Hepatic resection or transarterial chemoembolization for hepatocellular carcinoma within Milan criteria

A propensity score matching analysis

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Abstract

This study aimed to compare the long-term survival of patients with hepatocellular carcinoma (HCC) within the Milan criteria who underwent hepatic resection (HR) or transarterial chemoembolization (TACE).

Medical records were retrospectively analyzed for HCC patients within the Milan criteria treated at Affiliated Tumor Hospital of Guangxi Medical University between March 2003 and March 2008, 159 of whom underwent HR and 42 of whom underwent TACE. Long-term overall survival (OS) was evaluated using the Kaplan–Meier method before and after propensity score matching. Cox proportional hazard modeling was used to identify possible predictors of OS.

Propensity score matching was used to generate 32 pairs of patients, for which OS was significantly higher after HR than TACE at 1 year, 96.6% versus 84.4%; 3 years, 75.4% versus 53.1%; 5 years, 48.8% versus 29.7%, respectively ($P = .038$). Among all patients with multinodular HCC (2–3 tumors ≤ 3 cm), HR was also associated with significantly higher OS than TACE at 1 year, 95.2% versus 72.7%; 3 years, 71.4% versus 9.1%; 5 years, 35.1% versus 0%, respectively ($P < .001$). By contrast, among all patients with a single HCC tumor ≤ 5 cm, HR and TACE were associated with similar OS at 1 year, 85.9% versus 90.3%; 3 years, 62.0% versus 61.3%; 5 years, 42.1% versus 33.2%, respectively ($P = .332$).

HR provides survival benefit over TACE in HCC patients within the Milan criteria, especially patients with multinodular HCC involving 2 to 3 tumors ≤ 3 cm. However, HR and TACE appear to be similarly effective for patients with single-tumor HCC ≤ 5 cm.

Abbreviations: AFP = alpha-fetoprotein, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BCLC = Barcelona Clinic Liver Cancer, BMI = body mass index, CT = computed tomography, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HR = hepatic resection, HRs = hazard ratios, OS = overall survival, TACE = transarterial chemoembolization.

Keywords: hepatic resection, hepatocellular carcinoma, Milan criteria, transarterial chemoembolization

1. Introduction

Hepatocellular carcinoma (HCC) is the 5th most common malignancy worldwide and the 3rd-leading cause of cancer-related mortality.[1] According to internationally recognized guidelines of HCC management published by the American Association for the Study of Liver Diseases, liver transplantation is a first-line option for patients with HCC who fit the so-called Milan criteria,[2,3] namely a single tumor with a diameter ≤ 5 cm or 2 to 3 tumors with a maximum diameter ≤ 3 cm, no major vascular invasion, and no extrahepatic metastases.[2] Post-transplantation overall survival (OS) at 5 years among such

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patients can reach more than 70%.[4–6] However, shortage of donor liver tissue and long transplantation queues increase the risk that disease may progress while the patient awaits transplantation. Therefore, clinicians often recommend hepatic resection (HR) for patients who fit the Milan criteria. Postresection OS among such patients can reach up to 50% at 5 years.[7–10]

Recently transarterial chemoembolization (TACE) has emerged as an alternative to HR for treating patients within Milan criteria,[7,11–13] with 1 study suggesting that OS can rival that reported after HR.[7] This use of TACE contrasts with the widely used Barcelona Clinic Liver Cancer (BCLC) staging system, which recommends TACE only for patients with advanced HCC.[14,15] Therefore, the application of TACE to patients with early-stage HCC, including those fitting Milan criteria, remains controversial.

In order to assess the safety and efficacy of TACE for such patients, particularly in comparison with the well-established treatment option of HR, we performed a retrospective analysis of HCC patients satisfying the Milan criteria who were treated by either procedure at Affiliated Tumor Hospital of Guangxi Medical University. To minimize potential bias in the results due to baseline confounders, we also analyzed propensity score-matched pairs of patients.

