Liver Transplantation Criteria For Hepatocellular Carcinoma Should Be Expanded

A 22-Year Experience With 467 Patients at UCLA

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Objective: To assess the efficacy of orthotopic liver transplantation (OLT) for hepatocellular carcinoma (HCC) and the impact of current staging criteria on long term survival.

Summary Background Data: HCC is becoming an increasingly common indication for OLT. Medicare approves OLT only for HCCs meeting the Milan criteria, thus limiting OLT for an expanding pool of potential liver recipients. We analyzed our experience with OLT for HCC to determine if expansion of criteria for OLT for HCC is warranted.

Methods: All patients undergoing OLT for HCC from 1984 to 2006 were evaluated. Outcomes were compared for patients who met Milan criteria (single tumor ≤5 cm, maximum of 3 total tumors with none >3 cm), University of California, San Francisco (UCSF) criteria (single tumor <6.5 cm, maximum of 3 total tumors with none >4.5 cm, and cumulative tumor size <8 cm), or exceeded UCSF criteria.

Results: A total of 467 transplants were performed for HCC. At mean follow up of 6.6 ± 0.9 years, recurrence rate was 21.2%, and overall 1, 3, and 5-year survival was 82%, 65%, and 52%, respectively. Patients meeting Milan criteria had similar 5-year post-transplant survival to patients meeting UCSF criteria by preoperative imaging (79% vs. 64%; $P = 0.061$) and explant pathology (86% vs. 71%; $P = 0.057$). Survival for patients with tumors beyond UCSF criteria was significantly lower and was below 50% at 5 years. Multivariate analysis showed that tumor number ($P < 0.001$), lymphovascular invasion ($P < 0.001$), and poor differentiation ($P = 0.002$) independently predicted poor survival.

Conclusions: This largest single institution experience with OLT for HCC demonstrates prolonged survival after liver transplantation for tumors beyond Milan criteria but within UCSF criteria, both when classified by preoperative imaging and by explant pathology. Measured expansion of OLT criteria is justified for tumors not exceeding the UCSF criteria.

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The incidence of hepatocellular carcinoma (HCC) in the United States has nearly doubled over the last 2 decades, and an estimated 8500 to 11,000 new cases of HCC occur annually in the United States.[1,2] This increase has been attributed to infections with hepatitis C virus (HCV) from the 1970s and 1980s, and HCV-associated HCC is expected to further double within the next 20 years.[3,4] Outcomes for patients with HCC have been historically poor, regardless of treatment, with overall 5-year survival rates of 20% to 40%. For patients with HCC and end-stage cirrhosis, survival without liver transplantation is often less than 1 year.

Over the past quarter century, orthotopic liver transplantation (OLT) has been established as a durable therapy for all forms of end-stage liver disease.[5,6] OLT appears ideally suited for HCC, as it provides complete oncologic resection and correction of the underlying liver dysfunction. Early experience with OLT for HCC resulted in poor post-transplant survival and high recurrence rates that were attributed to suboptimal patient selection.[7–10] In 1996, Mazzaferro and colleagues reported improved results with OLT in patients with a single tumor ≤5 cm or no more than 3 tumors, each no larger than 3 cm.[11] For patients meeting these so-called Milan criteria, overall and recurrence-free survivals were 85% and 92%, respectively, and overall recurrence rate was 8% at 4 years' follow-up.[11] As the Milan criteria consistently have been associated with improved survival,[11,12] they are currently used by the United Network for Organ Sharing (UNOS) and Medicare to guide patient selection for cadaveric OLT for HCC.

More recent studies have proposed expanded criteria to offer OLT to a broader group of patients with HCC.[13–16]

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Using explant pathologic data, Yao and coworkers at the University of California, San Francisco (UCSF) reported 5-year post-transplantation survival of 75% in patients with tumors as large as 6.5 cm and cumulative tumor burden ≤8 cm.[13] These results have been challenged because of a small sample size and use of explant pathology, rather than preoperative imaging, as the determinant for tumor stage. As a result, the role of OLT for tumors beyond the conventional Milan criteria remains controversial.

Currently, preoperative imaging criteria based on size and number of tumors are used to select candidates for OLT. The Model for End Stage Liver Disease (MELD) scoring system introduced in 2002 now offers priority for patients with HCC within conventional Milan criteria.[17] The present study was undertaken to examine outcomes for a large series of patients who received OLT for HCC in a single institution. The goal was to determine whether expansion of Milan criteria, based on preoperative imaging and explant pathology, could be justified by post-transplant survival of at least 50% at 5 years, as proposed by Llovet.[18–20]

METHODS

Using a prospectively collected transplant database, we performed a review of all patients who underwent OLT for HCC at UCLA Medical Center from 1984 to 2006. Disease extent was determined by preoperative computed tomography (CT) or magnetic resonance (MR) images. Pretransplant adjuvant treatments included chemotherapy, radiofrequency ablation (RFA), transarterial chemoembolization (TACE), and liver resection in selected patients. When imaging studies were unable to differentiate between treatment defects and residual tumors for patients who had received RFA or TACE, dimensions of the radiologic defect were used for analysis. All explants were examined by experienced hepatopathologists and categorized based on tumor number, size, distribution, HCC histologic grade,[21] and lymphovascular invasion. Patients with fibrolamellar HCC or cholangiohepatocellular cancers were excluded from this analysis.

