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Transarterial chemoembolization combined with radiofrequency ablation for solitary large hepatocellular carcinoma ranging from 5 to 7 cm: an 8-year prospective study

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Abstract

Purpose This prospective study was performed to investigate long-term (8-year) survival in patients with solitary large hepatocellular carcinoma (HCC) ranging from 5 to 7 cm who underwent transarterial chemoembolization (TACE) combined with radiofrequency ablation (RFA) and identify factors that significantly affected outcomes.

Methods Forty-eight patients with large HCC (36 men, 12 women; mean age, 57.0 ± 11.2 [range, 37–82] years) without fever or signs of infection were enrolled. All patients were treated with TACE + RFA. Overall survival (OS) and disease-free survival (DFS) were calculated using the Kaplan–Meier method. Prognostic factors were assessed using the Cox hazards regression method.

Results The median OS duration was 47.0 months, and the 1-, 3-, 5-, and 8-year OS rates were 73%, 57%, 53%, and 27%, respectively. The median DFS duration was 9.05 (3.99–12.01) months, and the 1-, 3-, and 5-year DFS rates were 35%, 9%, and 0%, respectively. Cox hazards regression analysis revealed that the Child–Pugh class, platelet count, lymphocyte-to-monocyte ratio (LMR), and DFS were independent predictive factors of OS ($p = 0.000$, 0.003, 0.020, and 0.000, respectively). The LMR and platelet-to-lymphocyte ratio (PLR) were independent predictive factors of recurrence ($p = 0.046$ and 0.016, respectively).

Conclusion TACE + RFA may be a safe and effective treatment for selected solitary large HCC ranging from 5 to 7 cm. Measurement of the LMR (> 4) and PLR (≤ 100) in peripheral blood before the intervention might help to identify which patients with solitary large HCC are suitable for TACE + RFA.

Registration number: ChiCTR-TRC-12002768 (https://www.chictr.org.cn).

Keywords Hepatocellular carcinoma (HCC) · Radiofrequency ablation (RFA) · Survival · Recurrence · Lymphocyte-to-monocyte ratio (LMR)

Abbreviations

HCC	Hepatocellular carcinoma
CLIP	Cancer of the liver Italian program
CT	Computed tomography
TACE	Transarterial chemoembolization
RFA	Radiofrequency ablation
ECOG	Eastern cooperative oncology group
CR	Complete response
BCLC	Barcelona clinic liver cancer group
OS	Overall survival
DFS	Disease-free survival
PLR	Platelet-to-lymphocyte ratio
LMR	Lymphocyte-to-monocyte ratio
AFP	Alpha fetoprotein

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Introduction

HCC is the seventh most common cancer and the third most frequent cause of cancer-related death worldwide, and its incidence has increased in recent years [1]. It is generally believed that only patients with early-stage HCC can benefit from curative methods such as surgical resection, liver transplantation, or percutaneous ablation, and the optimal treatment for large HCC is still controversial [2]. Transarterial chemoembolization (TACE) has been widely used in the management of large HCCs. However, residual lesions often remain viable after TACE, and in one study, a complete response (CR) occurred in only 16.9% of the patients [3]. The "up-to-seven" criterion reported by Mazzaferro et al. [4], which is a better substitute measure of the tumor burden, has recently been used to choose patients with a large solitary HCC of appropriate size to undergo surgery. At present, the more common view is that the long-term outcomes of radiofrequency ablation (RFA) for solitary HCC measuring ≤ 5 cm are similar to those of surgical resection [5, 6]. Several clinical studies have shown that RFA might be beneficial for the long-term survival of patients with intermediate or advanced HCC [7–9], especially those with a single large HCC, by reducing the tumor load. However, data are lacking on the long-term follow-up outcomes of TACE + RFA in patients with a solitary HCC ranging from 5 to 7 cm. This prospective study was performed to investigate long-term (8-year) survival of patients with a solitary large HCC (5–7 cm) who underwent TACE + RFA and evaluate factors that significantly affected treatment outcomes.

Patients and methods

Sixty-two patients with HCC met the enrollment criteria, but 14 patients underwent surgery and were not enrolled. Therefore, we prospectively enrolled 48 patients with HCC involving a single lesion (range, 5–7 cm; 36 men and 12 women; mean age, 57.0 ± 11.2 [range, 37–82] years) without fever or signs of infection who had been treated at a university hospital from December 2009 to January 2019. A flowchart of the study is shown in Fig. 1. The first patient entered the group in December 2009 and the last patient in February 2011. Although all patients met the indications for hepatectomy, all declined to undergo hepatectomy. This prospective case series was conducted at a single center. The inclusion criteria for this study were as follows: (1) age of > 18 years; (2) a single nodular lesion with maximum size of 5 to 7 cm; (3) absence of vascular invasion, lymph node involvement, and distant metastases; (4) Child–Pugh class A or B liver function; (5) platelet count of $> 50 \times 10^9$/L; (6) no ascites or only a small amount of ascites; and (7) refusal to undergo partial hepatectomy. The exclusion criteria for this study were as follows: (1) fever or additional manifestations of acute infection; (2) previous or secondary cancers or coexistent hematological disorders; (3) lack of information required for the present study or loss to follow-up within 6 months; and (4) Child–Pugh class C liver function.

