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Accuracy of Milan, University of California San Francisco, and Up-To-7 Criteria in Predicting Tumor Recurrence Following Deceased-Donor Liver Transplant in Patients With Hepatocellular Carcinoma

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Abstract

Objectives: We aimed to investigate the accuracy of the Milan, University of California San Francisco, and Up-to-7 criteria in predicting tumor recurrence after liver transplant for hepatocellular carcinoma.

Materials and Methods: For this study, 165 patients with deceased-donor liver transplant for hepatocellular carcinoma were evaluated. The Milan, University of California San Francisco, and Up-to-7 criteria were calculated based on explant pathology.

Results: Tumor recurrence rate after liver transplant was 14.6%. Of 165 patients, 115 (70%) were within Milan, 131 (79%) were within University of California San Francisco, and 135 (82%) were within Up-to-7 criteria. The odds ratio of tumor recurrence in patients outside versus within criteria for Milan, University of California San Francisco, and Up-to-7 was 3.6 (95% confidence interval, 1.5–9.1; $P = .005$), 7.5 (95% confidence interval, 2.5–19.3; $P < .001$), and 7.5 (95% confidence interval, 2.9–19.6; $P < .001$) times higher, respectively. The sensitivity of being outside of Milan in predicting tumor recurrence was comparable to University of California San Francisco and Up-to-7 criteria (56.5%, 56.5%, and 52.2%, respectively). Specificity was highest in Up-to-7

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(87.3%) versus 85.2% for University of California San Francisco and 73.9% for Milan criteria. The area under the curve for Milan, University of California San Francisco, and Up-to-7 criteria was 0.63, 0.65, and 0.63.

Conclusions: Application of standard criteria has significantly improved prediction of hepatocellular carcinoma recurrence. However, these criteria are inadequate, supporting the importance of other factors, including tumor biology. Research is ongoing in discovering novel biomarkers as predictors of tumor recurrence.

Keywords

Cancer recurrence; Explant pathology; Transplant eligibility

Introduction

Hepatocellular carcinoma (HCC) is the 5th most common cancer in men, the 7th most common cancer in women, and is the second leading cause of cancer-related mortality in the world.^{1,2} Although there are multiple treatment modalities for HCC, including transarterial chemoembolization (TACE), radiofrequency ablation, and surgical resection, liver transplant (LT). The later is an attractive option, particularly in patients with cirrhosis, as it is both curative and addresses the underlying chronic liver disease.^{2,3}

Recurrence of HCC is a dreaded and ominous event after LT.⁴ It is associated with a significant decrease in post-LT survival and has limited therapeutic options.⁵ When LT was first accepted as a treatment option for patients with HCC in the 1980s, there were no published criteria to guide patient selection, and the rate of postoperative cancer recurrence was reported to be high as 70%.^{6,7} These initial disappointing results led centers to reconsider the feasibility of transplant in patients with HCC. However, subsequent reports of satisfactory survival among patients with incidental findings of small HCCs on explant pathology prompted efforts to develop criteria to select LT candidates with the lowest risk of tumor recurrence, which could thus optimize utilization of this scarce resource.⁸⁻¹⁰

Therefore, standard criteria were designed to aid in appropriate patient selection for LT in patients with HCC. The Milan criteria (MC) were first described in 1996, in a pivotal study that established LT as a viable treatment option for HCC.¹¹ In this study, transplant eligibility criteria were as follows: a single lesion ≤ 5 cm or 3 or fewer lesions all < 3 cm and no evidence of macrovascular invasion, lymph node involvement, or extrahepatic metastasis. The MC were subsequently adopted by the United Network of Organ Sharing and are currently the criterion standard in transplant programs to select and list patients with HCC for LT.¹²

Since the introduction of MC, additional models have been proposed to safely expand the indications for LT in patients with HCC in an effort to include more patients without compromising recurrence-free survival. In 2001, the University of California San Francisco (UCSF) criteria were published, which expanded tumor size criteria. Thus, transplant eligibility criteria were as follows: a single tumor ≤ 6.5 cm in diameter or up to 3 lesions each ≤ 4.5 cm in diameter with a total diameter of ≤ 8 cm.¹³ In this study, patients with HCC

who fell within the more liberal UCSF criteria had posttransplant survival rates comparable to those who fell within MC. Subsequently, Mazzaferro and associates described the “Up-to-Seven” model (otherwise known as the “New Milan criteria”) as follows: the sum of the total number of HCC lesions plus the size of the largest tumor in centimeters up to 7.¹⁴ The 5-year survival rate of those who fell within these criteria was also shown to be comparable to MC.^{13,14} The definitions of the MC, UCSF criteria, and Up-to-7 criteria are summarized in Table 1.

