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Clinical impact of the treatment modality on small, solitary, recurrent intrahepatic hepatocellular carcinomas after primary liver resection

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Purpose: The aim of this study was to determine the survival benefit based on different treatment strategies in patients with small, solitary, recurring intrahepatic hepatocellular carcinomas (HCCs) that were defined as recurred Barcelona Clinic Liver Cancer stage 0 (reBCLC-0).
Methods: Among the 917 patients with HCC recurrence after primary hepatic resection, 394 patients with reBCLC-0 were selected. Of these, 150 patients underwent curative treatment (re-resection, radiofrequency ablation, and liver transplantation) and 203 underwent transarterial chemoembolization (TACE) group for recurrent HCC. After propensity score matching (PSM), both the groups were well balanced (89 patients in each group).
Results: Before PSM, the 1-, 3-, and 5-year overall survival (OS) rates of patients in the curative treatment group (96.7%, 78.6%, and 70.5%, respectively) were significantly better than those in the TACE treatment group (95.6%, 53.7%, and 44.2%, respectively) ($P < 0.001$). After PSM, the 1-, 3-, and 5-year OS rates also differed significantly (92.0%, 79.6%, and 71.1% in the curative treatment group *vs*. 88.8%, 65.6%, and 57.9% in the TACE group) ($P = 0.005$). The independent predictors of worse OS were tumor number at the time of resection and treatment modality for the recurrence, time interval to recurrence, and prothrombin time international normalized ratio and alpha-fetoprotein levels at the time of recurrence.
Conclusion: The OS of patients in the curative treatment group was better than that in the non-curative treatment group after PSM. Based on our results, curative treatment should be strongly recommended in the patients with reBCLC-0 recurrence for better survival.
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Key Words: Hepatocellular carcinoma, Treatment outcome, Propensity score match, Recurrence, Resection

INTRODUCTION

Hepatocellular carcinoma (HCC) is the second leading cause of cancer-related deaths worldwide [1]. The Barcelona Clinic Liver Cancer (BCLC) staging system has been widely accepted as a guideline for HCC treatment [2]. According to this system, liver resection, liver transplantation (LT), and local ablation are curative treatment modalities that improve survival outcomes in selected patients with good reserve liver function. Among these modalities, LT results in the best survival outcome. However, liver resection remains the first-line treatment option in many centers because of the severe organ shortage and increased waiting time. Over the past decade, the survival outcome of patients after liver resection has improved significantly because of advances in surgical skills and devices as well as postoperative management. However,

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long-term survival outcomes are unsatisfactory owing to the high recurrence rate after treatment [3-7]. Most studies show a high incidence of intrahepatic HCC recurrence [8-12]. Moreover, to date, well-designed comparative studies on the treatment of intrahepatic HCC recurrence are sparse, and it is still unclear which treatment modality will guarantee better survival outcomes in patients with intrahepatic HCC recurrence.

Therefore, this study aimed to investigate the survival outcomes according to the treatment modality in selected patients with small (<2 cm), solitary, intrahepatic recurrent HCCs after primary liver resection that were classified as recurred Barcelona Clinic Liver Cancer stage O (reBCLC-O) and to determine the risk factors associated with survival outcomes in these patients.

METHODS

This study included all the patients with HCC recurrence who underwent primary hepatic resection at the Seoul National University Hospital and Samsung Medical Center in Korea, between 2005 and 2011. To evaluate survival outcome according to the treatment modality, patients with intrahepatic reBCLC-O were divided into 2 groups; the curative treatment group (treated with re-resection, salvage LT, or radiofrequency ablation [RFA]) and the transarterial chemoembolization (TACE) group.

The reBCLC-O was defined as a small (<2 cm), solitary HCC with a performance status score of 0–1 and Child-Pugh score A or B, regardless of the primary HCC stage and time interval to recurrence.

After primary hepatic resection, all patients were followed up every 3–4 months to check for recurrence by monitoring α-FP levels and using dynamic CT or MRI. Hepatic recurrence was defined as new lesions observed with at least one imaging modality according to the guidelines provided by the European Association for Study of the Liver and Korean Association for Study of the Liver [13,14].

