, with regard to transplantation-related survival benefit. **METHODS:** We modeled the post-transplantation survival of adult, first-time liver transplant recipients with HCC (n = 9135) or without (n = 25,890) from 2002 through 2013 using Cox proportional hazards regression. We modeled waitlist survival of patients listed for transplantation with HCC (n = 15,605) or without (n = 85,229) using competing risks analysis and combined outcomes of death or liver failure (defined as MELD score $\geq$30). We used these survival models to calculate monthly transition probabilities and 5-year life expectancies. Survival benefit was calculated as the difference between post-transplantation and waitlist life expectancy. **RESULTS:** The 5-year survival benefit increased with actual MELD score for patients with and without HCC, ranging from just a few months in patients with low MELD scores (ie, 6–8) to 4 years in patients with the highest MELD scores (ie, 36–40). The survival benefit of patients with HCC was similar to that of patients without HCC who had the same actual MELD score, irrespective of tumor burden or serum level of α-fetoprotein. However, because patients with HCC received liver transplants when they had a lower mean MELD score (13.3 ± 6.2) than patients without HCC (21.8 ± 8.0), a much lower mean 5-year survival benefit was achieved by providing liver transplants to patients with HCC (0.12 years/patient) than patients without HCC (1.47 years/patient). **CONCLUSIONS:** The HCC MELD exception policy has unintentionally resulted in a large reduction in transplantation-related survival benefit.

Keywords: Liver Cancer; UNOS; Priority; Exception Points.

Priority among patients listed for liver transplantation in the United States has been based on the Model for End-Stage Liver Disease (MELD) scoring system since 2002, such that patients with the highest MELD score receive the highest priority, other than status 1 patients with acute liver failure. Patients with T2 hepatocellular carcinoma (HCC) (single tumor 2–5 cm or 2–3 tumors $\leq$3 cm) currently receive priority MELD exception points in order to ensure that their tumor does not grow substantially, cause vascular invasion, or metastasize while they are waiting for liver transplantation.[1] Such patients are listed with an "artificial" MELD score of 22, which increases by 3 points every 3 months, unless their actual MELD score is higher.

This system was designed to lead to an equal rate of drop out between patients with and without HCC. However, studies suggest that drop-out rates are lower in patients with HCC than those without.[2] In addition, minimizing drop-out rates is not necessarily the best outcome measure of a transplant allocation system because it completely ignores post-transplantation survival and because a drop out might have different implications in patients with or without HCC.

A better system might be one that attempts to maximize the survival benefit achieved by liver transplantation, defined as the mean life expectancy with transplantation minus the mean life expectancy without transplantation.[3–6] Under such a system, a patient with HCC would be transplanted if and when his survival benefit matches or exceeds the survival benefit of other patients without HCC. It has been suggested that, under the current allocation system, certain patients who are transplanted with T2 HCC, such as patients with Child's A cirrhosis,[6] have a much lower survival benefit than patients without HCC, who almost universally have Child's C cirrhosis and very high MELD scores at the time of transplantation. This is because patients with HCC who have Child's A cirrhosis or low MELD score at the time of their transplantation have a substantial life

Abbreviations used in this paper: **AFP, α-fetoprotein; HCC, hepatocellular carcinoma; MELD, Model for End-Stage Liver Disease; UNOS, United Network for Organ Sharing.**

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expectancy without transplantation, which has to be subtracted from their post-transplantation life expectancy when calculating transplantation-related survival benefit.

We aimed to compare the survival benefit experienced by patients transplanted in the United States with or without HCC between 2002 and 2013. Because patients with HCC are transplanted at significantly lower mean MELD score than patients without HCC, due to the HCC MELD exception policy, we hypothesized that patients with HCC might derive a substantially lower survival benefit.

Methods

Study Design

In order to calculate the survival benefit of patients who underwent liver transplantation in the United States with or without HCC, we need to estimate their post-transplantation life expectancy and subtract from that the life expectancy that they would have experienced if they had not undergone liver transplantation. Post-transplantation life expectancy can be estimated by modeling the observed post-transplantation survival of liver transplant recipients using Cox proportional hazards regression. Estimating what the life expectancy of liver transplant recipients would have been if they had not undergone liver transplantation is more complicated because it is not directly observed. We chose to estimate life expectancy without transplantation by modeling the pretransplantation survival of patients on the waiting list (henceforth referred to as "waitlist survival") using competing risks analysis.[4] This method has the advantage that patients on the liver transplant waiting list are very similar to liver transplant recipients. However, the real mortality of patients on the waiting list is masked by the fact that many undergo liver transplantation, requiring special methods outlined here, including the use of competing risks models, to determine what their life expectancy would have been without transplantation.

Study Population

Post-Transplantation Survival. We identified all patients aged 18 years or older who underwent first-time liver transplantation in the United States from February 27, 2002 (the date the MELD allocation system was introduced) until September 30, 2013 (N = 45,193), using data provided by the United Network for Organ Sharing (UNOS). We excluded patients with HCC who did not have T2 HCC at the time of transplantation (n = 1958, including 1809 with single tumors <2 cm and 149 with tumors exceeding T2 stage) because only patients with T2 tumors can currently receive an HCC-MELD exception. Patients with HCC who did not have tumor burden data or serum α-fetoprotein (AFP) level (n = 932) were excluded. Finally, we excluded status 1 patients (acute liver failure) (n = 1860), living donor transplants (n = 1937), split liver transplants (n = 571), transplantation of multiple simultaneous organs (n = 2606), patients with acute hepatic necrosis (n = 139), and tumors other than HCC (n = 155), leaving 35,025 transplant recipients in the current analysis, including 9135 with HCC and 25,890 without HCC.

Waitlist Survival

Starting with all adult patients who were listed for first-time transplantation from 2002 to 2013 (N = 114,362) and using identical criteria as for post-transplantation survival, we excluded patients with HCC who did not have T2 tumors (n = 3764, including 2959 with single tumors <2 cm and 805 with tumors exceeding T2 stage); patients with HCC who were missing tumor burden or serum AFP level (n = 3499); and patients with status 1, acute hepatic necrosis, tumors other than HCC or were listed for multiple organ, split liver, or living donor transplantation (n = 6265), leaving 100,834 in the current analysis (15,605 with HCC and 85,229 without HCC), including the 35,025 transplant recipients who were used to estimate post-transplantation survival.