In the present study, we aimed to assess how well the MC, UCSF, and Up-to-7 criteria can predict tumor recurrence in our patient population following deceased-donor LT for HCC.

Materials and Methods

Study population

We retrospectively studied 170 patients who underwent LT with a diagnosis of HCC at the Johns Hopkins University Comprehensive Liver Transplant Center between 2005 and 2015. We excluded 4 patients who underwent living-donor LT and 1 patient due to quality of data. Thus, 165 total patients were included in the final analysis. Clinical characteristics, including age, sex, and tumor recurrence, and explant pathology, including tumor size, were obtained from patient medical records.

Pathology

Data regarding number and size of the tumors were collected based on the explant pathology. In addition, data on percent necrosis for each tumor were calculated. The MC, UCSF, and Up-to-7 criteria were calculated based on the original size of the tumors on pathology. All 3 criteria were then recalculated based on the amount of necrosis and percentage of viable tumor after downstaging post-TACE.

Statistical analyses

Categorical variables are reported as percentages, and continuous variables are reported as medians and ranges. To evaluate the diagnostic value of MC, UCSF, and Up-to-7 criteria, we determined the sensitivity, specificity, positive predictive value, and negative predictive value. The overall predictive performance of MC, UCSF, and Up-to-7 were measured by area under the receiver operating characteristic curve (AUC). Statistical significance was based on $P < .05$. Statistical analyses were performed using STATA version 13 (StataCorp, College Station, TX, USA). Logistic regression analysis was used to determine associations between MC, UCSF, and Up-to-7 criteria and tumor recurrence after deceased-donor LT. For comparison between AUC of MC, UCSF, and Up-to-7 criteria, the DeLong nonparametric approach was applied.¹⁵

Results

Study population

Characteristics of the 165 included patients are summarized in Table 2. The mean age was 59 years, and 127 patients (77%) were males. Milan, UCSF, and Up-to-7 criteria were

evaluated based on explant pathology as described in the Materials and Methods section pre-TACE (original tumor size) and post-TACE. In total, 115 patients (70%) were within MC based on explant pathology, and 50 patients (30%) were outside of MC. Overall, 131 patients (79%) were within UCSF criteria, and 135 patients (82%) were within Up-to-7 criteria. All 115 (70%) patients who were within MC were also within UCSF and Up-to-7 criteria (Table 3). There were 27 patients (16%) who were outside of all 3 criteria. In addition, there were 13 patients who were within UCSF and Up-to-7 criteria but fell outside of MC. Three patients who were within UCSF were also outside of Up-to-7. On the other hand, 7 patients who were within Up-to-7 were not within UCSF criteria (Table 3; pre-TACE). The above information was recalculated based on percent necrosis and viable tumor as a result of post-TACE effect (Table 3).

Tumor recurrence and logistic regression analyses

We then applied logistic regression analysis to evaluate the association between tumor recurrence and being outside of individual criteria. The overall rate of HCC recurrence after LT within our population was 14.6%. The odds ratio (OR) of tumor recurrence in patients outside of MC was 3.6 times higher than patients who were within MC (95% confidence interval [CI], 1.5–9.1; $P = .005$) (Table 4). The OR for UCSF criteria was 7.5 (95% CI, 2.5–19.3; $P < .001$), and the OR for Up-to-7 criteria was 7.5 (95% CI, 2.9–19.6; $P < .001$) (Table 4; pre-TACE). The ORs were comparable when post-TACE data were applied (Table 4).

Predictive validity

Next, we determined the performance characteristics of the MC, UCSF, and Up-to-7 criteria. The 2-by-2 tables, pre-TACE and post-TACE, are shown in Table 5. In addition, the sensitivity, specificity, positive predictive value, negative predictive value, and AUC for the 3 criteria are summarized in Table 6. The sensitivity for tumor recurrence for patients outside of MC, UCSF, and Up-to-7 criteria pre-TACE was 56.5%, 56.5%, and 52.2%, respectively. The specificity was highest in Up-to-7 at 87.3% versus 85.2% for UCSF criteria and 73.9% for MC. The positive predictive value was 40% for Up-to-7 and 38.2% for UCSF versus 26% for MC. The negative predictive value was similar among the 3 criteria. The AUC for MC, UCSF criteria, and Up-to-7 criteria was 0.65, 0.71, and 0.7, respectively (Table 6; pre-TACE). The above information was also calculated based on percent necrosis and viable tumors as a result of post-TACE effects (Table 6).