Statistical analysis was performed using IBM SPSS Statistics ver. 20 (IBM Corp., Armonk, NY, USA). Categorical data were compared using the Pearson chi-square test or Fisher exact test, as appropriate. Continuous data were compared using the Wilcoxon rank-sum test. A P-value of <0.05 was considered to indicate statistical significance. The overall survival (OS) rate was defined as the interval between the time of recurrence and patient's death. Survival curves were generated using the Kaplan-Meier method and compared using the log-rank test. To determine the risk factors for OS in the entire cohort, a stratified Cox proportional hazard regression model was used.

The propensity score matching (PSM) method was performed for 1:1 matching of the primarily selected 353 patients. The 2 matched groups (i.e., the curative resection group and the TACE group) were compared to examine co-variable balance and determine any significant differences in baseline co-variables. Propensity score values were generated for characteristics at baseline (age, sex, tumor size, and albumin level) and the time

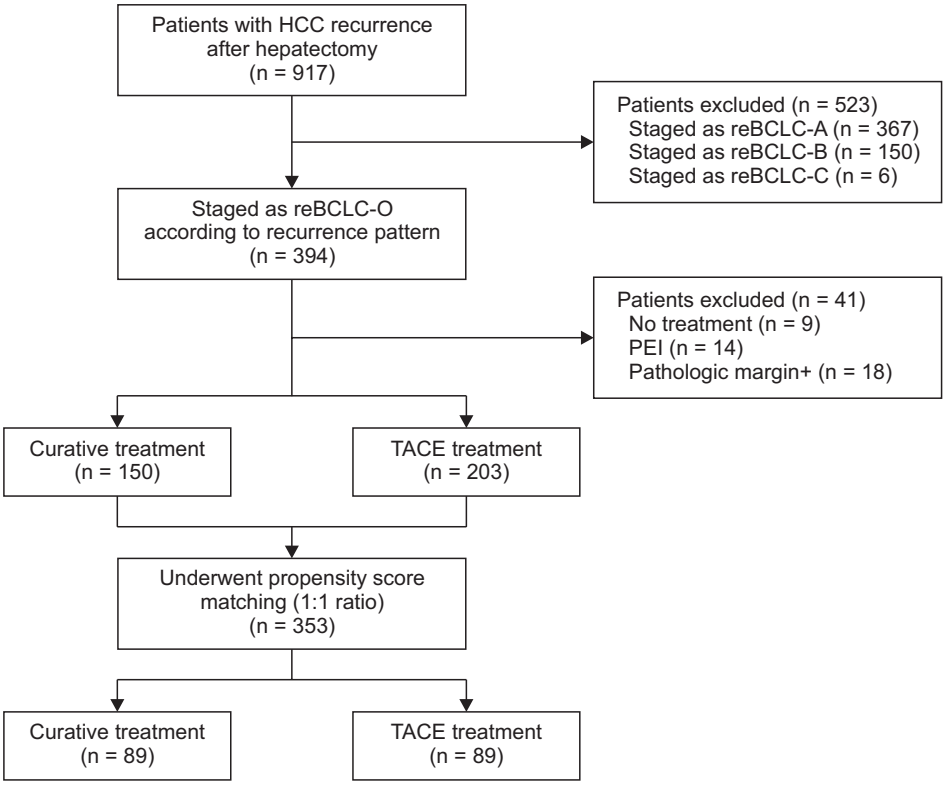

Fig. 1. Flow chart of patients' selection. HCC, hepatocellular carcinoma; reBCLC, recurred Barcelona Clinic Liver Cancer; reBCLC-O, reBCLC stage O; PEI, percutaneouse ethanol injection; TACE, transarterial chemoembolization.

