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ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

Survival Advantage of Radiofrequency Ablation Over Transarterial Chemoembolization for Patients with Hepatocellular Carcinoma and Good Performance Status Within the Milan Criteria

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ABSTRACT

Background. Performance status is closely linked with survival in patients with hepatocellular carcinoma (HCC). We evaluated the impact of performance status on patients with small HCC receiving radiofrequency ablation (RFA) versus transarterial chemoembolization (TACE).

Methods. A total of 424 and 282 patients within the Milan criteria undergoing RFA and TACE, respectively, were analyzed. Patients were classified as performance status 0 (n = 516) and performance status $\geq$1 (n = 190) groups. A propensity-score matching analysis with preset caliper width was used. A total of 167 and 68 matched pairs were selected from patients with a performance status of 0 and $\geq$1, respectively.

Results. Radiofrequency ablation provided significantly better long-term survival than TACE for patients within the Milan criteria ($p < 0.01$). After being stratified by performance status and matched in the propensity model, the baseline characteristics were similar between the RFA and TACE groups for patients with a performance status of 0 or $\geq$1. RFA provided significantly better long-term survival than TACE in patients with a performance status of 0 in the propensity model ($p < 0.05$); TACE was significantly associated with 1.784-fold increased risk of mortality (95 % confidence interval 1.075–2.506) by using the Cox proportional hazards model. TACE was not a significant prognostic predictor in patients with a performance status $\geq$1 in the propensity model.

Conclusions. For HCC patients within the Milan criteria with a performance status of 0, RFA provides better long-term survival than TACE. RFA should be considered a priority treatment in inoperable HCC patients within the Milan criteria. Performance status is a feasible surrogate marker to enhance treatment allocation.

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide, accounting for nearly 700,000 deaths annually.[1] According to the HCC management guidelines published by the American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver (EASL), the therapeutic options for HCC are surgical resection (SR), liver transplantation, percutaneous ablation, transarterial chemoembolization (TACE) and targeted therapy.[2,3] In early-stage HCC, SR, percutaneous ablation, and liver transplantation are widely used treatment modalities that may provide 5-year survival rate up to 75 %.[4,5] Among various local ablation therapies, radiofrequency ablation (RFA) is considered the treatment of choice for small HCC.[6] Alternatively, for patients not suitable for curative treatments, TACE is an effective approach and can provide better local-regional tumor control and long-term survival compared with best supportive care alone.[7]

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The Milan criteria (a single tumor ≤5 cm or three or fewer nodules ≤3 cm in diameter, with no extrahepatic spread or vascular invasion) are used to define early-stage HCC and are utilized as the reference system for liver transplantation.[4] Patients with HCC within the Milan criteria may receive SR, liver transplantation, or RFA as the primary curative treatment.[2,3] However, candidates of liver transplantation far outnumber liver donors by a significant margin.[8] Moreover, liver functional reserve, tumor location, and tumor number may limit the possibilities of SR and local ablation. TACE thus remains the only plausible treatment for patients with unresectable HCC not eligible for liver transplantation and RFA. Recent studies reported satisfactory results with TACE for small HCC with compensated liver function.[9,10] However, the long-term survival of HCC patients within the Milan criteria receiving TACE as their primary treatment remains largely undetermined due to insufficient clinical evidence.

The performance status scale developed by the Eastern Cooperative Oncology Group (ECOG) measures how daily living ability is affected by the disease, and is extensively used by clinicians to evaluate functional status in cancer patients.[11] Performance status scale is a major predictor of survival in HCC and is specifically included in the Barcelona Clinic Liver Cancer (BCLC) staging system as an important parameter for treatment allocation.[2,12,13] A recent large-scale study suggested that performance status plays a crucial role in determining treatment outcomes independent of treatment strategy.[14] Until now, very few studies specifically compared the long-term survival of RFA versus TACE when used as the primary treatment for HCC within the Milan criteria. This study aimed to investigate the impact of performance status on long-term survival in a large cohort of HCC patients within the Milan criteria who received RFA and TACE as their initial treatment. Patients receiving RFA or TACE had discrete prognostic characteristics, including severity of cirrhosis, tumor burden, and general performance status. A propensity-score matching analysis was utilized in order to generate matched groups of HCC patients and to minimize potential bias inherent to a retrospective, non-randomized study.