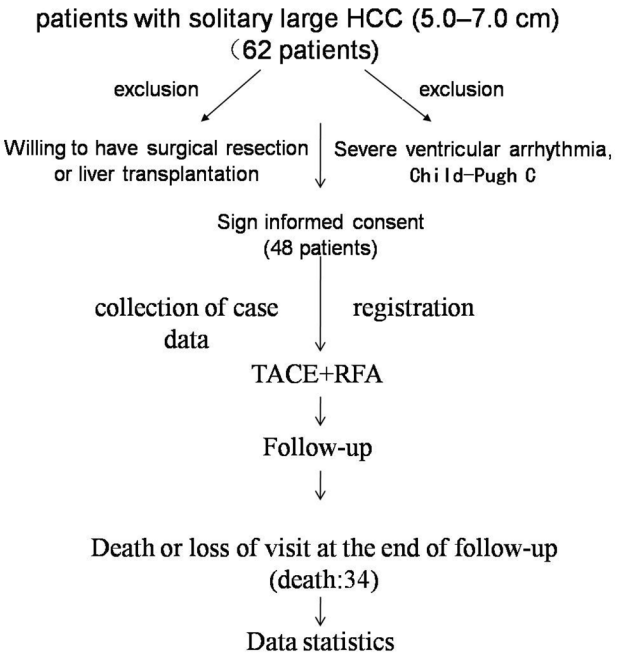

Fig. 1 Flow diagram of the study. *HCC* hepatocellular carcinoma, *TACE* transarterial chemoembolization, *RFA* radiofrequency ablation

Forty-eight patients were treated with nucleoside analogs: lamivudine ($n = 13$), telbivudine ($n = 6$), and entecavir ($n = 29$). All patients started taking nucleoside analogs at least 1 month prior to TACE, and they continue them after. All patients were diagnosed with HCC and underwent TACE + RFA. Follow-up was performed monthly for the first 3 months, once every 3 months for the next 6 to 12 months, and once every 6 months thereafter. We evaluated liver function, renal function, routine blood test parameters, tumor biomarkers, blood coagulation parameters, and contrast-enhanced computed tomography (CT) and magnetic resonance imaging findings. Immediate ablation was performed as soon as recurrence was found during follow-up. All patients had hepatitis B virus (HBV)-associated hepatitis and/or cirrhosis and Child–Pugh class A or B liver function. The diagnosis of HCC in all 48 patients (100%) was confirmed by histopathologic examination of biopsy specimens. No microvascular invasion was present, and 11 (23%) patients had poorly differentiated tumors. These patients underwent TACE 4.4 ± 2.5 (range, 2–13) + RFA 2.2 ± 1.6

(range, 1–8) times. The mean diameter of the lesions was 5.99 cm (range, 5.0–7.0 cm). Liver function was staged according to the Child–Pugh classification system and Cancer of the Liver Italian Program (CLIP) score. We evaluated diagnostic data including sex, age, hepatitis B surface antigen level, hepatitis C virus antibody level, blood biochemical parameters (total bilirubin level, albumin level, and coagulation time), serum alpha fetoprotein (AFP) level (<20, 20 to <100, or ≥ 100 ng/mL), tumor diameter, pathological findings, Child–Pugh score, CLIP score, presence or absence of cirrhosis, and survival. The neutrophil, platelet, monocyte, and lymphocyte counts were determined 3 days before RFA.

The equipment used in this study were a flat-panel digital subtraction angiography system (Siemens AXIOM Artis dTA; Siemens Healthineers, Erlangen, Germany), spiral CT scanner (GE HiSpeed; GE Healthcare, Chicago, IL, USA), radiofrequency generator (RITA 1500X; AngioDynamics, Latham, NY, USA), RFA electrode probe (StarBurst XL; AngioDynamics), RFA system (Cool-tip; Valleylab, Boulder, CO, USA), and gamma ray stereotactic body radiotherapy system (SGS-I; Huiheng Medical Inc., Shenzhen, China).

TACE

TACE was performed as follows. Using the Seldinger technique, angiography of the hepatic artery was conducted to identify and ultraselect the nutrient artery supplying the tumor. The catheter is inserted selectively and superselectively into the hepatic segment or subsegmental artery where the tumor is located, then tumor vascular disorder was found. The application of microcatheter can avoid arterial vasospasm and ensure that there is a smooth flow of blood to the lesion during the injection of embolic material. Hydroxycamptothecin (20 mg), pirarubicin (20 mg), and 5-fluorouracil (1000 mg) were then injected into this artery. Finally, the artery was embolized by application of lipiodol and gelatin sponge granules (350–560 μm), lipiodol selectively deposits in tumor. When the injection of lipiodol emulsion causes the blood flow to slow down, the appropriate amount of gelatin sponge granules should be injected to reach the end point of embolism.