Downstaging after transarterial chemoembolization

The size and number of lesions were recalculated based on percent necrosis and viable tumor on explant pathology. The patients were then recategorized into MC, UCSF criteria, and Up-to-7 criteria based on this information. On the basis of explant pathology post-TACE, 19 patients were downstaged to MC, 8 patients were downstaged to UCSF criteria, and 11 patients were downstaged to Up-to-7 criteria. The post-TACE sensitivity for tumor recurrence for patients outside of MC, UCSF, and Up-to-7 criteria dropped to 41.7%, 41.7%, and 33.3%, respectively. However, the specificities increased to 85.1%, 88.7%, and 92.2%, respectively. The post-TACE AUC for MC, UCSF, and Up-to-7 criteria decreased to 0.63, 0.65, and 0.63, respectively (Table 6).

Comparison of areas under the curve

To compare the AUCs for MC, UCSF, and Up-to-7 criteria, we applied the Delong nonparametric approach.¹⁵ There were no statistical differences between AUCs of the 3 criteria, for both pre- and post-TACE data, in predicting tumor recurrence after LT.

Discussion

Liver transplant remains one of the main treatment options in patients with cirrhosis and HCC, and it is a particularly attractive option because it also generally cures the underlying cirrhosis.¹⁶ After the development of MC in 1996, outcomes of LT for HCC have improved drastically. In the original series of 48 patients, in which the average follow-up was 26 months (range, 9–54), 35 patients who fell within MC were compared with 13 patients whose tumors were outside of the criteria. The overall mortality rate was reported as 17%. The 4-year overall and recurrence-free survival rates in patients who met the criteria were 85% and 92%, respectively, compared with 50% and 59% in patients whose tumors were outside of the criteria.¹¹ The MC have since been further validated.¹⁷ In a 2009 study that included 4482 patients with HCC who were on wait lists for LT, 65% received a LT. The 1- and 5-year survival rates in patients within MC were 89% and 61%, respectively, compared with 70% and 32% in those who exceeded the MC.¹⁸ Overall, tumor recurrence can occur in 15% to 20% of patients after LT, who then have limited curative treatment options.¹⁹

Although the MC have been widely adapted by many transplant centers, it has been proposed that MC may be too restrictive, thus preventing patients from receiving a potentially lifesaving treatment such as LT.^{20–22} Therefore, various groups have attempted to expand beyond the MC through “extended criteria.”^{23–26} Two of the more commonly used criteria are the UCSF criteria¹³ and the Up-to-7 criteria.¹⁴

In a 2001 study from the University of California San Francisco, 70 patients with HCC who underwent LT over a 12-year period were evaluated. Patients who fell within the UCSF criteria had 1- and 5-year survival rates of 90% and 75.2% compared with a 1-year survival rate of 50% in patients who fell outside the criteria. In addition, in a univariate analyses, an alpha-fetoprotein (AFP) level of > 1000 ng/mL, total tumor diameter of > 8 cm, age > 55 years, and poor differentiation grade were significant predictors of decreased survival. On multivariate analysis, only pT4 tumor stage and total tumor diameter remained statistically significant. The overall HCC recurrence after LT in this population was reported to be 11.4%.^{13,27}

In the study describing the Up-to-7 criteria, 1112 patients with HCC who were outside of MC were evaluated and were compared to 444 patients with tumors within MC. Patients who were outside of the MC and received transplants had a 5-year overall survival rate of 53.6% compared with 73.3% for patients who met the criteria. Of 1112 patients, 454 (41%) had microvascular invasion. The presence of microvascular invasion doubled the hazard ratio for tumor recurrence. A subset of 283 patients who fell within the Up-to-7 criteria (7 as the sum of the size of the largest tumor in centimeters and the number of tumors) without microvascular invasion achieved a 5-year overall survival of 71.2%, which was comparable to those who fell within MC.¹⁴