Patients with HCC were classified as having tumors either meeting Milan criteria, beyond Milan criteria but within UCSF criteria, or exceeding UCSF criteria. Patients were listed for OLT based on UNOS criteria from 1984 to 2002 and according to the MELD system after February 27, 2002.[17] In accordance with the MELD exception, patients with HCC were awarded additional points according to their predicted mortality rate over the subsequent 3 months.[22] Patients with T1 tumors <1.9 cm received 20 MELD points, and patients with T2 tumors within the Milan criteria received 24 points.

Liver transplantation was performed using standard techniques as described previously,[23] including orthotopic implantation with removal of the retrohepatic vena cava and adjacent lymph nodes in all cases. Immunosuppression included a triple drug regimen of cyclosporine (Sandimmune Novartis, Basel, Switzerland), azathioprine (Imuran, Glaxo-SmithKline, Triangle Park, NC) and prednisone from 1984 to 1994. Routine use of tacrolimus (Prograf, Astellas Pharma, Tokyo, Japan) was begun in 1995 as part of a dual or triple drug regimen with prednisone and mycophenolate mofetil (CellCept, Hoffman-LaRoche, Nutley, NJ), the latter starting in 1997.

Statistical Analysis

Primary endpoints included both patient and recurrence-free survival. Statistical analysis was performed according to the methods of Kaplan and Meier, and resultant curves were compared using the log-rank test. Multiple logistic regressions were performed to identify independent factors that affected post-transplant survival. χ^2 and Student *t* test analyses were used as appropriate using JMP statistical software (SAS corporation, Cary, NC). Significance was assigned at the 0.05 level.

RESULTS

From 1984 to 2006, 467 patients underwent OLT for HCC at UCLA Medical Center (Table 1). Average age was 57 years, and 60% were male. Most patients were Caucasian, followed by Asian and Hispanic. Underlying liver disease was present in all patients and most commonly was caused by HCV, followed by Hepatitis B virus and alcohol. Tumors were found before transplantation in 364 patients (78%) and incidentally at time of OLT in 103 (22%). In the latter patients, imaging studies performed before OLT did not reveal the presence of HCC. Using pretransplant imaging, 173 tumors (37%) were within Milan criteria, 185 (40%) were beyond Milan but within UCSF criteria, and 109 (23%) exceeded UCSF criteria. Imaging modalities included CT in 297 patients (64%) and MR in 182 patients (39%).

Preoperative treatments were used in 229 patients (49%) and included locoregional ablative therapy with TACE in 122 patients (26%) and RFA in 60 (13%), systemic

TABLE 1. Characteristics of Patients

n	467
Age (yr)	56.6 ± 3.9
Range	19–78
Sex	
Male, n (%)	281 (60)
Female, n (%)	186 (40)
Race	
Caucasian, n (%)	290 (62)
Asian, n (%)	65 (14)
Hispanic, n (%)	61 (13)
African American, n (%)	28 (6)
Other, n (%)	23 (5)
Etiology of liver disease	
Hepatitis C, n (%)	257 (55)
Hepatitis B, n (%)	79 (17)
Alcoholic, n (%)	62 (13)
Cryptogenic, n (%)	37 (8)
Autoimmune, n (%)	23 (5)
Other, n (%)	9 (2)
Diagnosis of HCC	
By preoperative imaging, n (%)	364 (78)
Incidental at time of OLT, n (%)	103 (22)

TABLE 2. Assignment of Tumors to Criteria Groups

	Milan	UCSF	Beyond UCSF
Preoperative imaging	173	185	109
Explant pathology	126	208	133

chemotherapy in 63 (14%), and combined modalities in 38 (8%). Liver resections were performed in 25 patients (5.4%) and included wedge resections in 12 patients, segmental resections in 8, right lobectomies in 3, and left lobectomies in 2.

The 467 patients received 487 liver transplants. Graft types included cadaveric whole organs in 482 patients (99%), cadaveric split liver grafts in 4, and a living-related graft in 1. Combined liver-kidney transplants were performed in 3 patients. Retransplantation was necessary in 20 patients (4.2%). Post-transplantation 30-day mortality was 5.3%. Adjuvant chemotherapy was given in 89 patients (19%). Mean follow up was 6.6 ± 0.9 years.

Criteria Groups and Tumor Characteristics

Assignments of tumors to criteria groups based upon preoperative imaging studies and explant pathology are compared in Table 2. Of 173 tumors classified within the Milan criteria by imaging, 47 (27%) were reassigned to other groups following pathologic examination.

Tumor characteristics are shown in Table 3. The majority of tumors (51%) were multiple, particularly when within or beyond UCSF criteria. Tumors were well or moderately differentiated in 325 patients (68%). Lymphovascular invasion was present in 136 tumors (29%). There were no statistically significant differences in histologic grade or the presence of lymphovascular invasion among patients within Milan, within UCSF, or beyond UCSF criteria. Tumor size ranged from microscopic foci to 21 cm, with a mean tumor size of 4.7 cm. Tumors occurred in the right lobe in 246 (53%), in the left lobe in 101 (21%), and both lobes in 120 patients (26%).