2. Patients and methods

The study protocol was approved by the Human Research Ethics Committee of the Tumor Hospital of Guangxi Medical University, Nanning, China. Written informed consent was obtained from all patients before they underwent HR or TACE.

2.1. Patients and treatments

Medical records were retrospectively analyzed for all HCC patients who satisfied the Milan criteria,[2] who had Child-Pugh A grade liver function, and who were initially treated at Affiliated Tumor Hospital of Guangxi Medical University with HR or TACE between March 2003 and March 2012. Patients who satisfied the indications for both HR and TACE were treated with HR, unless they specifically requested TACE. The following were indications for HR: lack of ascites, hypersplenism, Child-Pugh A liver function, and adequate residual liver as determined by volumetric computed tomography (CT).[16] The HR technique was performed as described.[17,18] Indications for TACE were Child-Pugh A liver function, lack of ascites or main portal vein tumor thrombus, and presence of hypervascular tumors on dynamic imaging.[7] The TACE technique was performed as described.[18,19] CT was performed 1 month after the last course to assess lipiodol retention within the tumor and residual viable tumor tissue. Complete response to TACE was defined as homogeneous, dense lipiodol uptake with no additional contrast enhancement. TACE was repeated at intervals of 4 to 8 weeks until one of the following end points was reached: complete response; failure to embolize the residual tumor, such as in the case of tumors supplied only by an extrahepatic collateral artery; development of contraindications to TACE; or patient refusal of further treatment.[18]

2.2. Propensity score matching

To reduce bias in our analyses arising from the fact that patients were not randomized to receive HR or TACE, such that the 2 treatment groups may have had confounding differences at baseline, we used logistic regression to generate propensity scores for all patients. The regression model incorporated the following clinical variables that previous work has suggested to be important for outcomes[20]: age; gender; body mass index; hepatitis B virus (HBV) infection status; family history of HCC; levels of alpha-fetoprotein (AFP), total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and albumin; prothrombin time; platelet count; and tumor size and number. Matching was performed using a 1:1 ratio without replacement and a caliper width of 0.1. The resulting subset of score-matched pairs was analyzed as indicated in Section 3.

2.3. Follow-up

Patients were followed up at 1 month after HR or TACE, every 3 months for the rest of the 1st year, and every 6 months thereafter. Follow-up visits comprised physical examination, liver function tests, serum AFP assay, abdominal ultrasonography, and liver CT or magnetic resonance imaging. Follow-up was conducted until death or 5 years after initial HR or TACE, which ever occurred earlier. Patients still alive at 5 years were defined as having a survival time of 5 years.

2.4. Statistical analysis

All analyses were performed using SPSS 19.0 (IBM, New York). Intergroup differences in categorical data were assessed for significance using the chi-squared test; differences in continuous data were assessed using the t test or Mann–Whitney U test. Survival was analyzed using the Kaplan–Meier method, and differences between treatment arms were assessed for significance using the log-rank test. Cox regression was used to assess clinicopathological variables for their ability to predict OS. Whenever possible, outcomes were reported using hazard ratios (HRs) and associated 95% confidence intervals (95% CIs). The threshold of significance in all analyses was defined as a 2-sided $P < .05$.

3. Results

3.1. Clinicopathological characteristics (all patients)

During the study period, 2195 patients with HCC were admitted to our hospital, of whom 553 (25%) had received initial HCC treatment at other centers and so were excluded from our study. Among the remaining 1642 patients, 245 (15%) satisfied the Milan criteria and were treated initially with HR or TACE at our center. Of these, 44 (18%) were excluded from our study because they had Child-Pugh B or C liver function (n = 34) or were lost to follow-up (n = 10). In the end, our study contained the remaining 201 (82%) with Child-Pugh A liver function, of whom 159 were treated by HR and 42 were treated by TACE.