Identification of Patients With Hepatocellular Carcinoma and Their Tumor Characteristics

Post-Transplantation Survival. Patients with a diagnosis of HCC at the time of transplantation or listing, an HCC MELD exception, or HCC tumor records were identified as having HCC at transplantation. Tumor size and number and serum AFP level at the time of transplantation were ascertained.

Waitlist Survival. We identified patients with HCC at listing using either listing diagnosis codes or receipt of HCC MELD exception at the time of listing or HCC tumor records. Tumor size and number and serum AFP level at the time of listing were ascertained.

Modeling Survival

Post-Transplantation Survival. We used Cox proportional hazard regression to model time to death separately for patients with and without HCC. The assumption of proportional hazards was tested and met using weighted residual methods. Survival time was defined as days from transplantation until the earliest of either date of last follow-up or death as determined by the UNOS public use and linked Social Security Death Master File. Linkage to Social Security Death Master File allowed identification of deaths that occurred even after potential loss to follow-up by the transplantation center. The models used the following predictors, selected a priori based on previous published studies,[7,8] and ascertained at the time of transplantation:

1. MELD score at the time of transplantation, provided by UNOS as variable "FINAL_MELD_PELD_LAB_SCORE" categorized as 6−9, 10−13, 14−17, 18−21, 22−25, 26−29, 30−34, 35−40. MELD score was grouped to prevent instability in estimates due to small sample sizes. This is the actual MELD score calculated using the levels of international normalized ratio, bilirubin, and creatinine.
2. Underlying cause of liver disease categorized in Tables 1–4.
3. Age at transplantation.
4. Sex.
5. Race/ethnicity.
6. Diabetes.
7. Body mass index at transplantation.

Table 1. Transplant Population: Recipient and Donor Characteristics at the Time of Transplantation of Adult, Deceased-Donor, First-Time Liver Transplantations Performed in the United States From 2002 to 2013, Presented Separately for Patients With and Without Hepatocellular Carcinoma

Characteristics	HCC (n = 9135)	No HCC (n = 25,890)
Follow-up, *mo*, mean ± SD	40.0 ± 31.6	45.9 ± 36.5
Deaths, n	2384	6029
Deaths per 100 patient-years, n	7.8	6.1
Tumor characteristics (at transplantation)		
AFP, *ng/mL*, mean ± SD	182.6 ± 1157.5	NA
0–13, %	52.2	NA
14–56, %	24.9	NA
57–281, %	14.4	NA
>282, %	8.5	NA
Tumor burden, %		
2–3 nodules <2 cm or 1 nodule 2–3 cm	53.7	NA
2–3 nodules 2–3 cm or 1 nodule >3–5 cm	46.3	NA
MELD score at transplant, mean ± SD	13.3 ± 6.2	21.8 ± 8.0
≤21, %	91.8	54.3
>21, %	8.2	45.7
Underlying liver disease, %		
Hepatitis C virus	67.7	41.6
Hepatitis B virus	7.7	2.7
Alcoholic liver disease	7.5	16.8
Primary biliary cirrhosis	1.1	4.8
Primary sclerosing cholangitis	0.6	6.8
Cryptogenic	3.5	8.7
Nonalcoholic steatohepatitis	4.5	8.6
Autoimmune hepatitis	1.0	3.3
Hemochromatosis	0.6	0.7
Other	5.7	6.0
Male, %	78.4	65.9
Race or ethnicity, %		
White	68	78
Black and African American	9.1	8
Hispanic	13	11
Other (mostly Asian)	9.2	3
Diabetes, %	27	22
Dialysis twice in week before transplantation, %	1.1	5.4
Age, *y*, mean ± SD	57.4 ± 7.3	53.3 ± 9.5
Body mass index, mean ± SD	28.4 ± 5.1	28.4 ± 5.7
Donor characteristics		
Male, %	59.6	59.2
Race or ethnicity, %		
White	66.5	68.9
Black and African American	17.6	17.0
Hispanic	12.1	10.8
Other (mostly Asian)	3.8	3.3
Height (cm), mean ± SD	171.6 ± 10.9	171.6 ± 11.0
Hepatitis B virus core antibody positive, %	0.1	0.1
Hepatitis C virus antibody positive, %	4.4	3.2
Age, *y*, mean ± SD	42.7 ± 17.0	42.5 ± 17.3
Cold ischemia time, *h*, mean ± SD	6.9 ± 3.4	7.1 ± 3.4
Deceased cardiac donor, %	5.4	5.0
Donor cause of death, %		
Trauma	34.2	35.9
Anoxia	20.0	18.5
Cerebrovascular accident	43.1	43.0
Other	2.7	2.6
Organ location, %		
Local	78.2	72.5
Regional	17.4	20.8
National	4.4	6.7

NA, not applicable.

Table 2. Waiting List Population: Patient Characteristics at the Time of Listing for Liver Transplantation for Adults Listed in the United States from 2002 to 2013, Presented Separately for Patients With and Without Hepatocellular Carcinoma

Characteristics	HCC (n = 15,605)	No HCC (n = 85,229)
Follow-up, *mo*, mean ± SD	7.5 ± 9.8	18.1 ± 24.0
Deaths, n	1817	17517
Deaths per 100 patient-years, n	18.6	13.7
Tumor characteristics (at listing)		
AFP, *ng/mL*, mean ± SD	212.0 ± 1234.2	NA
0−13, %	50.0	NA
14−56, %	25.4	NA
57−281, %	14.9	NA
≥282, %	9.8	NA
Tumor burden		
2−3 nodules <2 cm or 1 nodule 2−3 cm, %	53.7	NA
2−3 nodules 2−3 cm or 1 nodule >3−5 cm, %	46.3	NA
MELD score at listing, mean ± SD	12.2 ± 5.7	18.0 ± 8.5
≤21, %	95.1	74.3
>21, %	4.9	25.7
Underlying liver disease, %		
Hepatitis C virus	56.6	38.7
Hepatitis B virus	6.1	2.6
Alcoholic liver disease	8.3	19.0
Primary biliary cirrhosis	0.9	3.9
Primary sclerosing cholangitis	0.5	5.4
Cryptogenic	3.3	8.4
Nonalcoholic steatohepatitis	4.7	7.5
Autoimmune hepatitis	1.1	3.5
Hemochromatosis	0.6	0.5
Other	17.8	10.5
Male, %	77.5	63.2
Race or ethnicity, %		
White	65.3	73.9
Black and African American	9.6	7.8
Hispanic	14.5	14.3
Other (mostly Asian)	10.6	4.0
Diabetes, %	27.5	24.3
Dialysis twice in week before listing, %	1.3	5.8
Age, *y*, mean ± SD	57.5 ± 7.3	53.0 ± 9.7
Body mass index, mean ± SD	28.6 ± 5.3	28.6 ± 5.9

NA, not applicable.