Table 1. Baseline characteristics before and after propensity score matching

Characteristic	Before matching			After matching		
	Curative treatment	TACE treatment	P-value	Curative treatment	TACE treatment	P-value
No. of patients	150	203		89	89	
Clinical data at the time of hepatic resection						
Age ≤ 60 yr	111 (74.0)	140 (69.0)	0.342	69 (77.5)	60 (67.4)	0.179
Male sex	130 (86.7)	170 (83.7)	0.547	78 (87.6)	74 (83.1)	0.525
Child-Pugh classification A–B						
A	134 (89.3)	185 (91.1)	0.588	78 (87.6)	83 (93.3)	0.308
HBV-related	111 (74.0)	136 (66.9)	0.080	70 (78.6)	66 (74.1)	0.507
HCV-related	13 (8.6)	18 (8.8)	>0.999	6 (6.7)	8 (8.9)	0.590
Tumor size on imaging (cm)	4.2 ± 2.9	5.33 ± 3.8	0.003	4.1 ± 2.7	3.9 ± 2.3	0.479
No. of tumors	1.2 ± 0.6	1.37 ± 1.0	0.074	1.1 ± 0.4	1.3 ± 0.6	0.055
Bilirubin ≤ 1.2 mg/dL	120 (80.0)	175 (86.2)	0.146	19 (21.3)	14 (15.7)	0.441
INR ≤ 1.1	120 (80.0)	149 (73.3)	0.120	13 (14.6)	20 (22.4)	0.247
Creatinine ≤ 1.2 mg/dL	133 (88.7)	187 (92.1)	0.261	8 (9.0)	7 (7.9)	>0.999
Albumin ≤ 3.5 g/dL	9 (6.0)	30 (14.8)	0.010	6 (6.7)	9 (10.1)	0.591
Platelet count ≤ 100 × 10^3/μL	31 (20.7)	34 (16.7)	0.405	18 (20.2)	13 (14.6)	0.430
Pathologic data						
Vascular invasion-macroscopic						
Positive	41 (27.3)	46 (22.6)	0.606	26 (29.2)	16 (17.9)	0.201
Vascular invasion-microscopic						
Positive	63 (42.0)	90 (44.3)	0.666	40 (44.9)	42 (47.2)	0.881
Histologic grade, worst grade[a]						
III, IV	56 (37.3)	84 (41.4)	0.509	32 (36.0)	29 (32.6)	0.752
Characteristics of patients at time of recurrence						
Recurrence time interval						
≤12 mo	57 (38.0)	130 (64.0)	<0.001	40 (44.9)	41 (46.1)	>0.999
α-FP > 200 ng/mL	11 (7.3)	46 (22.6)	<0.001	8 (9.0)	6 (6.7)	0.782
Bilirubin ≤ 1.2 mg/dL	127 (84.7)	178 (87.7)	0.435	15 (16.9)	7 (7.9)	0.109
INR ≤ 1.1	77 (51.3)	86 (42.3)	0.055	34 (38.2)	41 (46.0)	0.437
Creatinine ≤ 1.2 mg/dL	128 (85.3)	178 (87.6)	>0.999	4 (4.4)	7 (7.8)	0.535
Albumin ≤ 3.5 g/dL	131 (87.3)	162 (79.8)	0.064	11 (12.4)	16 (18.0)	0.404
Treatment modality						
TACE	NA	203 (100)		NA	89 (100)	
RFA	109 (72.7)	NA		63 (70.8)	NA	
Resection	28 (18.6)	NA		19 (21.3)	NA	
Salvage transplantation	12 (8.0)	NA		7 (7.9)	NA	

Values are presented as number only, number (%), or mean ± standard deviation.
TACE, transarterial chemoembolization; RFA, radiofrequency ablation; NA, not applicable.
[a]Edmondson-Steiner grade.

of recurrence (time interval to recurrence and α-FP level).

This study was performed in accordance with the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Institutional Review Boards of Samsung Medical Center (2013-05-013) and Seoul National University Hospital (H1303-061-474). This study does not require patient consent.

RESULTS

Among 917 patients with HCC recurrence after primary hepatic resection, 394 patients with reBCLC-O were selected (Fig. 1). Untreated patients (n = 9), patients who received percutaneous ethanol injection (n = 14), and patients who had positive pathologic margins (n = 18) were excluded. No patient underwent systemic therapy for reBCLC-O. Among the 353 included patients, 150 (42.5%) were in the curative treatment group and 203 (57.5%) in the TACE group. Several characteristics of the patients were significantly different between the 2 groups (Table 1). In the curative treatment group, we observed smaller tumors, lower baseline albumin levels, patients with a time interval of ≤12 months until tumor recurrence, and lower α-FP levels at the time of recurrence ($P < 0.05$ for all).