Comparison of the 2 treatment groups (Table 1) showed that they were similar in gender distribution, age, prevalence of HBV, platelet count, and tumor size, as well as serum levels of AFP, bilirubin, AST, and ALT (all $P > .05$). The HR group showed significantly higher serum albumin, platelet count, and prevalence of solitary tumors (all $P < .05$). The TACE group showed significantly longer prothrombin time ($P = .024$).

3.2. Mortality and morbidity (all patients)

No study patients died within 30 days of HR or TACE, and 90-day mortality was similar between the HR group (3.1%) and TACE group (4.8%, $P = .611$). Based on Clavien–Dindo classification of complications, the 2 groups showed a similar

Table 1

Clinicopathological variables in hepatocellular carcinoma patients within Milan criteria treated by HR or TACE.

Variables	Before propensity score matching			After propensity score matching		
	HR (n=159)	TACE (n=42)	P	HR (n=32)	TACE (n=32)	P
Male, n (%)	137 (86.2)	38 (90.5)	.459	27 (84.4)	28 (87.5)	.719
Age, y	47.9±10.4	50.8±12.9	.136	50.4±8.8	48.6±13.3	.53
BMI, kg/m^2	22.1±3.2	22.8±2.5	.076	22.6±3.6	22.9±2.8	.265
HBsAg-positive, n (%)	144 (90.6)	38 (90.5)	.986	27 (84.4)	29 (90.6)	.45
AFP ≥ 400 ng/mL, n (%)	45 (2.3)	14 (33.3)	.524	12 (37.5)	12 (37.5)	1.000
Total bilirubin, μmol/L	15.7 (11.5–18.5)	19.6 (11.9–21)	.09	14.1 (11.5–18.5)	17.0 (11.9–21)	.783
ALT, U/L	54.7 (30–61)	55.5 (30.8–59.3)	.643	42 (30–61)	41.5 (30.8–59.3)	.672
AST, U/L	49.4 (32–54)	53.3 (30.8–67.3)	.36	40 (32–54)	41 (30.8–67.3)	.436
Albumin, g/L	39.6±4.4	36.9±5.7	.001[*]	37.5±3.3	38.3±5	.473
Prothrombin time, s	13.4±1.8	14.2±2.4	.024[*]	14.1±1.6	13.7±1.6	.348
Platelet count, 10^9/L	165.9±66.6	118.0±57.4	<.001[*]	129.4±55.0	133.4±54.6	.771
Tumor size, cm	3.2±1.1	3.4±0.9	.308	3.3±1	3.5±1	.432
Solitary tumor, n (%)	138 (86.8)	31 (73.8)	.041[*]	28 (87.5)	26 (81.3)	.491

Data are mean ± standard deviation or median (interquartile range), unless otherwise indicated.

[*] $P < .05$ was considered statistically significant.

AFP = alpha-fetoprotein, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, HR = hepatic resection, TACE = transarterial chemoembolization.

distribution of severity grades (Table 2). The most frequent complication was pulmonary infection among HR patients (5%) and acute hepatic function failure among TACE patients (4.7%).

3.3. OS (all patients)

Median follow-up was 39 months in the HR group and 33 months in the TACE group. The proportion of patients dying during follow-up due to HCC or complications related to underlying liver disease was similar in the HR group (n=85, 54%) and in the TACE group (n=29, 69%; P=.07). However, OS was significantly higher in the HR group at 1 year, 87.1% versus 85.7%; 3 years, 63.3% versus 43.6%; 5 years, 41.3% versus 26%, respectively (P=.028; Fig. 1).

Dichotomized factors linked to survival were included in the survival analysis. Univariate analysis identified several factors significantly associated with poor OS: serum AFP level ≥400 ng/mL, platelet count <100 × 10^9/L and TACE treatment (Table 3). Of these factors, serum AFP level ≥400 ng/mL and TACE treatment were identified in multivariate Cox proportional hazard modeling as independent predictors of poor OS.