8. Dialysis twice in the week before transplantation.
9. For patients with HCC at the time of transplantation, we ascertained tumor burden at transplantation (categorized into: 2−3 nodules <2 cm or 1 nodule 2−3 cm or 2−3 nodules 2−-3 cm or 1 nodule >3−5 cm) and serum AFP level at transplantation (categorized using the 50th [13 ng/mL], 75th [56 ng/mL], and 90th [282 ng/mL] percentiles).[9]

In addition, the following donor characteristics, which included all components of the donor risk index,[8] were also used as predictors.

1. Age.
2. Sex.
3. Race/ethnicity.
4. Height.
5. Cold ischemia time.
6. Cause of death, categorized as trauma, anoxia, cerebrovascular accident, or other.
7. Hepatitis B virus core antibody.
8. Hepatitis C virus antibody.
9. Donation after circulatory death.
10. Organ location, categorized as local, regional or national.

Waitlist Survival. Our purpose was to model the survival of patients on the waiting list in the absence of transplantation. To this end, we used a competing risks model[10] with death or liver failure (defined as MELD ≥30) as the outcome of interest and transplantation as a competing risk. Competing risks models yield "sub−hazard ratios" for each competing risk, as opposed to hazard ratios derived from Cox proportional

Table 3. Predictors of Waiting List Survival and Post-Transplantation Survival in Patients With HCC[a]

Predictors	Waiting list survival, adjusted sub−hazard ratio[b]	Post-transplantation survival, adjusted hazard ratio[c]
MELD score		
6−9	1	1
10−13	1.53 (1.37−1.70)	0.97 (0.87−1.08)
14−17	2.61 (2.32−2.93)	0.97 (0.85−1.09)
18−21	4.11 (3.56−4.75)	1.08 (0.93−1.27)
22−25	7.97 (6.42−9.88)	1.12 (0.88−1.42)
26−29	12.56 (8.25−19.14)	1.44 (1.06−1.95)
30−34	NA[d]	1.44 (0.94−2.20)
35−40	NA[d]	1.58 (1.12−2.24)
Serum AFP, *ng/mL*[a]		
0−13	1	1
14−56	1.14 (1.02−1.26)	1.39 (1.25−1.55)
57−281	1.44 (1.28−1.62)	1.54 (1.36−1.74)
>282	2.10 (1.85−2.38)	2.23 (1.95−2.54)
Tumor burden		
2−3 nodules <2 cm or 1 nodule 2−3 cm	1	1
2−3 nodules 2−3 cm or 1 nodule >3−5 cm	1.19 (1.10−1.30)	1.12 (1.03−1.21)
Age	1.01 (1.01−1.02)	1.02 (1.01−1.03)
Body mass index	1.00 (0.99−1.01)	0.99 (0.98−1.00)
Underlying liver disease		
Hepatitis C virus	1	1
Hepatitis B virus	0.79 (0.63−0.98)	0.73 (0.60−0.90)
Alcoholic liver disease	1.00 (0.86−1.16)	0.81 (0.68−0.96)
Primary biliary cirrhosis	0.81 (0.52−1.26)	0.38 (0.22−0.66)
Primary sclerosing cholangitis	1.60 (0.98−2.60)	0.79 (0.41−1.53)
Cryptogenic	1.00 (0.81−1.25)	0.87 (0.69−1.09)
Nonalcoholic steatohepatitis	0.89 (0.72−1.10)	0.84 (0.66−1.07)
Autoimmune hepatitis	0.84 (0.56−1.26)	0.56 (0.33−0.95)
Hemochromatosis	1.49 (0.96−2.32)	0.78 (0.47−1.30)
Other	1.00 (0.89−1.12)	0.86 (0.72−1.04)
Sex		
Male	1	1
Female	1.02 (0.92−1.12)	1.00 (0.90−1.11)
Race or ethnicity		
White	1	1
Black and African American	1.02 (0.89−1.18)	1.34 (1.17−1.53)
Hispanic	1.23 (1.10−1.37)	0.88 (0.77−1.00)
Other (mostly Asian)	1.11 (0.95−1.30)	0.60 (0.50−0.74)
Diabetes		
No	1	1
Yes	1.05 (0.96−1.16)	1.16 (1.06−1.28)
Dialysis twice in previous week		
No	1	1
Yes	0.59 (0.41−0.86)	1.22 (0.79−1.89)

NA, not applicable.
[a]Note that the best predictors of survival benefit are factors that strongly predict waitlist survival but not post-transplantation survival or vice versa.
[b]Adjusted for listing MELD score, listing AFP, listing tumor burden, age at listing, BMI at listing, underlying liver disease, sex, race/ethnicity, diabetes, and dialysis twice in the week before listing. Sub−hazard ratios are derived from competing risks analysis, while hazard ratios are derived from Cox proportional hazards analysis.
[c]Adjusted for transplant MELD score, transplant AFP, transplant tumor burden, age at transplantation, body mass index at transplantation, underlying liver disease, sex, race/ethnicity, diabetes, dialysis twice in the week before transplantation, and donor predictors age, sex, race/ethnicity, height, cold ischemia time, cause of death, deceased cardiac donor, organ location, and presence of hepatitis B virus core antibody or hepatitis C virus antibody.
[d]According to our models shown in Figure 1, when patients on the waitlist with HCC reached a MELD score ≥30 they fulfilled the outcome of "death of liver failure" and were assigned a survival time of 3.2 months (for MELD scores 30−34) or 1.8 months (for MELD scores 35−40). Therefore, patients with a MELD score ≥30 are not included in this table.