In our single-center retrospective study of 165 patients, we aimed to evaluate the accuracy of MC, UCSF, and Up-to-7 criteria in predicting HCC recurrence after LT. Given that there was evidence of necrosis in most explants as a result of prior TACE, we have described the results as pre-TACE and post-TACE based on the pathology reports. Limitations of our study include its retrospective nature and small sample size. However, the sensitivities for predicting tumor recurrence were comparable between pathologic MC, UCSF, and Up-to-7 at 56.5%, 56.5%, and 52.2%. In addition, the specificities of MC, UCSF, and Up-to-7 were 74.5%, 85.1%, and 87.2% (Table 5 and Table 6). In other words, when a patient is within the criteria, the tests are relatively reliable in predicting patients who will not have HCC recurrence following LT. However, when a patient is outside of the criteria, the tests do poorly in predicting tumor recurrence. After we considered percentage of necrosis, the sensitivity of the tests dropped further and the specificities slightly increased. The AUC ranges for MC, UCSF, and Up-to-7 criteria were 0.63 to 0.65, 0.65 to 0.71, and 0.63 to 0.7, respectively. Similar to our findings, in a recent study of 339 patients, C statistics results for radiologic MC and UCSF criteria for prediction of HCC recurrence after LT were 0.63 and 0.57, respectively.²⁸ In addition, in a study of 865 HCC patients, Agopian and associates showed similar prediction of tumor recurrence with C statistics of MC and UCSF criteria (C statistics 0.64).²⁹ Although these criteria have significantly improved the outcomes of LT in patients with HCC, it appears that they are still not ideal in predicting tumor recurrence, suggesting that criteria solely based on tumor size and number of lesions have limitations and are inadequate.

It is now apparent that tumor biology is an important feature that determines tumor behavior in both the transplant and nontransplant settings.¹⁹ Investigators have attempted to address this by studying different biomarkers to predict tumor recurrence after LT for HCC.^{30,31} Alpha-fetoprotein and des-gamma-carboxy prothrombin (DCP) have been established as specific tumor markers for HCC,³² and AFP has been increasingly accepted as a marker for poor prognosis in HCC after LT.³³ In a study by Hameed and associates, predictors of HCC recurrence included vascular invasion, pathologic tumor stage beyond UCSF criteria, and AFP level > 1000 ng/mL (hazard ratio of 4.5; 95% CI, 1.3–15.3; $P = .02$).³⁴ Another study evaluated the predictive value of AFP and DCP in combination with MC criteria for HCC recurrence after LT. The hazard ratios were 3.5 for DCP > 7.5 ng/mL and 2.8 for AFP > 250 ng/mL. When biomarkers were evaluated in combination with the tumor being outside of MC, the hazard ratio was increased from 2.6 to 8.6 for tumors outside the MC and AFP > 250 ng/mL and from 3.5 to 7.2 for tumors outside the MC and DCP > 7.5 ng/mL.³⁵ In a study by Halazun and colleagues, pretransplant Model of Recurrence After Liver Transplant scores were used to evaluate recurrence-free survival. Three independent predictors were used, including neutrophil-to-lymphocyte ratio > 5, AFP > 200 ng/mL, and tumor size > 3 cm. In this study, pretransplant Model of Recurrence After Liver Transplant scores were superior to MC in predicting tumor recurrence after LT (C statistic of 0.82 compared with 0.63).²⁸

Based on these observations, it is becoming more evident that novel tumor biomarkers are needed to predict tumor behavior and recurrence after LT. Newer technologies are being actively investigated in patients with HCC, such as genomic sequencing and liquid biopsy.³⁶ Application of these new technologies in clinical practice, including in the field of LT, has

yet to be established.³⁷ Genomic studies have revealed the mutational profile of HCC, which involves various molecular pathways.³⁸ In a study from Nault and associates, a 5-gene signature score that incorporated expression levels of HN1, RAN, RAMP3, KRT19, and TAF9 could predict prognosis in patients with HCC after liver resection.³⁹ Liquid biopsy, a new concept that refers to collection of molecular information from cancer byproducts from peripheral blood circulating tumor cells, DNA, or RNA,^{36,37} has also been investigated. In a study of 46 patients with HCC who were undergoing liver resection or transplant, 7 patients had circulating DNAs. Tumor recurrence and metastatic disease were significantly higher in patients with circulating DNA than in the DNA-negative group. Multivariate analyses identified circulating DNA as an independent predictor of microvascular invasion of portal vein.⁴⁰

In summary, after the introduction of MC and other extended criteria in patients with HCC, tumor recurrence after LT has significantly decreased. However, the accuracy of these tools is still not optimal (AUC between 0.63 and 0.70). These criteria focus mainly on tumor volume and do not factor in tumor biology. Recent advancements in newer technologies have shown promise in discovering novel biomarkers as potential predictors of tumor recurrence after LT.

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Table 1.