3.4. Subgroup analysis (all study patients)

All patients in the cohort were stratified by tumor number and treatment. Among patients with multinodular HCC involving

2 to 3 tumors ≤3 cm, HR (n=21) was associated with significantly higher OS rates than TACE (n=11) at 1 year, 95.2% versus 72.7%; 3 years, 71.4% versus 9.1%; 5 years, 35.1% versus 0.0%, respectively (P<.001; Fig. 2). Among patients with a single HCC tumor ≤5 cm, OS was similar between the HR (n=138) and TACE (n=31) groups at 1 year, 85.9% versus 90.3%; 3 years, 62.0% versus 61.3%; 5 years, 42.1% versus 33.2%, respectively (P=.389; Fig. 3).

3.5. Clinicopathological characteristics (propensity-score-matched patients)

Propensity score matching (1:1 ratio) based on variables associated with therapeutic strategy and long-term prognosis generated 32 pairs of patients from each treatment arm. The pairs were similar across all baseline characteristics examined (Table 1).

3.6. OS (propensity-score-matched patients)

As in the analysis of all patients in our cohort, analysis of propensity score-matched patients showed significantly higher
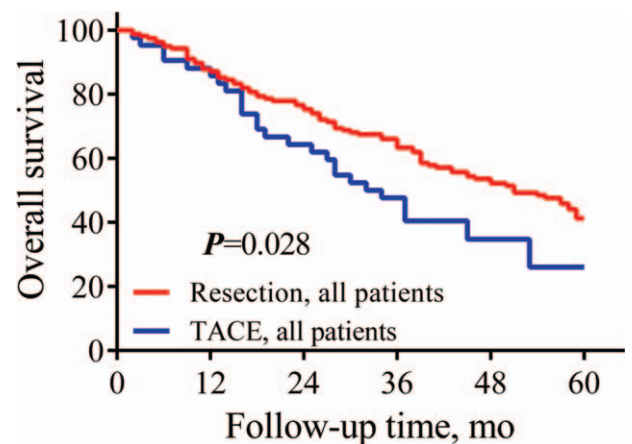
Table 2

Clavien–Dindo classification of postoperative complications in patients with hepatocellular carcinoma within Milan criteria treated by HR or TACE.

Grade	n (%)		
	HR (n=159)	TACE (n=42)	P
I	5	1	.601
II	9	3	
III-a	6	1	
III-b	2	0	
IV-a	1	0	
IV-b	0	0	
V	1	0	

HR = hepatic resection, TACE = transarterial chemoembolization.

Figure 1. Overall survival in patients with hepatocellular carcinoma within Milan criteria following hepatic resection or transarterial chemoembolization (TACE). Resection was associated with significantly better long-term survival.

Table 3

Univariate and multivariate analyses to identify predictors of poor overall survival in patients with hepatocellular carcinoma within Milan criteria.

Variables	Univariate analysis			Multivariate analysis		
	HRs	95% CI	P	HRs	95% CI	P
Male gender	0.94	0.554–1.595	.819			
Age (≥50 y)	1.145	0.760–1.723	.518			
BMI (≥25 kg/m^2)	0.878	0.58–1.329	.538			
HBsAg-positive	1.64	0.799–3.367	.178			
AFP (≥400 ng/mL)	1.639	1.115–2.410	.012[*]	1.729	1.168–2.56	.006[*]
Total bilirubin (>17.1 μmol/L)	1.263	0.866–1.842	.226			
ALT (≥80 U/L)	0.757	0.396–1.45	.401			
AST (≥80 U/L)	1.303	0.745–2.28	.354			
Albumin (<35 g/L)	1.407	0.868–2.282	.166			
Prothrombin time (>14 s)	0.929	0.624–1.384	.718			
Platelet count (<100 × 10^9/L)	1.561	1.017–2.396	.041[*]			
Tumor size (>3 cm)	1.209	0.8–1.827	.368			
Tumor number (multiple)	1.497	0.937–2.392	.091			
Treatment (TACE)	1.61	1.052–2.462	.028[*]	1.579	1.031–2.418	.036[*]

[*] $P < .05$ was considered statistically significant.