Outcome

Survival data after transplantation are shown in Table 4. Overall survival for the entire group at 1, 3, and 5 years after transplantation was 82%, 65%, and 52% respectively (Fig. 1). Survival exceeded 50% at 5 years for all patients in the series and for all patients with disease within Milan and UCSF criteria, whether determined by pretransplant imaging or pathologic examination. Survival for tumors beyond UCSF criteria was below 50% at 3 and 5 years. Survival curves by pretransplant imaging (Fig. 2) and pathologic (Fig. 3) staging were similar for tumors within Milan and UCSF criteria, whereas patients with tumors beyond UCSF criteria had significantly worse survival.

Tumor recurrence rate was 21.2% at mean follow up of 6.6 ± 0.9 years. Recurrence-free survival results (Figs. 4 and 5) again were similar for tumors within Milan or UCSF criteria by pretransplant imaging assessment and by explant pathology and were significantly better than for tumors beyond UCSF criteria. At 5 years after OLT, recurrence-free survival was 74% for the Milan group and 65% for the UCSF group ($P = 0.09$).

Patients who underwent OLT after institution of MELD priority scoring for HCC (n = 118) had improved survival when compared with the 349 patients transplanted before the scoring exception (Fig. 6). Three-year survival for the former group was 74%, compared with 47% for the latter ($P = 0.001$).

Univariate analysis (Table 5) showed that multifocal tumors, lymphovascular invasion, poor differentiation, male sex, age greater than 60 years, and preoperative care without locoregional therapy were significantly associated with reduced survival after OLT for HCC. On multivariate analysis (Table 6), only tumor number ($P < 0.001$), lymphovascular invasion ($P < 0.001$), and poor differentiation ($P = 0.002$) independently predicted reduced survival; age, gender, and preoperative locoregional therapy did not independently influence post-transplant survival.

Preoperative systemic chemotherapy was administered in 63 (14%) patients, and adjuvant chemotherapy was given

TABLE 3. Explant Pathology

	All Patients (n = 467)	Milan (n = 126)	UCSF (n = 208)	Beyond UCSF (n = 133)	*P*
Number of tumors					
Single	215	81	111	23	—
Multiple	240	33	97	110	—
Single	215	81	111	23	—
2–3	128	33	70	25	—
>3	112	—	27	85	—
No gross mass	12	7	5	—	—
Grade					
Well-differentiated	144 (31%)	44 (35%)	62 (30%)	38 (29%)	NS
Moderately differentiated	248 (53%)	68 (54%)	114 (55%)	66 (50%)	NS
Poorly differentiated	75 (16%)	14 (11%)	32 (15%)	29 (21%)	NS
Lymphovascular invasion	136 (29%)	22 (18%)	66 (32%)	48 (36%)	NS

TABLE 4. Patient Survival

	Survival (%)		
	1 Yr	3 Yr	5 Yr
All patients	82	65	52
Milan			
Preoperative imaging	91	85	79
Pathology	96	89	86
UCSF			
Preoperative imaging	88	74	64
Pathology	92	83	81
Beyond UCSF			
Preoperative imaging	71	49	41
Pathology	80	48	32

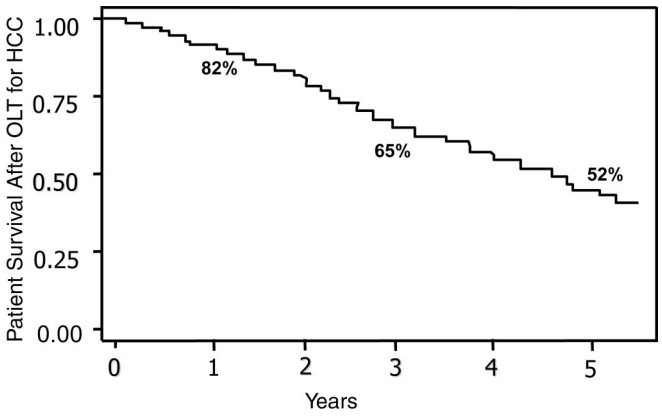

FIGURE 1. Overall survival estimate for 467 patients who received liver transplantation for hepatocellular carcinoma.

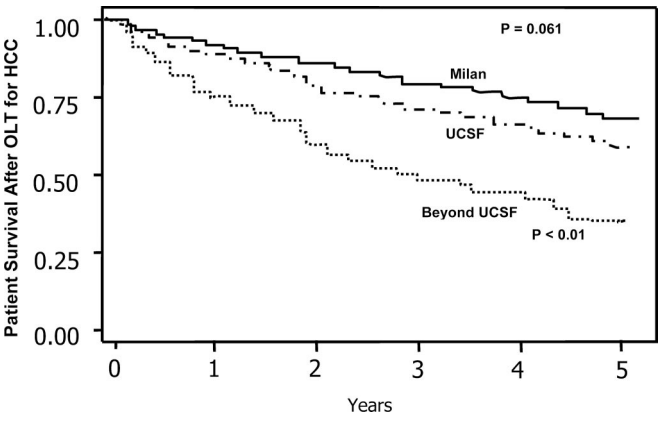

FIGURE 2. Survival estimate by preoperative imaging assessment.