After PSM, both groups were well matched (89 patients in each group); the patient characteristics are summarized in Table 1. Of the 89 patients in the curative treatment group, 63 (70.8%) underwent RFA, 19 (21.3%) underwent re-resection, and 7 (7.9%) underwent salvage LT.

OS after recurrence

Before PSM, the patients in the curative treatment group exhibited a significantly better OS than those in the TACE treatment group ($P < 0.001$) (Fig. 2A). The estimated 1-year, 3-year, and 5-year OS rates were 96.7%, 78.6%, and 70.5%, respectively, for the curative treatment group and 95.6%, 53.7%, and 44.2%, respectively, for the TACE treatment group.

After PSM, there was a significant difference in the OS between the groups ($P = 0.005$) (Fig. 2B). The estimated 1-year, 3-year, and 5-year OS rates were 92.0%, 79.6%, and 71.1%, respectively, for the curative treatment group and 88.8%, 65.6%, and 57.9%, respectively, for the TACE treatment group.

Analysis of the prognostic factors for OS

After PSM, the prognostic factors among the baseline characteristics were analyzed using a Cox proportional hazards model. Univariate analysis of baseline characteristics revealed that the primary prognostic factor for worse OS was the initial number of tumors (hazard ratio [HR], 0.40; 95% confidence interval [CI], 0.23–0.67; $P = 0.001$). Univariate analysis of the factors at the time of recurrence revealed that the prognostic factors for worse OS were treatment for recurrence (HR, 0.49; 95% CI, 0.30–0.81; $P = 0.006$), time interval to recurrence (HR, 0.45; 95% CI, 0.27–0.75; $P = 0.002$), INR level (HR, 0.32; 95% CI, 0.18–0.55; $P < 0.001$), albumin level (HR, 4.95; 95% CI, 1.82–13.46; $P = 0.002$), and α-FP level (HR, 0.44; 95% CI, 0.21–0.89; $P = 0.024$; Table 2).

Multivariate analysis revealed that the independent risk factors for worse OS were the initial number of tumors (HR, 0.43; 95% CI, 0.25–0.76; $P = 0.004$) among the baseline characteristics and treatment for the recurrence (HR, 0.43; 95% CI, 0.25–0.77; $P = 0.004$), time interval to recurrence (HR, 0.47; 95% CI, 0.27–0.82; $P = 0.008$), INR level at the time of recurrence (HR, 0.39; 95% CI, 0.22–0.69; $P = 0.001$) and α-FP level at the time of recurrence (HR, 0.33; 95% CI, 0.15–0.72; $P = 0.006$; Table 2).

DISCUSSION

In the present study, we demonstrated that curative treatment is the preferred option for patients with small (<2 cm), solitary, recurring intrahepatic HCC carcinoma that was defined as reBCLC-O. There were 2 major findings. One is that curative treatment did result in significantly better survival outcomes than TACE after patient selection using PSM. The second finding was that curative treatment was an independent prognostic factor in multivariate analysis.

Several curative treatments have been proposed for early-stage intrahepatic recurrent HCC over the past decades. Curative treatments consist of 3 treatment modalities: repeated hepatectomy, RFA, and salvage LT. Repeated hepatectomy has provided favorable outcomes in treating recurrent HCC; however, only a minority of patients are eligible for this because most patients have liver cirrhosis [15-17]. Therefore, a strategy of primary resection and salvage LT for intrahepatic recurrent HCC has been suggested [18,19]. This strategy showed the best long-term survival outcome among the curative treatments; the outcome was comparable to that of primary LT. In several studies, RFA has yielded a survival outcome comparable to that of repeated hepatectomy. This is considered more effective and safer than repeated resection in the aspects of lower severity; when compared to repeated hepatectomy, RFA shows a lower incidence of complication [20-22].

The results of the studies mentioned above support our results. One of the limitations seen in these studies was that the indications for each treatment modality were not consistent. To overcome this issue, this study limited the size and number of recurrent tumors, which enabled us to define specific treatment targets. In addition, this study is unique in that the results were derived using PSM to overcome the limitation of the retrospective study design.

Our study demonstrated that a single tumor at an initial stage, longer time interval to recurrence (more than 12 months), normal INR value, and lower serum α-FP level (<200 ng/mL) were correlated with better patient survival.