AFP = alpha-fetoprotein, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, CI = confidence interval, HRs = hazard ratios, TACE = transarterial chemoembolization.
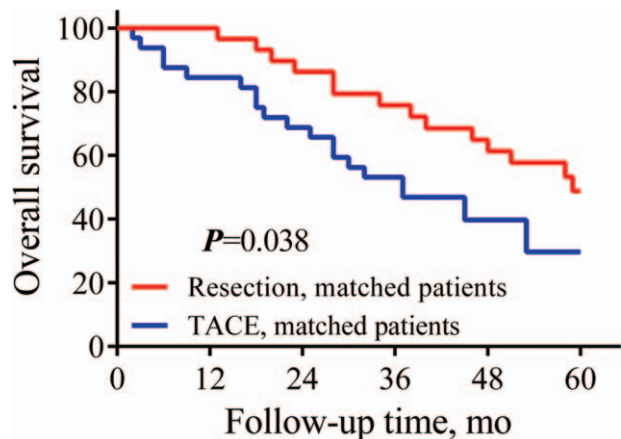

Figure 2. Overall survival in patients with multinodular hepatocellular carcinoma involving 2 to 3 tumors ≤3 cm following hepatic resection or transarterial chemoembolization (TACE). Resection was associated with significantly better long-term survival.
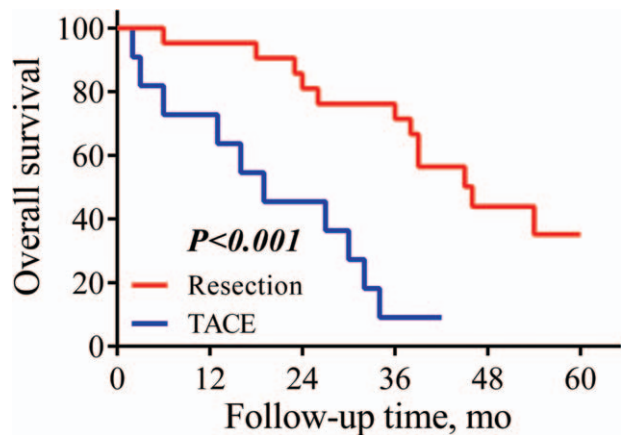
OS rates in the HR group at 1 year, 96.6% versus 84.4%; 3 years, 75.7% versus 53.1%; 5 years, 48.8% versus 29.7%, respectively ($P = .038$; Fig. 4).

4. Discussion

The present retrospective study suggested that HR was associated with significantly higher survival rates than TACE in HCC patients within the Milan criteria, especially patients with multinodular HCC involving 2 to 3 tumors ≤3 cm. By contrast, TACE and HR show comparable efficacy in patients with single-tumor HCC ≤ 5 cm.

While liver transplantation is considered the most effective treatment for HCC, many patients can not benefit from this procedure because donor livers are unavailable, or their disease progresses while they await transplantation. HR has been used as an alternative to transplantation for HCC patients who fulfill the Milan criteria and have Child-Pugh A grade liver function.[9,10,21] Some studies suggest similar or even better OS after HR than after
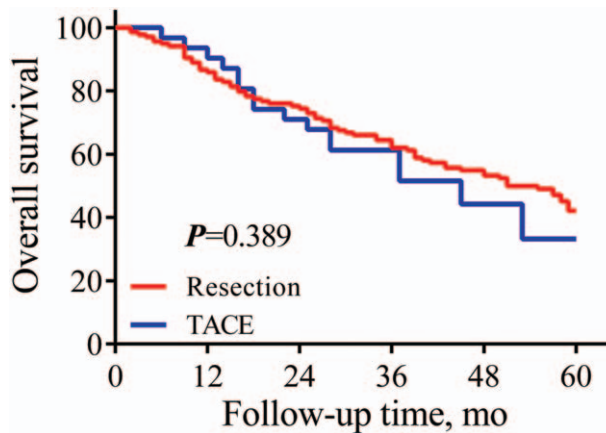