Table 4. Predictors of Waiting List Survival and Post-Transplant Survival in Patients Without HCC

Predictors	Waiting list survival, adjusted sub−hazard ratio[a]	Post-transplant survival, adjusted hazard ratio[b]
MELD score		
6−9	1	1
10−13	1.37 (1.31−1.43)	0.85 (0.71−1.02)
14−17	1.61 (1.54−1.68)	0.82 (0.69−0.96)
18−21	1.97 (1.87−2.06)	0.95 (0.80−1.12)
22−25	2.64 (2.50−2.80)	1.04 (0.88−1.24)
26−29	5.03 (4.72−5.36)	1.15 (0.97−1.37)
30−34	NA[c]	1.24 (1.03−1.49)
35−40	NA[c]	1.32 (1.09−1.59)
Age	1.02 (1.01−1.02)	1.02 (1.02−1.02)
Body mass index	1.00 (1.00−1.00)	0.99 (0.98−0.99)
Underlying liver disease		
Hepatitis C virus	1	1
Hepatitis B virus	0.74 (0.68−0.82)	0.47 (0.38−0.57)
Alcoholic liver disease	0.78 (0.76−0.81)	0.72 (0.66−0.78)
Primary biliary cirrhosis	0.89 (0.84−0.95)	0.53 (0.45−0.61)
Primary sclerosing cholangitis	0.69 (0.64−0.73)	0.47 (0.41−0.54)
Cryptogenic	0.79 (0.75−0.83)	0.64 (0.57−0.71)
Nonalcoholic steatohepatitis	0.76 (0.72−0.80)	0.65 (0.58−0.73)
Autoimmune hepatitis	0.82 (0.76−0.89)	0.72 (0.61−0.85)
Hemochromatosis	0.76 (0.62−0.92)	0.60 (0.43−0.85)
Other	0.91 (0.87−0.95)	0.69 (0.61−0.78)
Sex		
Male	1	1
Female	0.90 (0.87−0.92)	0.95 (0.89−1.01)
Race or ethnicity		
White	1	1
Black and African American	1.00 (0.95−1.05)	1.27 (1.16−1.40)
Hispanic	1.24 (1.20−1.28)	0.88 (0.80−0.96)
Other (mostly Asian)	1.06 (0.98−1.13)	0.91 (0.76−1.07)
Diabetes		
No	1	1
Yes	1.15 (1.11−1.18)	1.27 (1.19−1.35)
Dialysis twice in previous week		
No	1	1
Yes	0.74 (0.68−0.80)	1.39 (1.23−1.57)

[a]Adjusted for listing MELD score, age at listing, body mass index at listing, underlying liver disease, sex, race/ethnicity, diabetes, and dialysis twice in the week before listing. Sub−hazard ratios are derived from competing risks analysis, while hazard ratios are derived from Cox proportional hazards analysis.
[b]Adjusted for transplant MELD score, age at transplant, body mass index at transplant, underlying liver disease, sex, race/ethnicity, diabetes, dialysis twice in the week before transplantation, and donor predictors age, sex, race/ethnicity, height, cold ischemia time, cause of death, deceased cardiac donor, organ location, and presence of hepatitis B virus core antibody or hepatitis C virus antibody.
[c]According to our models shown in Figure 1, when patients on the waitlist without HCC reached a MELD score ≥30 they fulfilled the outcome of "death of liver failure" and were assigned a survival time of 3.3 months (for MELD scores 30−34) or 1.8 months (for MELD scores 35−40). Hence patients with a MELD score ≥30 are not included in this table.

hazard regression. The HCC and non-HCC populations were analyzed separately. Patients were censored if they were still alive without having undergone transplantation by September 30, 2013. Survival time was defined as days from registration (INIT_DATE) until death before transplantation, liver failure, transplantation, or last day of follow-up, whichever was earliest. Linkage to Social Security Death Master File allowed identification of deaths that occurred after drop out from the waiting list and, therefore, drop out was not analyzed as a competing risk. The competing risks models of waiting list survival employed the same patient predictors listed here for post-transplantation survival, except that each predictor had the value ascertained at the time of listing rather than at the time of transplantation (including calculated MELD score at listing based on values of international normalized ratio, bilirubin, and creatinine).

Transplantation not only masks the event of interest (death), a problem that can be accounted for by performing a competing risks analysis, but also causes a bias in patients with larger MELD scores due to their greater likelihood of being transplanted. Even models that treat transplantation as a competing risk to death do not provide a

satisfactory solution, as they overestimate survival for patients with high MELD scores.[4,5] Vitale et al[4] described that their competing risks model still required the use of post-hoc calibration of hazard ratios to compensate for the unrealistically high life expectancy of those with MELD score >30.[4] Schaubel et al[5] used an inverse probability of censoring weight applied to a Cox proportional hazards model to address the bias caused by increased rates of transplantation in higher MELD scores. Their results also suggest an overestimation of survival time when compared with published findings regarding the high mortality of patients with high MELD scores.[11] To deal with this problem in our competing risks models, we used a novel combined outcome of death or liver failure, which we defined as MELD score ≥30 (Figure 1). We reasoned that because survival time after a MELD ≥30 is very short, an arbitrary short additional survival time can be substituted for those with MELD scores ≥30. UNOS waiting list history data, which capture MELD scores after listing, were used to determine when a patient reached a MELD score ≥30.

Life Expectancy Estimations

Post-Transplantation Life Expectancy. A standard Cox proportional hazard model was run separately for those with and without HCC using Stata SE-13 software (StataCorp, College Station, TX). A baseline cumulative hazard of death function was extracted by month using the *stcurve* command. Covariates were held at their mean waiting list population values. Hazard ratios for covariates were also extracted. These hazard ratios were then applied to the baseline hazard function to get 5-year life expectancies by covariate group, as shown here. A time horizon of 5 years was chosen to allow comparison with other studies[4,5] and because most events were captured within this time period.