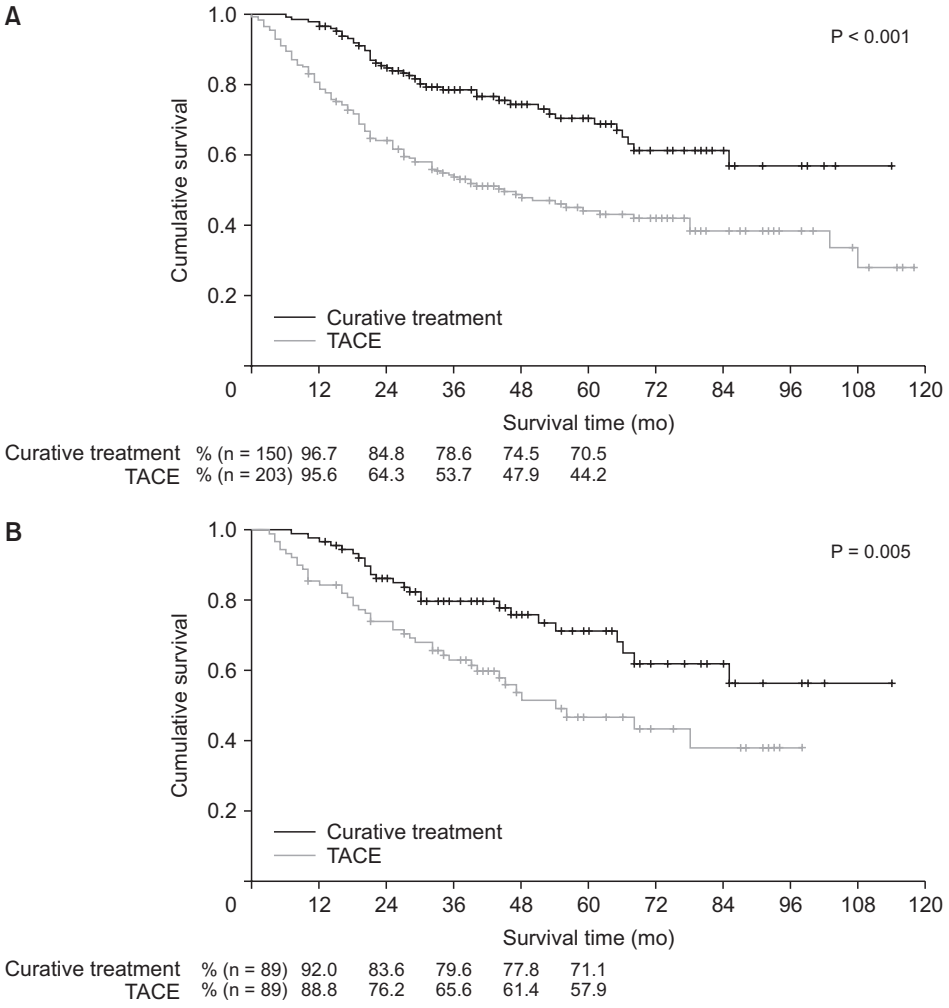

Fig. 2. Overall survival rates of patients in the curative and transarterial chemoembolization (TACE) treatment groups before (A) and after (B) propensity score matching.

The causes of tumor recurrence after hepatic resection may vary depending on the timing of the recurrence after initial treatment. In many studies, early recurrence means recurrence within 1 year after surgery caused by micrometastasis around the tumor at the time of surgery, and late recurrence means recurrence of *de novo* tumor in background cirrhosis [23-25].

Among these, the number of tumors and recurrence time interval have been considered as the tumor characteristics that are strongly correlated with the survival outcome [19,26,27]. It is noteworthy that the initial tumor characteristics have a significant impact on patient survival after recurrence. Several studies have reported that α-FP and INR levels are also closely related to the prognosis in the setting of primary resection. The α-FP has value both as a prognostic marker and predicting the response to therapy [28]. INR level is well known and widely used as a component of the model for end-stage liver disease score, which predicts survival expectancy in end-stage liver disease [29]. However, our study demonstrates that the α-FP and INR levels even at the time of recurrence have an impact on the survival outcome.

Therefore, initial tumor characteristics as well as the liver function and α-FP level at the time of recurrence should be considered as impact factors that influence the outcome of treatment in the reBCLC-O patient group.