Milan Criteria, University of California San Francisco Criteria, and Up-to-7 Criteria Definitions for Liver Transplant

Criteria	Definition
Milan ¹¹	Single lesion 5 cm Up to 3 lesions each 3 cm
UCSF ¹³	Single lesion 6.5 cm Up to 3 lesions each 4.5 cm with total diameter 8 cm
Up-to-7 ¹⁴	Largest lesion in cm + total number of lesions 7

Abbreviations: UCSF, University of California San Francisco

Table 2.

Characteristics of Study Patients (N = 165)

Variable	Result
Median age (range), y	59 (43–75)
Sex, No. (%)	
Male	127 (77.0)
Female	38 (23.0)
Pre-TACE Milan, No. (%)	
Within	115 (69.7)
Outside	50 (30.3)
Post-TACE Milan, No. (%)	
Within	134 (81.2)
Outside	31 (18.8)
Pre-TACE UCSF, No. (%)	
Within	131 (79.4)
Outside	34 (20.6)
Post-TACE UCSF, No. (%)	
Within	139 (84.2)
Outside	26 (15.8)
Pre-TACE Up-to-7, No. (%)	
Within	135 (81.8)
Outside	30 (18.2)
Post-TACE Up-to-7, No. (%)	
Within	146 (88.5)
Outside	19 (11.5)

Abbreviations: TACE, transarterial chemoembolization; UCSF, University of California San Francisco

Table 3.

Distribution of Study Patients Based on Criteria Before and After Transarterial Chemoembolization

	Number of Patients			
	Within Up-to-7		Outside Up-to-7	
	Within UCSF	Outside UCSF	Within UCSF	Outside UCSF
Pre-TACE				
Within Milan	115	0	0	0
Outside Milan	13	7	3	27
Post-TACE				
Within Milan	134	0	0	0
Outside Milan	4	8	1	18

Abbreviations: TACE, transarterial chemoembolization; UCSF, University of California San Francisco

Table 4.

Odds Ratios of Recurrence of Hepatocellular Carcinoma for Patients With Tumors That Were Outside of the Criteria for Liver Transplant Before and After Transarterial Chemoembolization

Criteria	Odds Ratio (95% CI)	P Value
Pre-TACE		
Milan	4.1 (1.7–10.0)	.002
UCSF	6.8 (2.7–17.1)	< .001
Up-to-7	6.8 (2.7–17.6)	< .001
Post-TACE		
Milan	4.1 (1.6–10.4)	.003
UCSF	5.6 (2.1–14.7)	< .001
Up-to-7	5.9 (2.1–16.9)	.001

Abbreviations: CI, confidence interval; TACE, transarterial chemo-embolization; UCSF, University of California San Francisco

Table 5.

Relationship Between Milan, University of California San Francisco, and Up-to-7 Criteria for Liver Transplant Before and After Transarterial Chemoembolization and Tumor Recurrence

	Recurrence	
	Yes	No
Milan criteria Pre-TACE		
Outside Milan	14	36
Within Milan	10	105
Milan criteria Post-TACE		
Outside Milan	10	21
Within Milan	14	120
UCSF criteria Pre-TACE		
Outside UCSF	13	21
Within UCSF	11	120
UCSF criteria Post-TACE		
Outside UCSF	10	16
Within UCSF	14	125
Up-to-7 criteria Pre-TACE		
Outside Up to 7	12	18
Within Up to 7	12	123
Up-to-7 criteria Post-TACE		
Outside Up to 7	8	11
Within Up to 7	16	130

Abbreviations: TACE, transarterial chemoembolization; UCSF, University of California San Francisco

Table 6.

Performance Characteristics of Criteria Before and After Transarterial Chemoembolization in Predicting Likelihood of Tumor Recurrence

	Sensitivity, %	Specificity, %	PPV, %	NPV, %	AUC (95% CI)
Pre-TACE					
Milan	58.3	74.5	28.0	91.3	0.66 (0.56–0.77)
UCSF	54.4	85.1	38.2	91.1	0.70 (0.59–0.80)
Up-to-7	50.0	87.2	40.0	91.1	0.69 (0.58–0.79)
Post-TACE					
Milan	41.7	85.1	32.3	89.6	0.63 (0.53–0.74)
UCSF	41.7	88.7	38.5	89.9	0.65 (0.55–0.76)
Up-to-7	33.3	92.2	42.1	89.0	0.63 (0.53–0.73)

Abbreviations: AUC, area under the curve; CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value; TACE, transarterial chemoembolization; UCSF, University of California San Francisco