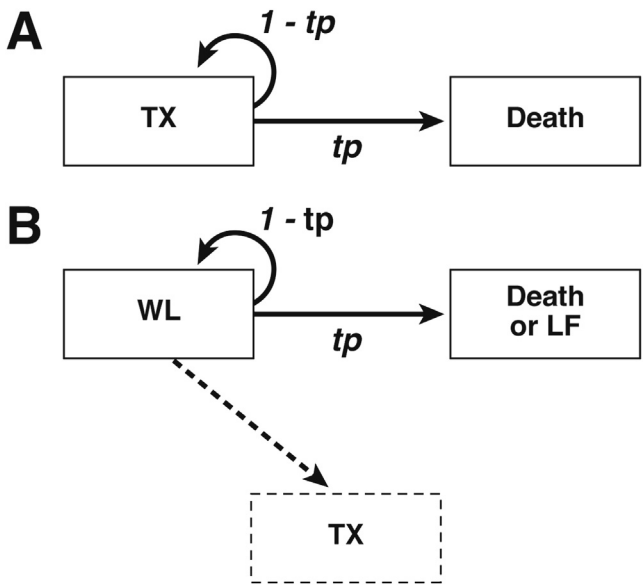

Figure 1. (*A*) Post-transplantation model, showing the monthly transition probability (*tp*) to death from the time of transplantation (TX). (*B*) Waitlist model, showing the monthly transition probability (*tp*) to death or liver failure (LF; defined here as a MELD score ≥30) from the time of being listed on the waiting list (WL), accounting for the competing risk of TX.

We defined:

$$\begin{aligned} H_0(t) &= \text{baseline cumulative (sub}-\text{)hazard at time } t \\ &\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad (\text{in months}) \\ h_0(t) &= \text{baseline instantaneous (sub}-\text{)hazard at time } t \\ &= H_0(t) - H_0(t-1) \\ H_\beta(t) &= \text{cumulative (sub}-\text{)hazard at time } t \\ &\quad \text{for predictor with (sub}-\text{)hazard ratio of } \beta \\ &\quad \text{compared to baseline} \\ &= \exp(\beta) H_0(t). \end{aligned}$$

Thus

$$\begin{aligned} h_\beta(t) &= H_\beta(t) - H_\beta(t-1) \\ &= \exp(\beta) * [H_0(t) - H_0(t-1)] \\ &= \exp(\beta) * h_0(t). \end{aligned}$$

Survival probability is calculated as follows[12]:

$$\begin{aligned} S_\beta(t) &= \text{survival probability at time } t \\ &= \exp(-H_\beta(t)) \\ &= \exp(-\exp(\beta) * H_0(t)). \end{aligned} \tag{1}$$

Each month a patient has a probability of transitioning to death and no longer accruing months alive (see Figure 1). The definition of this transition probability is[13]:

$$\begin{aligned} s_\beta(t) &= \text{instantaneous probability of surviving month } t \\ &= \frac{S_\beta(t)}{S_\beta(t-1)} \\ tp_\beta(t) &= \text{transition to death or LF probability in month } t \\ &= 1 - s_\beta(t) \\ &= 1 - \frac{S_\beta(t)}{S_\beta(t-1)} \\ &= 1 - \frac{\exp(-H_\beta(t))}{\exp(-H_\beta(t-1))} \\ &= 1 - \exp(-[H_\beta(t) - H_\beta(t-1)]) \\ &= 1 - \exp(-h_\beta(t)) \\ &= 1 - \exp(-\exp(\beta) h_0(t)). \end{aligned}$$

The monthly transition probability was used to calculate the sum of months alive over 60 months (5 years), which is the

definition of 5-year life expectancy. In sensitivity analyses we also calculated 1-year and 3-year life expectancies.

Waitlist Life Expectancy. Similarly to post-transplantation life expectancy estimation, both a baseline sub−hazard function and hazard ratio estimates are needed for estimation of life expectancy in the waiting list population. In this case, 2 steps were required to calculate the required estimates. The first step used the population of patients with a MELD score <30 to estimate a sub−hazard function and sub-hazard ratios. The second step was to use patients with a MELD score ≥30 to estimate just the hazard ratios associated with MELD score. The patient population was separated because those patients with a MELD score ≥30 were defined as having already reached the outcome of liver failure. These steps are elaborated here.

Estimation for Model for End-Stage Liver Disease Score <30. The competing risks model was run using the R package cmprsk.[10,14] The baseline subhazard of death or liver failure function was extracted by month from the results using the Breslow jumps.[10] Sub−hazard ratios, baseline sub−hazard functions, 5-year survival probability, and life expectancy were calculated as described here, with the difference that death or liver failure (defined as MELD score ≥30) were considered as a combined outcome and the competing risk of transplantation was accounted for by the competing risks analysis. For those with an outcome of liver failure, an additional 4 months were added to the survival time to account for the time between liver failure and death. Four months was chosen based on clinical experience and existing research.[11] Sensitivity analyses showed that varying the added survival time resulted in small changes in the magnitudes, but no changes in inference. The same value of added survival time was applied to both those with and without HCC to prevent a presupposed bias.

Sub−Hazard Ratio Estimation for Model for End-Stage Liver Disease Score ≥30. The high rates of transplantation and poor prognosis for those whose MELD score at listing was beyond our definition of liver failure required the application of additional estimation techniques. To this end, we chose as a reference an analysis performed by Kim et al,[11] which looked at 90-day mortality on the Organ Procurement and Transplantation Network liver transplant waiting list for the years 2005−2006. Kim et al found a survival probability of 34%−35% for those without HCC whose listing MELD was 32−40. Using Stata 13 software to generate Kaplan-Meier estimates of survival at 90 days, we found survival probabilities of 50% and 21% for those with a listing MELD of 30−34 and 35−40, respectively, in the population without HCC. Because Kim et al excluded patients with HCC, we were unable to compare our 90-day survival estimates in the HCC population of 42% and 14% for those with listing MELD scores of 30−34 and 35−40, respectively. We assumed that the mean values of covariate predictors like age, body mass index, tumor burden, etc, were the same in the MELD <30 and MELD ≥30 populations in order to use the baseline sub−hazard $H_0(t)$.