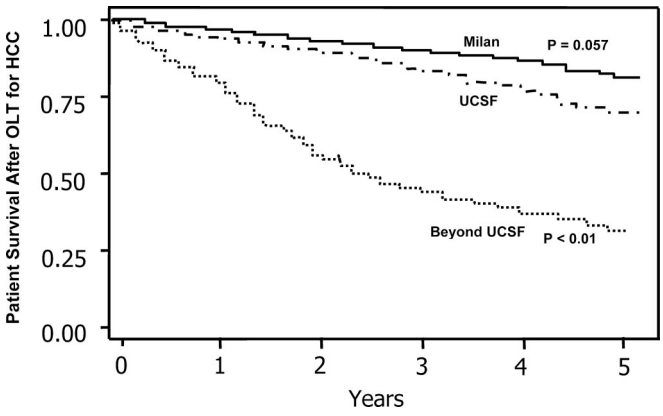

FIGURE 3. Survival estimate by pathologic explant examination.

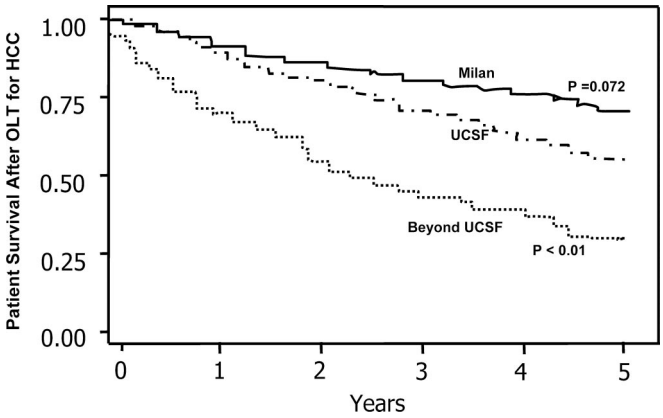

FIGURE 4. Recurrence-free survival estimate by preoperative imaging assessment.

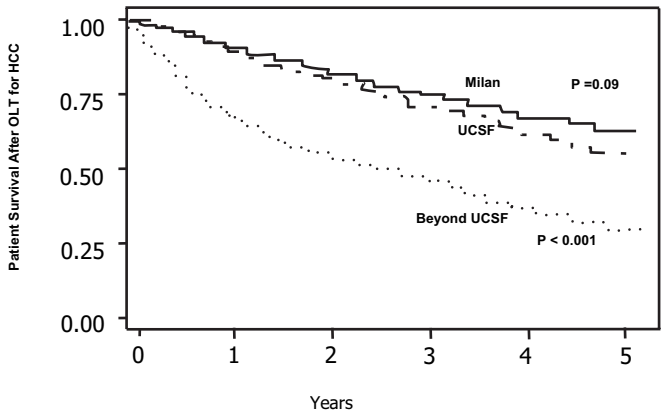

FIGURE 5. Recurrence-free survival estimate by pathologic explant examination.

in 89 patients (19%). Neither was found to be associated with improved post-transplant survival.

DISCUSSION

Most of the early results for OLT with HCC were disappointing, largely because of poor patient selection.[7–10] In 1991, Ringe reported 3 and 5-year survival of 15% after transplantation in 61 patients in whom 80% had tumors >5 cm.[7] Iwatsuki[8] and Bismuth[24] found 3 and 5-year survival rates below 50% after transplantation of advanced stage tumors. In their series, 17% to 35% of patients had portal vein invasion, 50% to 75% had multinodular disease, and nearly 50% were symptomatic from their tumors.[7–9] Recurrence

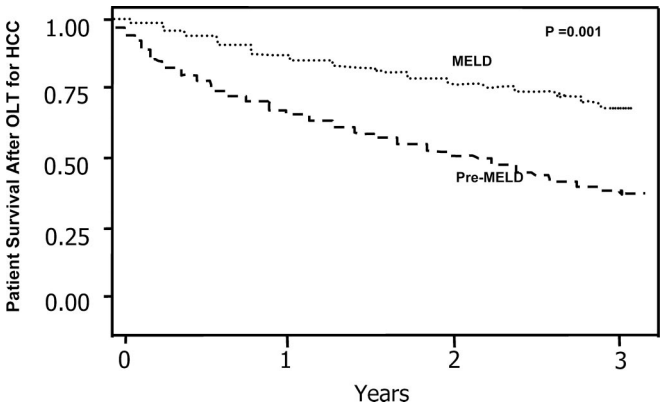

FIGURE 6. Survival estimate for patients who received transplants before or after MELD priority scoring. (MELD—Model for End-Stage Liver Disease.)

TABLE 5. Univariate Analysis of Factors Associated With Mortality After Liver Transplantation for HCC

Factor	Risk Ratio	*P*
Multifocal tumor	6.84	<0.001
Lymphovascular invasion	4.91	<0.001
Poor differentiation	3.13	<0.01
Age >60	2.44	0.022
Male sex	2.43	0.023
Locoregional therapy	2.02	0.038
Tumor size >3 cm	1.73	0.059
Hepatitis C	1.66	0.070
Hepatitis B	1.54	0.078
Time >6 mo after diagnosis	1.39	0.093
Prior resection	1.12	0.15
Incidental tumor	0.96	0.42

TABLE 6. Multivariate Analysis of Factors Associated With Mortality After Liver Transplantation for HCC