Figure 3. Overall survival in patients with a single hepatocellular carcinoma tumor ≤5 cm following hepatic resection or transarterial chemoembolization (TACE). Hepatic resection and TACE appear to be similarly effective.

Figure 4. Overall survival in propensity score-matched patients with hepatocellular carcinoma within Milan criteria following hepatic resection or transarterial chemoembolization (TACE). As in the unmatched cohort, resection was associated with significantly better long-term survival.

transplantation in such patients,[9,10] and the BCLC staging system recommends HR as a first-line treatment.

TACE is considered as a useful palliative treatment for advanced HCC in patients with adequate liver function.[22] Randomized controlled trials have shown that OS of patients with unresectable tumors is better after TACE than with conservative treatment.[15,23] Several studies have attempted to apply TACE as another alternative for HCC patients within Milan criteria,[11–13] with 1 study suggesting 5-year OS rates of 52%, similar to HR (57%).[7] These mixed results may reflect differences in which clinicopathological variables are used to choose the best treatment option. Actually, the bias could be addressed in controlled trials in which HCC treatment is allocated randomly rather than based on clinicopathological assessment, but such a design may raise ethical questions.

Since few studies have compared the 2 treatments in parallel while also controlling for baseline differences, we undertook a retrospective study to compare how well TACE compares to HR for patients within the Milan criteria. Our results suggest that HR provides a survival benefit over TACE in HCC patients within the Milan criteria, and this result was confirmed after using propensity score matching to generate patient pairs with no significant baseline differences. Our findings of a large survival benefit of HR for HCC patients within the Milan criteria are consistent with several previous findings.[11–13]

Our finding of OS benefit for HR over TACE for patients with multinodular HCC is consistent with a previous study by Kanematsu et al,[24] as is our finding of similar OS with HR or TACE in patients with single HCC.[25] These results can be attributed to different clinicopathological characteristics, tumor status, or treatment techniques. These results suggest that tumor number may be the most important factor for deciding between HR and TACE as initial treatment for patients meeting the Milan criteria and having compensated liver function. Among patients with single HCC up to 5 cm, TACE can be substituted for HR if appropriate.

The findings of our study should be interpreted with caution in light of several limitations. One is that nearly all our patients had chronic HBV infection and although the prevalence was similar in each treatment arm, we did not take into account possible differences in severity of infection, virus activity, or history of antiretroviral therapy. Another limitation is that we did not take into account possible differences between TACE patients depending on the number of treatment cycles they received. Preliminary work from our group suggests that OS is significantly higher for patients receiving ≥3 cycles of TACE than for those receiving <3 cycles.[26] A third limitation is that the prevalence of single-nodule HCC was much higher than that of multinodular HCC in our cohort, raising the possibility that our results may not be generalizable to other patient populations meeting Milan criteria. Finally, the retrospective nature of our study raises the risk of confounding, despite our use of propensity score matching. Our results should be verified in randomized studies, preferably involving patient populations at multiple sites.

Despite these limitations, our study further confirms the excellent long-term OS that can be obtained using HR rather than transplantation for HCC patients meeting the Milan criteria. This is an important result in light of growing shortages of donor livers and lengthening transplantation queues. In addition, our study helps identify subgroups of patients for whom HR may be much better than TACE or for whom the 2 treatments may give comparable outcomes. These insights may help guide treatment decisions, and they strengthen the case for updating international treatment guidelines such as the BCLC staging system.

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