PATIENTS AND METHODS

Patients

We retrospectively analyzed 3,007 patients with HCC admitted to the Taipei Veterans General Hospital in more than a decade (from 2002 to 2013). Patients within the Milan criteria who received RFA or TACE as their primary treatment were identified and formed the basis of this study. Comprehensive baseline information, including patient demographics, etiology of underlying liver disease, characteristics of tumor(s), serum biochemistry, tumor staging, severity and complication of cirrhosis, and performance status, was recorded at the time of diagnosis. The survival of patients was inspected every 3–4 months until death or dropout from the follow-up program. This study was approved by the Institutional Review Board and complies with the standards of the Declaration of Helsinki and current ethical guidelines.

Diagnosis and Definitions

The diagnosis of HCC was histologically confirmed or based on the findings of typical radiological features in a four-phase, multidetector, contrast-enhanced computed tomography (CT) scan or dynamic magnetic resonance imaging (MRI).[2,15] Alcoholism was diagnosed in patients with consumption of alcohol at least 40 g daily for 5 years or more.[16] The Child–Turcotte–Pugh (CTP) classification was used to define the severity of cirrhosis. Total tumor volume (TTV) was calculated as the sum of all tumor nodule volumes, and each tumor volume was calculated as $4/3 \times 3.14 \times (\text{maximum radius of the tumor in centimeters})^3$, as previously described.[17] Performance status was assessed at the time of diagnosis by using the ECOG performance scale ranging from 0 (asymptomatic) to 4 (confined to bed).[14] The Cancer of the Liver Italian Program (CLIP) classification was used to define staging.[18]

Treatment

RFA was performed using the standard procedure.[6] Under ultrasound guidance, the tumor(s) was ablated by using a 17-gauge, cooled-tip electrode with the Cool-Tip Radiofrequency System (Radionics, Burlington, MA, USA). The ablation was performed in automatic impedance control mode in which the current output was automatically adjusted. Post-RFA sonography was performed immediately to confirm that there was no definite hemorrhage or hematoma.

Transarterial chemoembolization was performed in patients who were not eligible or unwilling to receive SR, RFA, and liver transplantation, and with adequate liver function reserve and no signs of distant metastases or main portal trunk thrombosis.[19] The Seldinger's technique of arterial embolization was administered as the standard TACE procedure. After tumor stain was identified, infusion of a mixture of 20–30 mg adriamycin (Carlo Erba, Milan, Italy) and 5–10 mL lipiodol (Laboratoire Guerbet, Villepinte, France) was performed after the artery supplying the tumor was catheterized with a three-French catheter superselectively. Sufficient amounts of emulsion and 2- to 3-mm strips of Gelfoam (Upjohn, Kalamazoo, MI, USA) were delivered to the tumor area until complete flow stagnation was achieved.

Propensity-Score Matching Analysis

To investigate the association between treatment and outcome in an observational, non-randomized study, a propensity-score matching analysis without replacement was used in an attempt to reduce bias in patient selection and to generate a matched pair of patients to compare the long-term survival associated with RFA or TACE.[20,21] Possible variables associated with treatment selection, including age, sex, serum biochemistries, etiology of HCC, CTP score, CLIP score, tumor number, and TTV, were comprehensively included in the generation of propensity score. Binary logistic regression with the selected variables was used to generate a continuous propensity score from 0 to 1 to estimate the probability that a patient would undergo TACE or RFA. A nearest-neighbor match between the RFA and TACE groups was used to select patients into subsequent analyses and was stratified by performance status. A caliper width equal to 0.2 of the standard deviation of the logit of the propensity score was chosen for superior performance in the estimation of treatment effects.[22]