Factor	Hazard Ratio	*P*
Multifocal tumor	0.22	<0.001
Lymphovascular invasion	2.44	<0.001
Poor differentiation	4.53	0.002
Sex	0.64	0.165
Locoregional therapy	0.53	0.411
Age	1.11	0.903

rates at 3 years after OLT were 43% and 54%, respectively.[7–9] When tumor burden was limited (1 or 2 masses, tumors <3 cm), 3-year survival was far better at 83%.[23]

Reports of OLT for HCC after 1996 confirm superior results with use of Milan criteria.[11] For tumors within Milan criteria (n = 89) compared with tumors exceeding them (n = 33), 5-year survival was significantly better (87% vs. 62%; $P < 0.001$).[12] Some investigators have argued that the Milan criteria are too restrictive and limit the transplant option at a time when the incidence of HCC is increasing and OLT is recognized as the best therapeutic option. Although early UNOS data indicate that MELD priority scoring using Milan criteria has increased the number of transplants for HCC while decreasing wait-list time and mortality,[22,25] restrictive criteria can result in prolonged waiting time for OLT and 1-year wait-list dropout rate of 20% to 50%.[20]

Several recent series have demonstrated good outcomes using expanded criteria, with 5-year survival after OLT for HCC above 60%.[13–16,26–28] The UCSF criteria have been shown to be associated with long -term survival similar to Milan criteria[26–28] when based on explant pathology. In contrast, post-OLT 5-year survival rates are as low as 34% to 45% when based on pretransplant imaging evaluation.[29] Many of the studies examining UCSF criteria suffer from small sample size or limited data from multiple institutions.[14,26]

The Barcelona Clinic Liver Cancer Group has developed systems based on tumor stage, liver function, physical status, and cancer-related symptoms to select OLT candidates with emphasis on drop-out rate and intention-to-treat analyses.[18–20] Barcelona expanded criteria include 1 tumor <7 cm, 3 tumors <5 cm, 5 tumors <3 cm, or down-staging to conventional Milan criteria with pretransplant adjuvant therapies.[18–20] Using this approach, the Barcelona group has achieved 5-year post-transplant survival in excess of 50%, significantly greater than the 20% survival seen with palliative therapy alone.[20]

In the present report of 467 patients managed in a single institution, OLT is confirmed as appropriate and effective treatment for patients with HCC, with 1, 3, and 5-year survival rates of 82%, 65%, and 52%. Moreover, post-transplant survival for patients with tumors within UCSF criteria, either by pretransplant imaging or pathologic examination, was similar to tumors within Milan criteria. We found poor survival for patients with tumors beyond UCSF criteria, with 3 and 5-year survival rates below 50%. Finally, our results demonstrate improved 3-year outcomes for patients listed and transplanted using MELD priority scoring compared with earlier UNOS guidelines.

Series reporting use of expanded criteria for OLT in patients with HCC are compared in Table 7.[15–16,26–27,29–38] Overall results have uniformly achieved 50% survival at 5 years when tumor burden is categorized based on explant pathology. Furthermore, series comparing pretransplant imaging and pathologic data generally show higher overall survival using the latter, particularly for tumors beyond Milan criteria. Possible explanations include understaging of HCC by preoperative imaging, a lag or wait-list period between last imaging and OLT during which time tumor size and extent may progress, or variability in radiologists' interpretations of tumor size and number among regenerative nodules in cirrhotic livers.

Ours is the largest single-institution series to date of OLT for HCC, and it offers prospectively collected data from 1 institution, where patient selection, transplant technique, and postoperative care have been uniform and consistent. Our study also benefits from collection of both pretransplant imaging and pathologic data on all patients. In contrast to the report by Decaens, a retrospective multicenter experience with variability in patient evaluation and treatment,[29] we

TABLE 7. Collected Series, OLT for HCC Using Expanded Criteria

Author	Year	Total Pts, n	Staging	Patients by Criteria, n		1 Yr Survival (%)		5 Yr Survival (%)	
				Milan	Expanded	Milan	Expanded	Milan	Expanded
Yao et al.[27]	2002	70	Pathology	46	24	91	71	72	57
Roayaie et al.[15]	2002	43	Imaging	—	32*	—	88	—	55†
Fernandez et al.[16]	2003	53	Pathology	33	20	82	75	68	54
Khakhar et al.[30]	2003	39	Imaging	22	17	89	77	70	24
Marsh and Dvorchik[31]	2003	393	Pathology	248	145	—	—	67	—
Ravaioli et al.[32]	2004	63	Imaging	55	8	90	76	78	38
			Pathology	45	18	88	82	73	67
Kneteman et al.[33]	2004	40	Imaging	18	9	100	78	92	78
			Pathology	19	21	94	90	87	83
Leung et al.[34]	2004	144	Imaging	74	14	86	—	51	—
Cillo et al.[35]	2004	48	Pathology	30	18	93	94	72	64
Todo and Furukawa[36]	2004	316	Pathology	138	171	81	75	78‡	60‡
Zavaglia et al.[37]	2005	155	Pathology	130	25	88	85	74	55
Decaens et al.[29]	2006	479	Imaging	279	188	80	78	60	46
			Pathology	187	280	88	77	70	64
Onaca et al.[26]	2007	1206	Pathology	631	575	85	67	62	43
Parfitt et al.[38]	2007	75	Pathology	50	25	83‡	44‡	83	15
Present	2007	467	Imaging	173	294	91	88	79	64
			Pathology	126	341	96	92	86	71

*Based on tumor size 5–7 cm.
†Recurrence-free survival data.
‡3-yr survival.

found no statistical difference in 5-year post-transplant survival for Milan and UCSF criteria groups based on preoperative imaging or explant data. Five-year survival for the UCSF group based on preoperative imaging was not statistically lower than for the Milan group (64% vs. 79%; $P = 0.061$); and results were similar by explant pathology (71% vs. 86%; $P = 0.057$). Recurrence-free 5-year survival estimates also showed no significant difference for tumors within Milan or UCSF criteria by preoperative imaging (72% vs. 64%, $P = 0.1$) or by explant examination (74% vs. 65%; $P = 0.09$).