Now from equation (1) above:

$$S(\text{90-days}) = \exp(-\exp(\beta) * H_0(\text{90-days})).$$

So a sub−hazard ratio for each group can then be estimated using the Kaplan-Meier estimates of 90-day survival and the cumulative baseline sub-hazard $H_0(t)$ for those with a MELD <30 via

$$\beta = ln\left(\frac{-\ln(S(\text{90-days}))}{H_0(\text{90-days})}\right)$$

These β estimates resulted in a 5-year life expectancy of 3.2 and 1.8 months in the HCC population for those with MELD scores of 30−34 and 35−40, respectively, at the time of listing. For those without HCC, the 5-year life expectancy was 3.3 and 1.8 months for MELD scores of 30−34 and 35−40, respectively.

Transplant-Related Survival Benefit. The survival benefit at 5 years is calculated as the difference between post-transplantation and waitlist life expectancy at 5 years. In sensitivity analyses, we also calculated 1-year and 3-year survival benefits.

Results

Baseline Characteristics of the Transplanted Population at the Time of Transplantation

Compared with transplant recipients without HCC (n = 25,890), those with HCC (n = 9135) had a much lower actual MELD score, were older, more likely to be diabetic, male, and hepatitis C virus−positive, and less likely to be white (Table 1). All donor characteristics were very similar between transplant recipients with and without HCC.

Transplant recipients with HCC had a mean serum AFP level of 183 ± 1157 ng/mL and 9% had a serum AFP level >282 ng/mL. Greater tumor burden (2−3 nodules 2−3 cm or 1 nodule >3−5 cm) was present in 46.3%. Mean follow-up time was similar in those with HCC (40.0 ± 31.6 months) and those without (45.9 ± 36.5 months).

Baseline Characteristics of the Waiting List Population at the Time of Listing

Compared with patients without HCC (n = 85,229), those with HCC (n = 15,605) had a much lower actual MELD score, were older, more likely to be diabetic, male, and and hepatitis C virus−positive, and less likely to be white (Table 2). Among those with HCC, mean serum AFP was 212.0 ± 1234 ng/mL, 9.8% had a serum AFP level >282 ng/mL, and 46% had greater tumor burden (2−3 nodules 2−3 cm or 1 nodule >3−5 cm). Mean follow-up time was shorter in those with HCC (n = 7.5 ± 9.8 months) than those without (n = 18.1 ± 24.0 months).

Survival Models in Patients With Hepatocellular Carcinoma

The predictors of post-transplantation and waiting list survival for patients with HCC are shown side by side in Table 3, in order to demonstrate those characteristics that are especially strong predictors of one but not the other. Such characteristics would be expected to influence survival benefit greatly. The strongest predictor of waiting list survival was MELD score, followed by serum AFP level. Age, dialysis, tumor burden, and underlying liver disease also predicted waiting list survival. All these characteristics also

predicted post-transplantation survival to an extent similar to what they predicted for waiting list survival, with the exception of MELD score, which was a weak predictor of post-transplantation survival, but an extremely strong predictor of waitlist survival.

Survival Models in Patients Without Hepatocellular Carcinoma

Age, dialysis, diabetes, sex, and underlying liver disease predicted both waiting list and post-transplantation survival in patients without HCC (Table 4). MELD score was again the strongest and overwhelming predictor of waiting list survival, while having little association with post-transplantation survival.

5-Year Life Expectancy by Model for End-Stage Liver Disease Score

Mean 5-year, post-transplantation life expectancy decreased slowly with increasing MELD score for both patients with and without HCC and was lower for patients with HCC than those without HCC at the same MELD score (Figure 2*A*). In contrast, mean 5-year waitlist life expectancy decreased very dramatically with increasing MELD score for both patients with and without HCC. Mean 5-year waitlist life expectancy was similar in patients with and without HCC who had the same MELD score, but appeared slightly greater in patients without HCC for MELD scores >17 and slightly greater in patients with HCC for MELD scores <17.

Transplant-Related Survival Benefit by Model for End-Stage Liver Disease Score

The survival benefit at 5 years increased dramatically with MELD score for both patients with and without HCC from just a few months in patients with low MELD scores (ie, 6−9) to 4 years in patients with the highest MELD scores (ie, 35−40) (Figure 2*B*). The survival benefit of patients with HCC at any given MELD score was not substantially higher than the survival benefit of patients without HCC who had the same MELD score, irrespective of the tumor burden or serum AFP level of patients with HCC. When we looked at survival benefit at 1 or 3 years instead of 5 years as part of sensitivity analyses, identical conclusions were reached that survival benefit increased with