Statistics

The Chi-square test and two-tailed Fisher's exact test were used to compare categorical data. The Mann–Whitney U test was used to compare continuous variables between the two groups. The comparison of survival distribution was performed by the Kaplan–Meier method with log-rank test. To analyze the significance of prognostic predictors, continuous variables were split by the median values and were treated as dichotomous covariates. Prognostic factors that were possibly linked to survival, including age, sex, etiology of liver disease, severity of liver cirrhosis, size and number of tumor nodules, serum biochemistries, performance status, treatment modalities, and cancer staging were included in survival analysis. Factors that were significant in the univariate survival analysis were introduced into the multivariate Cox proportional hazards model to determine the adjusted hazard ratios (HR) and 95 % confidence intervals (CI). A p value less than 0.05 was considered statistically significant. All statistical analyses were conducted with SPSS for Windows version 19 (IBM Corporation, Armonk, NY, USA).

RESULTS

Identification of Study Patients

A total of 424 and 282 HCC patients within the Milan criteria who received RFA and TACE, respectively, as the primary treatment were identified. A total of 319 and 105 patients in the RFA group had a performance status of 0 and ≥1, respectively, whereas 197 and 85 patients in the TACE group had a performance status of 0 and ≥1, respectively. Overall, patients receiving RFA had significantly better long-term survival when compared with the TACE group (p = 0.001; Fig. 1); the 1- and 3-year estimated survival rates in the RFA and TACE groups were 89 versus 84 % and 71 versus 59 %, respectively. Of these patients, 167 pairs of patients with a performance status of 0 and 68 pairs of patients with a performance status of ≥1 were identified by the propensity-score matching analysis to compare the therapeutic efficacy.

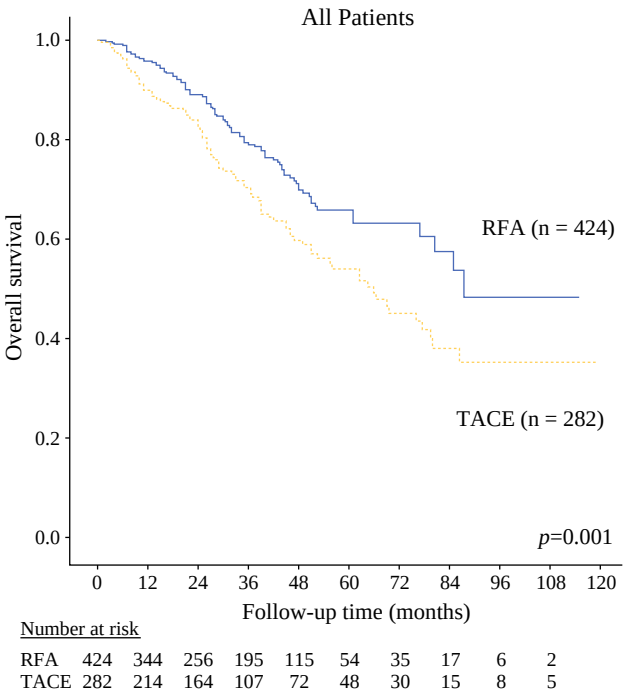

FIG. 1 Comparison of survival between HCC patients within the Milan criteria undergoing RFA or TACE. Patients receiving RFA had significantly better long-term survival than patients receiving TACE (p = 0.001). *HCC* hepatocellular carcinoma, *RFA* radiofrequency ablation, *TACE* transarterial chemoembolization

Characteristics and Survival of Patients with a Performance Status of 0

A total of 319 and 197 patients with a performance status of 0 received RFA and TACE, respectively (Table 1). Patients in the RFA group had fewer tumor nodules, smaller TTV, better CTP score, and lower CLIP score (all $p < 0.05$). Patients with a performance status of 0 undergoing RFA had significantly better long-term survival than patients receiving TACE ($p < 0.001$; Fig. 2a); the 1- and 3-year estimated survival rates in the RFA and TACE groups were 93 versus 87 % and 77 versus 63 %, respectively.