Although our data did not show numerical equivalency or superiority of outcome data for tumors within UCSF criteria over Milan criteria, this would not be expected given the increased tumor burden in the UCSF group. Nevertheless, it is our view that the very favorable results in these patients with unresectable HCC within UCSF criteria, either by preoperative imaging or explant pathology, justifies expansion of criteria for HCC treated by OLT.

Factors that predicted poor survival in our series included increased tumor number, presence of lymphovascular invasion, and poor tumor differentiation. These determinants have been associated with poor outcome in prior series[7–11,33,39–41] and serve to underscore the crucial principle that tumor biology determines outcome after OLT for HCC. One explanation for the good results in tumors within UCSF criteria is that many were well-differentiated or (n = 62) moderately differentiated (n = 114), whereas only 32 were poorly differentiated. However, there was no difference in the distribution of histologic grade among tumors within Milan, within UCSF, or beyond UCSF criteria. The multinational database analysis from Onaca also showed good results for some expanded tumors, with 5-year survival above 60% for patients with 2 to 4 tumors from 3 to 5 cm.[26] Some tumors, even large or extensive ones, exhibit less aggressive biology than do others.

The principal challenge is to identify and use preoperative criteria to select tumors with favorable biology and patients whose 5-year survival will meet or exceed 50%, as advocated by the Barcelona group.[18–20] At present, preoperative tumor staging is best accomplished with an up-to-date CT or MR scan within 6 months of the time of OLT.[42] However, the critical role of tumor biology, especially regarding histologic grade and lymphovascular invasion, suggests that tumor staging before OLT should include biopsy and histologic examination in all cases.[43] Although there are real concerns regarding patient acceptance, sampling error, and technical complications in patients with cirrhosis and coagulopathy, purported risk of tumor dissemination is minimal with proper patient selection and meticulous attention to biopsy technique.

Development of a reliable, noninvasive method to identify aggressive tumor biology without invasive biopsy remains a fertile area for technological research. Molecular imaging, utilizing MR with angiogenic factor labeling to identify tumor neoangiogenesis, may eventually prove to be an effective modality for pretransplant staging.[44,45] In vivo

MR imaging of the disorganized neovasculature prone to tumor invasion has been performed in animal models of malignant melanoma.[45] Shirabe and coworkers have measured des-gamma-carboxy-prothrombin in serum of patients with HCC and found elevated levels to have 75% sensitivity and 85% specificity for microvascular invasion.[46] Some groups have advocated use of HCC genotyping to identify additional prognostic factors and aid in pretransplant staging, although this technique requires liver biopsy.[47]

Preoperative locoregional therapy, used in nearly half of our patients, was not associated with improved post-transplant survival on multivariate analysis. Prior evidence from our institution has shown RFA to be an effective bridge to OLT, as it limited the dropout rate from OLT candidacy to only 5.8% and contributed to post-OLT survival rates of 85% and 76% at 1 and 3 years after transplant.[48] Porrett analyzed post-transplant outcomes for 31 treated and 33 untreated patients with HCC during the MELD priority era[49] and found that overall and disease-free survival were similar for both groups at 36 months of follow-up. Yao and colleagues were able to demonstrate improved post-transplant survival for patients with selected tumors treated locoregionally before OLT.[50] Lack of benefit in our study and in the era of MELD priority scoring might be explained by earlier transplantation and shorter waiting times for HCC patients with priority scores for OLT. Further prospective analyses are needed to assess the value of adjuvant locoregional treatments.

Although expansion of inclusion criteria must be done cautiously, our results clearly demonstrate that patients with HCC beyond Milan but within UCSF criteria have good outcomes after OLT. Long-term disease free survival of 65% in the latter group justifies the use of a scarce donor resource for these patients. Survival data were comparable for staging by pretransplant imaging when compared with explant pathology, although the latter had greater statistical power. OLT for tumors beyond UCSF criteria cannot be justified by current survival data. Tumor size and number, at present our best predictors for results after OLT for HCC, are relatively crude surrogates for the biology of these tumors. Pretransplant evaluations must be refined to include more precise assessments of tumor biology.

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Discussions

DR. GORAN B. KLINTMALM (DALLAS, TEXAS): The very first liver transplantations performed both by Dr. Starzl in Denver and Dr. Calne in Cambridge were on patients with malignant disease. It was believed that transplantation would be the optimal cure for such patients. However, it was soon discovered that this was not the case. Patients quickly developed extrahepatic and allograft metastasis and eventually succumbed. However, a smattering of patients survived for many years, apparently achieving a cure. Thus, the hope that transplantation would provide treatment for these desperate patients was maintained. Today, the UCLA group, under Dr. Ronald Busuttil, offered a thoughtful presentation of a large single center study on hepatocellular carcinoma.