This study has some limitations. A selection bias was present as the study had a retrospective design. The choice of treatment modality might have been influenced by patient characteristics and preferences owing to the lack of guidelines for treatment of HCC recurrence. Thus, the patients in the 2 groups exhibited some differences in clinicopathological characteristics, which may have acted as confounders that affected the oncologic outcome. Nevertheless, the results of our study are significant because several confounding factors were corrected for using PSM. Therefore, the results of this study could help in deciding a suitable treatment modality for patients with recurrent HCC.

In conclusion, the OS of patients in the curative treatments group was better than that of patients in the TACE treatment group after PSM. Curative treatments for recurred HCC, the nature of the original HCC (number and time interval to recurrence), and the INR and α-FP levels at the time of

Table 2. Cox proportional hazards analysis of prognostic factors for overall survival

Variable	Univariable analysis			Multivariable analysis		
	B	HR (95% CI)	P-value	B	HR (95% CI)	P-value
Prognostic factor at initial stage						
Age (yr), >60 *vs*. ≤60	0.07	1.08 (0.65–1.79)	0.769			
Sex, male *vs*. female	0.25	1.28 (0.69–2.40)	0.425			
Child-Pugh grade, B *vs*. A	–0.03	1.00 (0.45–2.19)	0.994			
HBV-related	–0.40	0.66 (0.31–1.47)	0.318			
HCV-related	0.06	1.07 (0.46–2.49)	0.873			
Tumor size (cm), >5	–0.34	0.71 (0.41–1.23)	0.225			
No. of tumor, multiple *vs*. single	–0.91	0.40 (0.23–0.67)	0.001	–0.83	0.43 (0.25–0.76)	0.004
Total bilirubin (mg/dL), >1.2 *vs*. ≤1.2	0.56	1.75 (0.87–3.55)	0.115			
PT INR, >1.1 *vs*. ≤1.1	–0.06	0.99 (0.54–1.82)	0.984			
Creatinine (mg/dL), >1.2 *vs*. ≤1.2	–0.21	0.80 (0.36–1.75)	0.584			
Albumin (g/dL), ≤3.5 *vs*. >3.5	–0.24	0.78 (0.35–1.71)	0.541			
Platelets ($\times 10^3/\mu L$), ≤100 *vs*. >100	–0.06	0.93 (0.48–1.79)	0.843			
Pathologic macrovascular invasion, + *vs*. –	–0.05	0.94 (0.54–1.64)	0.845			
Pathologic microvascular invasion, + *vs*. –	0.19	1.21 (0.74–1.98)	0.434			
Edmonson-Steiner grade, III–IV *vs*. I–II	–0.35	0.70 (0.43–1.14)	0.152			
Prognostic factor at recurrent stage						
Treatment for the recurrence, non-curative *vs*. curative	–0.69	0.49 (0.30–0.81)	0.006	–0.84	0.43 (0.25–0.77)	0.004
Time interval to recurrence (mo), ≤12 *vs*. >12	–0.79	0.45 (0.27–0.75)	0.002	–0.75	0.47 (0.27–0.82)	0.008
Total bilirubin (mg/dL), >1.2 *vs*. ≤1.2	0.01	1.01 (0.50–2.05)	0.960			
PT INR, >1.1 *vs*. ≤1.1	–1.12	0.32 (0.18–0.55)	<0.001	–0.95	0.39 (0.22–0.69)	0.001
Creatinine (mg/dL), >1.2 *vs*. ≤1.2	0.07	1.08 (0.39–2.98)	0.879			
Albumin (g/dL), ≤3.5 *vs*. >3.5	–0.63	0.52 (0.30–0.91)	0.024	0.11	1.12 (0.59–2.11)	0.729
α-FP (ng/mL), ≥200 *vs*. <200	–0.81	0.44 (0.21–0.89)	0.024	–1.12	0.33 (0.15–0.72)	0.006

HR, hazard ratio; CI, confidence interval.

recurrence were found to be important prognostic factors for patients with reBCLC-O. Therefore, based on our results, considering these prognostic factors, curative treatment is strongly recommended in the patients with reBCLC-O recurrence for better survival. Nevertheless, further prospective randomized studies are warranted to confirm these results.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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