TABLE 1 Comparison of baseline demographics between patients undergoing radiofrequency ablation and transarterial chemoembolization stratified by performance status

	Performance status = 0			Performance status ≥ 1		
	RFA (n = 319)	TACE (n = 197)	p value	RFA (n = 105)	TACE (n = 85)	p value
Age [years; mean ± SD]	66 ± 11	68 ± 10	0.137	67 ± 13	67 ± 11	0.813
Male [n (%)]	206 (65)	135 (69)	0.389	72 (69)	57 (67)	0.876
Positive for HBsAg [n (%)]	145 (46)	87 (44)	0.785	53 (51)	32 (38)	0.081
Positive for anti-HCV [n (%)]	140 (44)	95 (48)	0.363	37 (35)	39 (46)	0.140
Alcoholism [n (%)]	40 (13)	21 (11)	0.576	29 (28)	17 (20)	0.238
Serum biochemistry [mean ± SD]						
Albumin (g/dL)	3.9 ± 0.5	3.7 ± 0.5	0.010	3.4 ± 0.6	3.4 ± 0.6	0.896
Bilirubin (mg/dL)	0.9 ± 0.7	1.1 ± 0.6	0.001	1.6 ± 1.7	1.3 ± 1.2	0.803
Creatinine (mg/dL)	1.1 ± 0.9	1.0 ± 0.5	0.307	1.1 ± 1.1	1.2 ± 1.1	0.526
INR of PT	1.1 ± 0.1	1.1 ± 0.1	0.213	1.1 ± 0.2	1.2 ± 0.2	0.661
ALT (U/L)	67 ± 53	63 ± 50	0.663	59 ± 52	56 ± 46	0.366
Sodium (mmol/L)	139 ± 6.7	139 ± 9.4	0.104	138 ± 3.6	138 ± 3.2	0.882
AFP [ng/mL; mean ± SD]	314 ± 1,409	1605 ± 19,060	0.078	287 ± 984	755 ± 3,695	0.981
Performance status 0/1/2/3–4 (%)	100/0/0/0	100/0/0/0	1.000	0/60/32/8	0/61/32/7	0.692
CTP class A/B/C (%)	89/11/0	86/14/0	0.265	62/31/7	61/34/5	0.811
CTP score [mean ± SD]	5.5 ± 0.8	5.6 ± 0.8	0.034	6.6 ± 1.7	6.5 ± 1.6	0.857
Tumor number 1/2/3 (%)	84/12/4	68/19/13	<0.001	75/19/6	68/15/17	0.053
TTV [cm^3; mean ± SD]	9.4 ± 10.8	15.7 ± 15.4	<0.001	12.9 ± 13.7	17.1 ± 17.6	0.129
CLIP 0/1/2/3–6 (%)	69/27/4/0	45/44/11/0	<0.001	37/45/12/6	33/44/17/6	0.768

AFP α-fetoprotein, *ALT* alanine transaminase, *CLIP* Cancer of the Liver Italian Program, *CTP* Child–Turcotte–Pugh, *HBsAg* hepatitis B surface antigen, *HCV* hepatitis C, *INR* international normalized ratio, *PT* prothrombin time, *RFA* radiofrequency ablation, *SD* standard deviation, *TACE* transarterial chemoembolization, *TTV* total tumor volume

Characteristics and Survival of Patients with a Performance Status ≥1

A total of 105 and 85 patients with a performance status ≥1 underwent RFA and TACE, respectively (Table 1). The two groups of patients were similar in baseline demographics, serum biochemistries, and tumor characteristics. Patients with a performance status ≥1 undergoing RFA had similar long-term survival when compared with their TACE counterpart (p = 0.812; Fig. 2b); the 1- and 3-year estimated survival rates in the RFA and TACE groups were 78 versus 76 % and 38 versus 47 %, respectively.

Characteristics and Survival of Patients with a Performance Status of 0 in the Propensity Model

A total of 167 pairs of patients with a performance status of 0 were identified in the propensity model. There were no significant baseline differences in patients with a performance status of 0 receiving RFA or TACE in the propensity model (Table 2). The RFA group had significantly better long-term survival than the TACE group (p = 0.006; Fig. 2c); the 1- and 3-year estimated survival rates in patients receiving RFA and TACE were 90 versus 89 % and 77 versus 62 %, respectively. In the univariate survival analysis, TACE, CLIP score ≥1, CTP class B or C, and serum bilirubin level ≥0.9 mg/dL were associated with decreased long-term survival (all $p < 0.05$; Table 3). In the adjusted Cox proportional hazards model, TACE (HR 1.641; 95 % CI 1.075–2.506; p = 0.022) and CLIP score ≥1 (HR 1.926; 95 % CI 1.211–2.786; p = 0.004) were identified as independent predictors of poor prognosis.