In 1996, Dr. Mazzaterro published the results from a highly selected group of patients in the *New England Journal of Medicine*. The paper showed a 4-year survival rate of 85%. This demonstrated to the world that transplantation could indeed be a cure for these patients. These so-called Milan criteria were adopted more or less worldwide as proper indication for liver transplantation for hepatocellular carcinoma.

In recent years, facts have emerged that suggest that perhaps these criteria are too restrictive. Most notably the University of California at San Francisco group and the tumor group in Barcelona advocated widening these criteria. The International Registry of Tumors in Liver Transplantation in Dallas published a report a couple of months ago supporting such a proposal.

These particular studies were based on post-transplant pathology, suggesting increasing the acceptable indications for hepatocellular carcinoma to almost exactly the same as those reported at this meeting by Dr. Busuttil. Our proposed criteria are: 1 single lesion less than 6 centimeters or multiple lesions (no more than 4 lesions) with the largest being a maximum of 5 centimeters. If these criteria are exceeded, survival rapidly declines. This paper supports these findings.

Dr. Busuttil's paper raises many additional points. It proves that the waiting time between diagnosis of the tumor and the date of transplantation is important for subsequent survival. This is a point that has long been assumed but never proven. Another point of this paper is that it clarifies the difference in outcome between tumors defined by pretransplant imaging versus those defined by post-transplant pathology. Again, like the waiting time for transplant, this is an issue that has received much discussion but has never produced a definitive answer. I believe the UCLA group has given us that answer.

The question about neoadjuvant therapy for hepatocellular carcinoma is still a raging debate. In this paper, chemotherapy, either systemic or as an adjuvant, did not effect survival. Thus, what is current policy on chemotherapy at this time at UCLA? Do you use it, and if so, when?

You also show that adjuvant therapy in the form of preoperative ablative therapy significantly impacted the univariate analysis but not the multivariate analysis. Do you systematically use ablative therapy, and if you do, what is your current protocol?

To evaluate the effect of tumor criteria on outcome you must include patients, not just those with a small curable lesion tumor less than 3 centimeters, but also, and most importantly, you must include the large ones, those that notoriously lead to

bad outcomes. How did you accrue 109, a full 23%, of your patients who exceeded the UCSF criteria and were not eligible to receive the UNOS allocation priority?

Dr. John P. Duffy (Los Angeles, California): In answer to your first question about the role of chemotherapy with liver transplantation for HCC, as you know, your group and ours published series in the past showing a survival benefit of adjuvant chemotherapy following liver transplantation. However, these studies involved many patients with large or extensive tumors, and their applicability to today's liver recipient is probably not direct. There was 1 randomized control trial that demonstrated no substantial benefit for Adriamycin (Pharmacia & Upjohn S.p.A., Milan, Italy) in the post-transplant setting.

At UCLA we use a selective approach to chemotherapy. All patients who on their explant pathology show signs of adverse outcomes such as lymphovascular invasion, poor differentiation, or many multicentric sites, regardless of how large their tumor is or the extent of their tumor, receive chemotherapy.

In terms of local regional therapy, ablative therapy, or transarterial chemoembolization, all of our patients are presented to a multidisciplinary tumor board. This includes the presence of hepatologists, interventional radiologists, radiation oncologists and general oncologists. In our group the main benefit that we have seen from local regional therapy, although it did not show any significant benefit in our multivariate analysis, is a decrease in dropout rate from a national average of around 15% to 20% to 5.2% in our group, which was previously published in *Hepatology*. We are currently working together with our interventional radiologists to update our data on this point and hopefully further analysis will be able to shake this issue out even further.

And your last question asks about how we were able to transplant patients with tumors that were clearly outside of UNOS guidelines. Many of these transplants occurred in our earlier era of transplantation when the emphasis on patient selection was a new idea, or hadn't been born yet. The other way is through the use of extended criteria donors, which come to us essentially as open offers after the liver has been refused by other centers. For many patients with large or more extensive tumors exceeding UNOS guidelines, this is really the only way for them to receive what we believe is the best treatment, which is liver transplantation. However, we take this on an individual basis and offer it only to those patients who we think will do well, meaning their disease is, while extensive, not so extensive as to preclude transplant, and the donor is of sufficient quality to use. So, earlier era and extended criteria donors are essentially the way we transplanted the more extensive patients.

Dr. Andrew Cameron (Baltimore, Maryland): Preoperative predictions regarding outcome are now indeed reasonable. Some patients with small tumors, however, will still do poorly after transplant while others outside UCSF boundaries can still surprise us and do well. Lesion size, as you suggest, is perhaps just our current best surrogate for tumor biology available preoperatively. This study identifies, in multivariate analysis, both lymphovascular invasion and degree of tumor differentiation as predictors of survival. Perhaps these characteristics may be better indicators of post-OLT behavior. Nevertheless, preoperative biopsy has been mostly avoided, as you point out in your discussion, over concerns about sampling error, risk of bleeding, or even the possibility of tumor seeding. You comment that with careful patient selection and meticulous techniques these concerns can be minimized. What is the bottom line regarding the current practice with pre-OLT biopsy at UCLA? Is it considered helpful, safe, both, or neither? Are there better surrogates? You mentioned des-gamma carboxy prothrombin; is that the answer? Or will we be obtaining genetic signatures based on microarrays of tumors pretransplant in a few years?