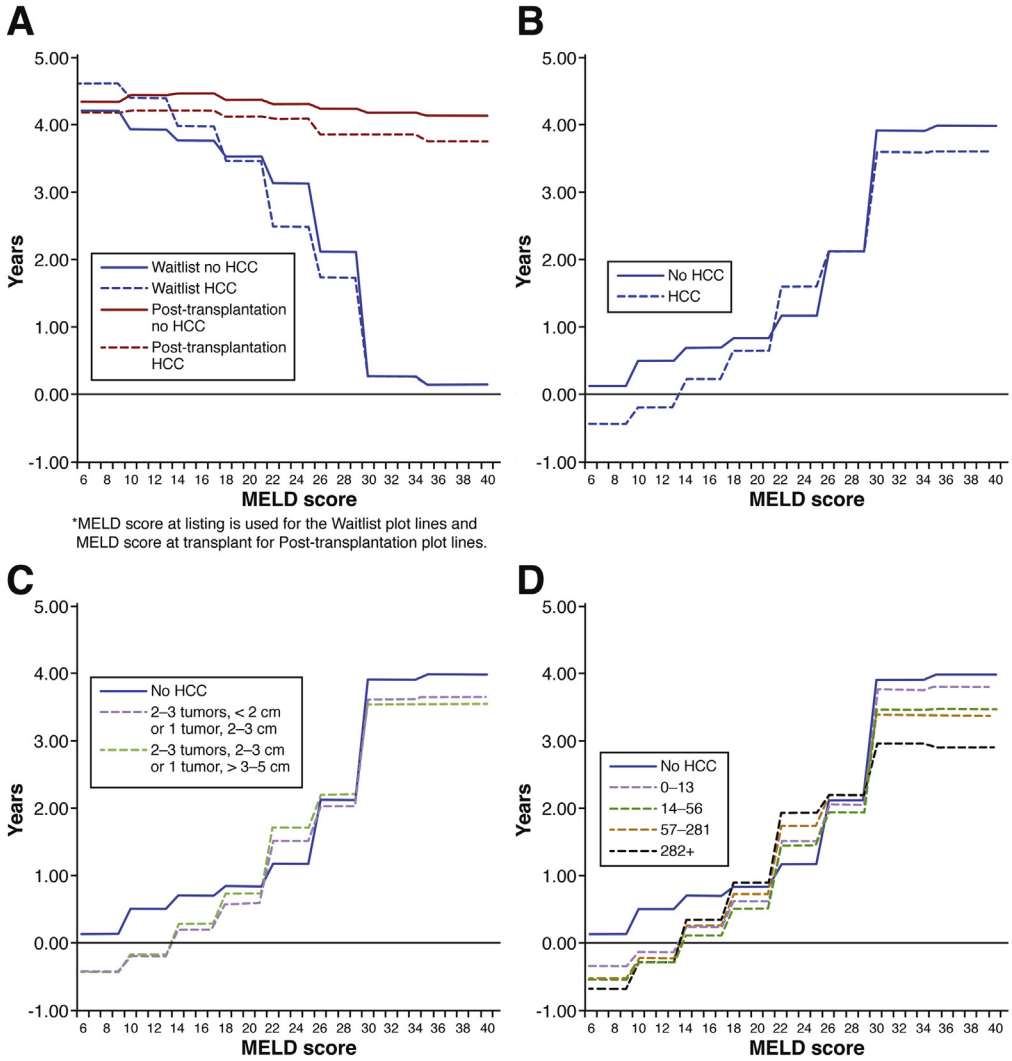

Figure 2. Five-year life expectancy and transplant-related survival benefit as a function of MELD score shown separately in patients with or without HCC. (*A*) Five-year waitlist and post-transplantation life expectancy by MELD score. (*B*) Transplant-related survival benefit in years plotted against MELD score. (*C*) Transplant-related survival benefit in years plotted against MELD score. Patients with HCC are divided according to tumor burden. (*D*) Transplant-related survival benefit in years plotted against MELD score. Patients with HCC are divided according to serum AFP level.

MELD score and that it was similar for patients with or without HCC who had the same MELD score (Supplementary Figure 5).

In patients with HCC, tumor burden (Figure 2*C*) or serum AFP level (Figure 2*D*) had little effect on survival benefit. This might be expected because increasing tumor burden or increasing serum AFP had effects of a similar magnitude in reducing both waitlist and post-transplantation survival, as shown by their associations in Tables 3 and 4. This is also shown by the plots of 5-year waitlist and post-transplantation survival against MELD score plotted separately for different categories of tumor burden or serum AFP level in Supplementary Figures 1–4.

Using the mean, 5-year survival benefit shown in Figure 2*B* for each MELD category, we calculated the total survival benefit experienced by all patients in each MELD category and all HCC and non-HCC transplant recipients combined (Table 5). Because patients with HCC were transplanted at a much lower mean MELD score (13.3 ± 6.2) than patients without HCC (21.8 ± 8.0) and most of them were concentrated in low-MELD categories with low survival benefit, a dramatically lower mean 5-year survival benefit was achieved by transplanting patients with HCC (0.12 years/patient or 1125 years in 9135 patients) than patients without HCC (1.47 years/patient or 38,072 years in 25,890 patients). Therefore, if 9135 patients without HCC had been transplanted instead of the patients with HCC, one would expect a survival benefit of 13,428 years (9135 × 1.47), which is 12,303 years greater than the survival benefit experienced by the patients with HCC.

Trends Over Time in Transplant-Related Survival Benefit

There were no substantial trends in transplant-related survival benefit of patients with or without HCC when comparing time periods 2002–2004, 2005–2007, and 2008–2010 and looking at 5-year survival benefit as well as 3-year survival benefit to ensure that all patients in the most recent time period had sufficient follow-up (Supplementary Figures 6 and 7).

Discussion

Using national transplantation data from UNOS, we found little difference in transplant-related survival benefit between patients with T2 HCC and patients without HCC who have the same actual MELD score. This argues against strategies that assign an artificially higher MELD score to patients with HCC, such as the current strategy in the United States. Because transplant-related survival benefit increased dramatically with MELD score at transplantation, our findings also demonstrate that a substantially lower mean 5-year survival benefit was achieved in the United States between 2002 and 2013 by transplanting patients with HCC (0.12 years/patient), who have a low actual MELD score at transplantation, than patients without HCC (1.47 years/patient), who have a high actual MELD score at transplantation. Therefore, the HCC MELD exception policy unintentionally resulted in a dramatic reduction in transplant-related survival benefit leading to thousands of years of cumulative "lost" survival benefit as compared with transplanting patients with high MELD scores.

The incidence of HCC has been increasing rapidly in the United States during the last 10–15 years, and is expected to continue to increase. Coupled with the introduction in 2002 of the MELD allocation, which assigns an artificially high MELD score to patients with T2 HCC who receive an HCC MELD exception, this has led to a very rapid increase in the proportion of liver transplant recipients who have HCC.[15] This, in turn, stimulated efforts to re-evaluate whether the current policies of eligibility and prioritization of patients with HCC are appropriate, whether they lead to the best possible outcomes for all patients and whether they unfairly disadvantage patients without HCC.[1]

Such efforts are hampered by lack of a universally accepted principle that should govern eligibility and prioritization for liver transplantation. One such recently advocated principle is that of maximizing the transplant-related survival benefit.[3–6] The survival benefit is defined as the life expectancy with transplantation minus the life expectancy without transplantation. Therefore, survival benefit combines the principle of urgency (or "sickest first"), which is quantified by a very low life expectancy without transplantation, and the

Table 5. Estimated Transplant-Related Survival Benefit at 5 Years Experienced by Patients Who Underwent Transplantation With or Without HCC, 2002–2013