Characteristics and Survival of Patients with a Performance Status ≥1 in the Propensity Model

A total of 68 pairs of patients with a performance status of 0 were identified in the propensity model. There were no significant baseline differences in patients with a performance status ≥1 receiving RFA or TACE in the propensity model (Table 2). Patients with a performance status ≥1 receiving RFA or TACE in the propensity model had similar prognosis (p = 0.813; Fig. 2d); the 1- and 3-year estimated survival rates in patients receiving RFA and TACE were 78 versus 73 % and 39 versus 43 %, respectively. In the univariate analysis, CTP class B or C, CLIP score ≥1 and serum albumin level <3.7 g/dL predicted

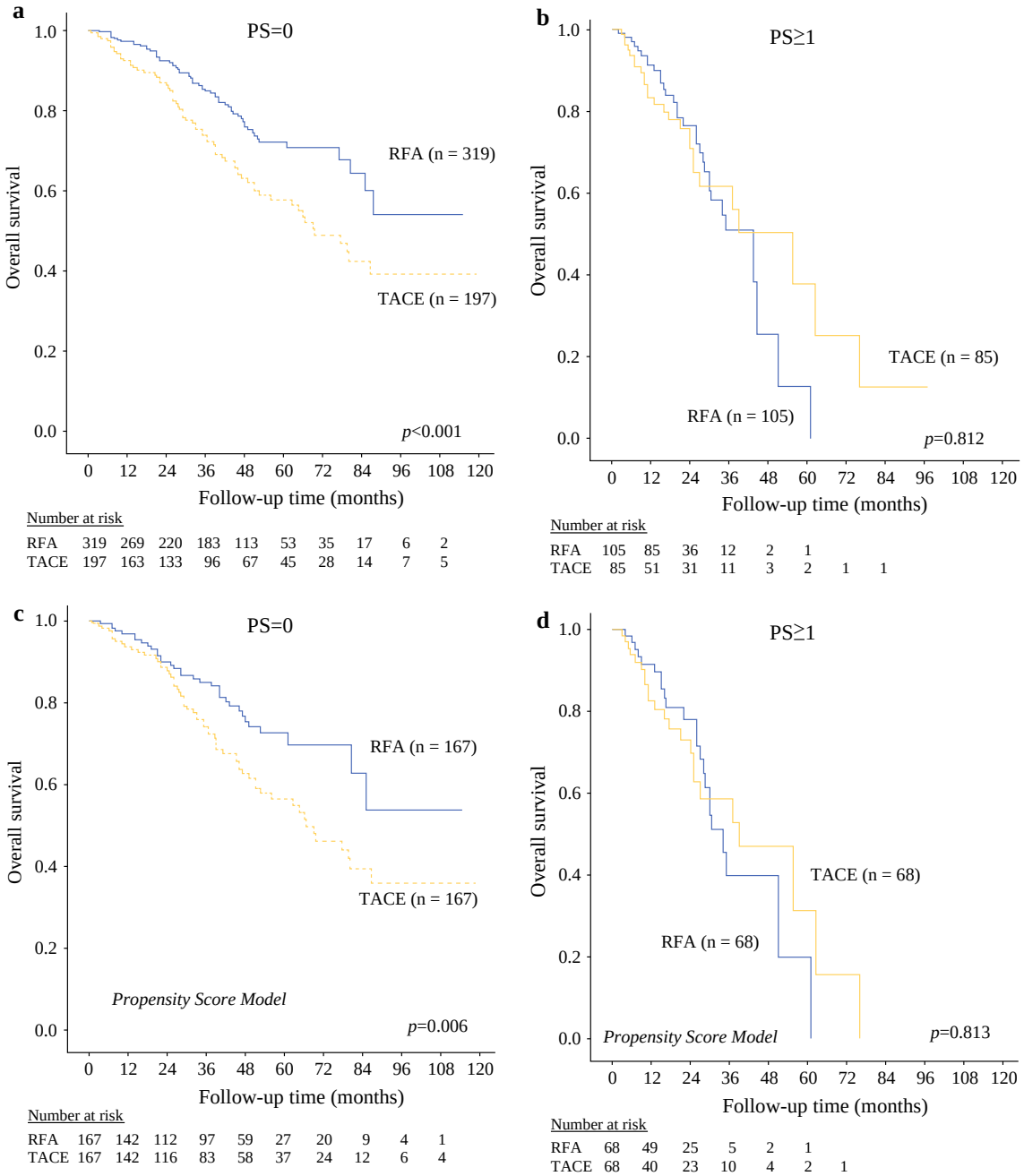

FIG. 2 Comparison of survival between HCC patients within the Milan criteria undergoing RFA or TACE stratified by PS in all study patients and patients selected in the propensity model. Patients with a PS of 0 receiving RFA had significantly better long-term survival than patients undergoing TACE in all patients and in patients selected in the propensity score model [$p < 0.001$ (**a**) and $p = 0.001$ (**c**), respectively]. Alternatively, the long-term survival in patients with a PS ≥ 1 receiving RFA or TACE was similar [$p = 0.812$ (**b**) and $p = 0.813$ (**d**), respectively]. *HCC* hepatocellular carcinoma, *RFA* radiofrequency ablation, *TACE* transarterial chemoembolization, *PS* performance status

decreased survival (all $p < 0.05$; Table 3). In the adjusted Cox proportional hazards model, CTP class B or C (HR 2.456; 95 % CI 1.352–4.462; $p = 0.002$) was the only independent predictor of poor prognosis.

DISCUSSION