Secondly, if we agree with your statement that tumor biology determines outcome after OLT, then what is the role of downstaging really? Yao and colleagues from UCSF described the role for pretransplant chemoembolization or RFA in treating patients outside UCSF criteria in an attempt to shrink the tumor back to within accepted boundaries. We would not expect these interventions to alter underlining cancer biology. So are we simply identifying the responders with presumably favorable biology who will then be expected to do well after OLT? Or are we bringing patients with bad biology back into the game who we would expect to do poorly?

What do we tell the candidate with a large tumor who shows up with an appropriate living donor? Do we deprive them of the opportunity for survival benefit or even cure because we would not allocate them a cadaveric organ in this time of scarcity? Or do we proceed with living donor transplant and accept inferior outcomes? And of course, what do we do with these recipients if their graft fails postoperatively for some non-oncologic reason, say hepatic artery thrombosis? Are they now back in play to draw from the cadaveric pool under urgent circumstances when they were previously judged inappropriate?

Lastly, you described mostly recipient characteristics for tumor recurrence. Did you happen to look at donor factors as well? Should we also be concerned that our current use of extended criteria donors will lead to higher rates of HCC recurrence in addition to more aggressive hepatitis C recurrence? Congratulations on your excellent work.

Dr. John P. Duffy (Los Angeles, California): As to your first question regarding the role of pretransplant biopsy at UCLA, for the majority of patients that we see in the transplant clinic with a hypervascular mass on magnetic resonance imaging or an elevated AFP or findings consistent

with hepatocellular carcinoma, it is not our practice to routinely biopsy these patients. However, we do receive a large referral base of patients who have been evaluated by outside hepatologists and who have had a preoperative biopsy. Based on our results showing the importance of lymphovascular invasion or poor differentiation, we may have to rethink our policy on this and in select patients perhaps provide a preoperative biopsy to guide our selection.

In terms of the role of RFA and chemoembolization and downstaging, again, the primary effect that we have seen is a decreased dropout rate in our patients. In our data today, obviously the local regional therapy did not provide a significant benefit to survival based on our multivariate analysis. Again, we are gathering more prospective data with our interventional radiologists and we hope to have an answer to this question in the future.

It is our practice at UCLA not to pursue living donor liver transplantation for these patients. With a carefully considered decision with poor outcomes with partial graft as well as with a 20% to 30% risk to the donor for morbidity as well as 0.3% to 0.5% risk for mortality, we believe that using living donor liver transplantation to expand criteria is probably not justified. We therefore prefer the cadaveric approach, and that is how we do it at UCLA.

We have not specifically looked at the donor characteristics. We do use a good percentage of extended criteria donors for some of the expanded criteria patients. And we think probably in the future that would be a good idea for us to do, but we have not specifically looked at donor characteristics to date.

Dr. Lynt B. Johnson (Washington, DC): I also want to congratulate the UCLA group for yet another important contribution to our understanding of disease-related issues in liver transplantation. I have a single question.

Your study clearly shows some of the shortcomings of our preoperative imaging in terms of underestimating tumor size, number of tumors, and vascular invasion. Although you showed no difference in 5-year survival between the Milan and the UCSF groups, there clearly appeared to be a difference based upon those cases determined by imaging and those determined by explant pathology.

Given your desire to expand the criteria, how do you suggest we improve on our preoperative staging? I would imagine that over the 22 years there was some evolution in your imaging techniques. Should we select these patients with larger tumors by observing them over a period of time to detect progression of disease or eliminate patients who may have disease progression that we would otherwise transplant and would exceed criteria? Can you elucidate some of the strategies you use in your group to eliminate these issues?

Dr. John P. Duffy (Los Angeles, California): In preoperative imaging, the modalities have changed over our 22-year period. But I think one of the strengths at UCLA is that the people in place looking at those images as well as the surgeons in place have been relatively stable. So we have had a high-volume center with constant communication between the same radiologists and the same surgeons. And our radiologists have published extensively showing that they have been able to determine pretty well the extent of the disease.

Nevertheless, as you saw by our data, the difference in survival was greater when based on preoperative imaging than for explant pathology. Clearly, explant pathology is the gold standard that gives us the extent of disease. We are hopeful that some molecular imaging techniques in the future such as MRI with labeling of nanoparticles detecting disordered vasculature or lymphovascular invasion may be on the horizon to help us better select patients radiographically.

Dr. Andreas G. Tzakis (Miami, Florida): Could you expand on the local regional therapy and the effects on the prognosis? There is a subgroup of patients who clearly respond to local regional therapy with a clear reduction of the size of the tumor. Have you looked into the effect of the reduction and the prognosis after transplantation? Should they be classified as the large tumors that they started with or the shrunken tumors that they end up with?

Dr. John P. Duffy (Los Angeles, California): In looking at the effects of local regional therapy we looked at all comers and we did not substratify them according to the size of tumor or extent of tumor. As I said, we are prospectively gathering this data with our interventional radiologists to update the series that we previously reported in *Hepatology*. Hopefully, we will be able to substratify those as you describe to provide more insight into the effect of local regional therapy. But as of yet we have not done that.