	HCC			No HCC		
MELD score	n	Survival benefit per patient, *y*	Total survival benefit, *y*	n	Survival benefit per patient, *y*	Total survival benefit, *y*
6–9	2684	−0.43	−1155	772	0.13	103
10–13	2928	−0.18	−528	2338	0.51	1193
14–17	1944	0.24	464	5332	0.70	3752
18–21	833	0.65	545	5627	0.84	4739
22–25	322	1.61	517	4643	1.18	5467
26–29	167	2.12	354	3038	2.13	6457
30–34	100	3.60	360	2114	3.92	8277
35–40	157	3.61	567	2026	3.99	8084
All patients	9135	0.12	1125	25,890	1.47	38,072

principle of utility, which is quantified by a high post-transplantation survival rate. The current MELD-based allocation system was based on prioritizing urgency because the MELD score is an excellent predictor of short-term mortality in patients with cirrhosis. Although it was not designed specifically for that purpose, MELD-based prioritization also goes a long way toward maximizing survival benefit in patients without HCC. This is because the MELD score is by far the strongest predictor of mortality without transplantation, while having relatively little effect on post-transplantation survival. Therefore, a patient with a very high MELD score will have extremely low life expectancy without transplantation, but still relatively preserved post-transplantation life expectancy, leading to a high survival benefit.

It is unclear, however, if the current MELD-based prioritization system, which assigns an "artificial" high MELD score to patients with T2 HCC, maximizes the transplant-related survival benefit of patients with HCC. It is also unclear whether patients with HCC who have an artificially assigned MELD score of 22 points (with a 3-point increase every 3 months) have the same survival benefit as patients without HCC who have the same actual MELD score. Recent European studies suggested that patients with HCC had a higher survival benefit than patients without HCC who had the same actual MELD score.[4] In addition, they proposed a new method of calculating an artificially high MELD score for patients with T2 HCC, that was a function of their actual MELD score and serum AFP level (HCC-MELD = 1.27 * MELD − 0.51 * logAFP + 4.59), such that their survival benefit would be approximately equal to that of patients without HCC who have the same actual MELD score.[4]

In contrast, we found that there was little difference in transplant-related survival benefit between patients with stage II HCC and patients without HCC who have the same MELD score (Figure 2*B*). This is not as counterintuitive as it might initially appear. Patients with T2 HCC can achieve very good control of their tumor by locoregional therapies that have advanced greatly in the last 10 years, such that their survival without transplantation is driven primarily by their MELD score rather than their HCC and is only slightly lower than the survival of patients without HCC who have the same MELD score, as shown in Figure 2*A*. At the same time, patients with T2 HCC have a slightly lower post-transplantation survival than patients without HCC, as shown in Figure 2*A*, as well as in multiple previous studies,[9,16] probably due to tumor recurrence in a small proportion of transplant recipients with HCC. The fact that patients with HCC have a slightly lower survival without transplantation and also slightly lower post-transplantation survival than patients without HCC who have the same MELD score results in a very similar survival benefit. This argues against assigning an artificially high MELD score to patients with HCC if the aim is to maximize survival benefit or to equalize the survival benefit achieved by HCC and non-HCC patients.

The most striking finding is the dramatic increase in transplant-related survival benefit that occurs with increasing actual MELD score in both patients with and without HCC (Figure 2*B*). This argues that any system that artificially raises the MELD score of patients has to be considered with great caution, as it will likely result in a decrease in survival benefit. The 5-year, transplant-related survival benefit according to MELD score was previously also estimated by Schaubel et al[5] using UNOS data from 2001−2007. Reassuringly, results similar to those presented here in Figure 2*B* were reported.

Although the concept of transplant-related survival benefit is relatively new in liver transplantation, it forms the basis of the Lung Allocation Score, which has been used since 2005.[17] The new kidney allocation system introduced in 2013 also aims to increase the survival benefit achieved by kidney transplantation.[18] We anticipate that maximizing survival benefit will also be used in the future to determine eligibility and prioritization for liver transplantation of patients with HCC.

Some important differences in the methods we used to address transplantation bias in waitlist life expectancy estimation likely explain the differences in the results between our study and the one by Vitale et al.[4] We used a model with a joint outcome of liver failure and death, which more closely mimics the biological progression of liver disease that has a very poor prognosis after liver failure. Vitale et al used a model with only death as an end point, and found that the model was unable to overcome the selection bias due to high transplantation rates in patients with MELD scores >30. To address the overestimation in life expectancy (>1 year) of those with a MELD >30, Vitale et al performed a post-hoc "calibration" of the hazard ratios associated with larger MELD scores. This resulted in unrealistically high 5-year waitlist survival rates predicted by their models in patients without HCC (eg, 5-year survival of approximately 30% in patients with a MELD score of 35 shown in Figure 2 of Vitale et al), which then led to low survival benefit in patients without HCC compared with patients with HCC. Another difference is that Vitale et al used data from the North Italy Transplant program, and our data from UNOS are representative of the US transplantation experience.

Recent papers have also raised concerns about the impact of the HCC MELD exception policy. Multiple studies demonstrated that patients on the waiting list with an HCC MELD exception have lower drop-out rates, lower waiting list mortality, higher transplantation rates, and shorter waiting times than patients without HCC.[2,15,19−21] Northup et al[15] recently suggested that the HCC MELD exception system is largely responsible for the steady increase in MELD scores at transplantation that occurred during the last 10 years across all regions.[15] In a counterintuitive study, Halazun et al[22] showed that patients with HCC MELD exception listed for liver transplantation in regions with long waiting times actually had better overall pre- and post-transplantation survival than patients with HCC MELD exception listed in regions with short waiting times, suggesting that expediting transplantation of patients with HCC can adversely affect patient outcomes.[22] Our study is the first, to our knowledge, to demonstrate that patients transplanted with HCC MELD exceptions derive significantly

reduced survival benefit from transplantation compared with patients transplanted without HCC. Combined with the aforementioned studies, our findings strongly argue against the current HCC MELD exception policy, and suggest that any system that artificially raises the MELD score of patients with HCC is likely to lead to a reduction in transplantation-related survival benefit.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2015.05.025.

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Reprint requests
Address requests for reprints to: George Ioannou, BMBCh, MS, Division of Gastroenterology, Department of Medicine, Veterans Affairs Puget Sound Health Care System, S-111-Gastro, 1660 S. Columbian Way, Seattle, Washington 98108. e-mail: georgei@medicine.washington.edu; fax: 206-764-2232.

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