There has been insufficient information regarding the selection of treatment in patients with inoperable HCC

TABLE 2 Comparison of baseline demographics between patients undergoing radiofrequency ablation and transarterial chemoembolization stratified by performance status in the propensity score model

Propensity score model	Performance status = 0			Performance status ≥ 1		
	RFA (n = 167)	TACE (n = 167)	p value	RFA (n = 68)	TACE (n = 68)	p value
Age [years; mean ± SD]	68 ± 11	67 ± 11	0.739	69 ± 11	68 ± 11	0.613
Male [n (%)]	119 (71)	115 (69)	0.720	48 (71)	45 (66)	0.713
Positive for HBsAg [n (%)]	80 (48)	74 (44)	0.583	30 (44)	29 (43)	1.000
Positive for anti-HCV [n (%)]	70 (42)	80 (48)	0.322	26 (38)	28 (41)	0.861
Alcoholism [n (%)]	24 (14)	18 (11)	0.410	19 (28)	13 (19)	0.312
Serum biochemistry [mean ± SD]						
Albumin (g/dL)	3.8 ± 0.5	3.8 ± 0.5	0.867	3.5 ± 0.6	3.5 ± 0.6	0.891
Bilirubin (mg/dL)	1.0 ± 0.8	1.1 ± 0.6	0.164	1.2 ± 1.1	1.2 ± 0.8	0.440
Creatinine (mg/dL)	1.0 ± 0.6	1.0 ± 0.5	0.878	1.2 ± 1.1	1.2 ± 1.2	0.401
INR of PT	1.1 ± 0.1	1.1 ± 0.1	0.832	1.1 ± 0.2	1.1 ± 0.2	0.558
ALT (U/L)	68 ± 56	63 ± 51	0.902	60 ± 54	48 ± 32	0.109
Sodium (mmol/L)	140 ± 3	140 ± 3	0.788	138 ± 4	138 ± 3	0.653
AFP [ng/mL; mean ± SD]	160 ± 1,578	1848 ± 20,670	0.365	319 ± 1,138	431 ± 2,756	0.449
Performance status 0/1/2/3–4 (%)	100/0/0/0	100/0/0/0	1.000	0/57/34/9	0/60/32/8	0.689
CTP class A/B/C (%)	87/13/0	86/14/0	0.749	63/31/6	65/32/3	0.704
CTP score [mean ± SD]	5.6 ± 0.9	5.6 ± 0.9	0.793	6.5 ± 1.7	6.4 ± 1.5	0.738
Tumor number 1/2/3 (%)	74/18/8	71/19/10	0.740	72/19/9	73/15/12	0.709
TTV [cm^3; mean ± SD]	13 ± 13	14 ± 13	0.958	14 ± 13	15 ± 16	0.684
CLIP 0/1/2/3–6 (%)	59/35/7/0	46/43/10/1	0.089	37/47/12/4	41/40/15/5	0.846

AFP α-fetoprotein, *ALT* alanine transaminase, *CLIP* Cancer of the Liver Italian Program, *CTP* Child–Turcotte–Pugh, *HBsAg* hepatitis B surface antigen, *HCV* hepatitis C, *INR* international normalized ratio, *PT* prothrombin time, *RFA* radiofrequency ablation, *SD* standard deviation, *TACE* transarterial chemoembolization, *TTV* total tumor volume

within the Milan criteria. Performance status is tightly associated with long-term prognosis and may be useful in guiding treatment selection for HCC.[14] We investigated a large cohort of HCC patients to clarify the impact of performance status on treatment allocation in these patients. Patients within the Milan criteria undergoing RFA or TACE were significantly different in baseline demographics. With propensity-score matching analysis, we were able to generate matched pairs of patients and to compare their outcomes stratified by performance status. For patients with a performance status of 0, TACE was associated with a 78 % increased risk of mortality compared with RFA after adjustment in the Cox multivariate model. However, for patients with a performance status ≥1, TACE was not an independent predictor of poor prognosis. This finding implies that performance status has a differential prognostic impact and could be pivotal to improve the rationale of treatment selection for patients with inoperable HCC within the Milan criteria.

In the current study, survival analysis outside the propensity score model showed significant survival benefits of RFA over TACE for HCC patients within the Milan criteria. However, patients undergoing RFA were less severe in cirrhosis and had smaller tumor volume. The therapeutic advantage of RFA versus TACE could be attributed to the difference in the severity of cirrhosis and extent of tumor burden. Traditional covariance analysis adjustments may be inadequate to eliminate these biases. Propensity-score matching analysis has been advocated to balance the covariates and to reduce biases between two patient groups.[21] With similar baseline characteristics generated by propensity score analysis, it is possible to inspect the impact of performance status on patient survival and treatment allocation.

In the group with a performance status of 0, TACE was identified as an independent predictor of poor prognosis. This finding is consistent in the propensity score model and is confirmed in the Cox multivariate model. Patients with a performance status of 0 and tumor burden within the Milan criteria may receive SR, RFA, or liver transplantation as their primary treatment. Liver transplantation is often limited by donor organ shortage, and the donation rate is exceedingly low in Asia.[8,23] RFA was found to have encouraging results and has been accepted as a relatively safe procedure for small HCC.[24–26] The result is in accordance with previous studies and provides support for the use of RFA in this patient group.[27] Although RFA is considered the treatment of choice for small HCC, a

TABLE 3 Prognostic predictors of survival for patients within the Milan criteria stratified by performance status in the propensity score model

	Performance status = 0					Performance status ≥ 1				
	$n = 334$	Univariate	Multivariate			$n = 136$	Univariate	Multivariate		
		p value	HR	95 % CI	p value		p value	HR	95 % CI	p value
Age (<68/≥68 years)	161/173	0.645				67/69	0.088			
Sex (male/female)	234/100	0.281				93/43	0.105			
HBsAg (negative/positive)	180/154	0.061				77/59	0.873			
Anti-HCV (negative/positive)	184/150	0.115				82/54	0.449			
Alcoholism (no/yes)	292/42	0.674				104/32	0.855			
Albumin (≥3.7/<3.7 g/dL)	199/135	0.053				52/84	0.039			
Bilirubin (<0.9/≥0.9 mg/dL)	175/159	0.010				68/68	0.226			
Creatinine (<0.95/≥0.95 mg/dL)	169/165	0.589				69/67	0.780			
INR of PT (<1.07/≥1.07)	194/140	0.274				44/92	0.583			
ALT (<45/≥45 U/L)	155/179	0.997				74/62	0.857			
Sodium (<140/≥140 mmol/L)	133/201	0.568				75/61	0.806			
AFP (<20/≥20 ng/mL)	156/178	0.146				63/73	0.050			
CTP class (A/B–C)	289/45	0.015				87/49	0.002	2.456	1.352–4.462	0.002
No. of tumors (single/multiple)	242/92	0.084				99/37	0.923			
TTV (<9/≥9 cm^3)	160/174	0.498				65/71	0.124			
CLIP score (0/1–6)	175/159	0.001	1.837	1.211–2.786	0.004	53/83	0.013			
Treatment (RFA/TACE)	167/167	0.006	1.641	1.075–2.506	0.022	68/68	0.813			

Each variable was dichotomized into two groups by the median value for survival prediction. The forepart of variables was set as the reference group in the multivariate analysis

AFP α-fetoprotein, *ALT* alanine transaminase, *CI* confidence interval, *CLIP* Cancer of the Liver Italian Program, *CTP* Child–Turcotte–Pugh, *HBsAg* hepatitis B surface antigen, *HCV* hepatitis C, *HR* hazard ratio, *INR* international normalized ratio, *PT* prothrombin time, *RFA* radiofrequency ablation, *TACE* transarterial chemoembolization, *TTV* total tumor volume

substantial number of patients have undergone TACE as the first-line anticancer treatment for several reasons, including patients' subjective concerns, objective medical parameters, or insurance coverage.[3,28] Our results confirmed that for inoperable HCC patients within the Milan criteria who have good performance status, RFA may confer long-term survival benefits compared with TACE.

Alternatively, in the group with a performance status ≥1, TACE was not identified as a predictor of decreased survival. Patients with a performance status ≥1 are classified as at least BCLC stage C according to the current AASLD and EASL guidelines, and are not good candidates for either RFA or TACE.[2,3] Palliative or investigative therapies have been suggested in these patients; however, little information is available regarding treatment efficacy in patients with small tumor burden and suboptimal performance status. This group of patients typically had locally controllable HCC burden, but their performance status generally precluded these patients from more aggressive treatment. Notably, RFA has been advocated to be used in patients with a performance status of 1.[29] On the other hand, TACE was shown to achieve encouraging outcome in selected patients with advanced HCC with acceptable side effects compared with sorafenib.[30,31] Up to now, the treatment option for patients with limited disease burden but suboptimal performance status is largely unanswered, and the long-term survival in these patients remains unsatisfactory. Our results suggest that RFA and TACE may be equally effective in this clinical setting. Further studies are required to justify our finding in this subgroup of patients.

Survival of HCC patients highly correlates with tumor burden, liver functional reserve, treatment modalities, and performance status. Intensive debates exist on the optimal treatment for different subgroups of patients with variable baseline characteristics. A well-designed, randomized controlled trial with adequate power is usually required to compare RFA and TACE in patients with inoperable HCC within the Milan criteria. However, such trials may be difficult to conduct, and could be unethical because current guidelines consider RFA as the preferred treatment for these patients. With recruitment of a large cohort of patients, we are able to reduce bias by using a propensity-score matching analysis. Our results provide crucial clinical information and are helpful in designing future clinical trials.

This study has a few limitations. First, the retrospective nature makes it vulnerable to potential bias. Even with

careful propensity-score matching analysis with a predefined caliper, these biases may still not be completely avoided. Second, although performance status was determined at the time of diagnosis, inter-observer bias could still exist. Third, this single-center study was performed in the Asia-Pacific region, a highly hepatitis B endemic area, and external validation is needed from different study groups.

CONCLUSIONS

Our results convey strong evidence that for HCC patients within the Milan criteria, RFA provides better long-term survival compared with TACE only in patients with good performance status. For HCC patients eligible for both RFA and TACE, performance status may play a pivotal role in improving treatment allocation.

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DISCLOSURES Po-Hong Liu, Yun-Hsuan Lee, Chia-Yang Hsu, Yi-Hsiang Huang, Yi-You Chiou, Han-Chieh Lin, and Teh-Ia Huo have no conflicts of interest.

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