RFA

RFA was performed as follows. Two weeks after TACE, the patients' liver function recovered and lipiodol could be selectively deposited in the tumor tissue. All patients were anesthetized with 0.5% lidocaine local infiltration, and the imaging modality was CT. The electrode needle was inserted directly into the lesion. According to the ablation range of each lesion, the RFA electrode needle was modulated for the next ablation until achieving an overlapping ablative margin that would theoretically include the tumor and 0.5 to 1.0 cm of surrounding tissue. In practice, ablation was performed on the tumor and residual liver tissues to achieve anatomic ablation of the liver segment or lobe. When the RITA radiofrequency generator was used, the sub-pin diameter was released based on the diameter of the thrombus. RFA was then carried out at low power (80–120 W) for 15 to 20 min. The RFA procedures were performed by three interventional oncologists (J.Z., J.L., and Q.S.) with >10 years of experience in interventional therapy. The therapeutic effect was evaluated by enhanced CT 3 days after ablation. Lesions were evaluated in accordance with the modified Response Evaluation Criteria in Solid Tumors criteria [10]. If a residual tumor was found, ablation was performed immediately. A CR was defined as disappearance of intratumoral arterial enhancement in all target lesions. An incomplete response was defined as a $\geq 30\%$ decrease in the sum of the diameters of viable (enhancement in the arterial phase) target lesions, taking the baseline sum of the diameters of the target lesions as a reference.

Statistical analysis

The Chi-square test and *t*-test were performed to evaluate differences in constituent ratios and means using SPSS 18.0 (SPSS Inc., Chicago, IL, USA). Multivariate analysis was carried out by Cox proportional hazards regression, and the survival curve was tested by the Kaplan–Meier method. A p value of <0.05 was considered statistically significant.

Results

Clinical characteristics

Prognosis of 48 HCC patients with solitary large HCC ranging from 5 to 7 cm. Sixty-two patients with HCC met the inclusion criteria, and 48 patients were enrolled after providing written informed consent. The initial local CR rate was 98% (ablation margin: 0.5–1.0 cm). The clinical characteristics, median overall survival (OS), and median disease-free survival (DFS) of the 48 patients with HCC are displayed in Tables 1, 2, and 3, respectively. All patients had intermediate-stage HCC according to the Barcelona Clinic Liver Cancer staging system, and 92% and 8% of patients had Child–Pugh class A and B liver function, respectively. The proportion of patients with a CLIP score of 0, 1, and 2 was 46%, 38%, and 17%, respectively. The mean tumor size was 5.99 (range, 5–7) cm. All patients had nodular HCC. In this cohort, 24 patients (50%) had a high serum AFP level (>20 ng/mL). Thirty-six patients (75%) had an Eastern Cooperative Oncology Group (ECOG) status of 0.

Table 1 Clinical characteristics of patients in the current study

Mean age, year (range)	56.96 (37–82)	
Male sex	36 patients	75.00%
Hepatitis B	48	100%
ECOG		
0	36	75%
1	12	25%
Cirrhosis	29	60%
Child—Pugh Grade		
A	44	91.67%
B	4	8.33%
Mean CLIP Score		
0	22	45.83%
1	18	37.50%
2	8	16.67
Pathology	48	
Well differentiated	10	20.83%
Moderately differentiated	22	45.83%
Poorly differentiated	9	18.75%
Effectiveness rate (CR)	48	100.0%
Metastasis	0	0
AFP distribution (ng/mL)		
< 20	24	50.00%
20–200	9	18.75%
> 200	15	31.25%

CLIP cancer of the liver Italian program, *CR* complete response, *ECOG* eastern cooperative oncology group, *AFP* alpha fetoprotein

Twenty-nine patients (60%) had liver cirrhosis. Twenty-four patients (50%) were negative for HBV-DNA (< 100 IU/mL).

Cumulative survival

The median OS for all patients in this cohort was 47 months. Figure 2a shows the cumulative survival curve for all patients with HCC: the 1-, 3-, 5-, and 8-year OS rates were 73%, 57%, 53%, and 27%, respectively. Figure 2b shows the DFS for all patients with HCC: the 1-, 3-, and 5-year DFS rates were 35%, 9%, and 0%, respectively. Figure 2c and d shows that both the OS and DFS were significantly longer in patients with a higher lymphocyte-to-monocyte ratio (LMR) (> 4) than lower LMR (≤ 4) before treatment. The initial local CR rate was 98% (ablation margin: 0.5–1.0 cm). Figure 3a to d shows the CT images of a 48-year-old woman with HCC before treatment and 3 months after ablation.

Intrahepatic recurrence and extrahepatic metastasis

Among the 48 patients, 44 developed intrahepatic recurrence and 1 developed lung metastasis after effective treatment. The longest DFS was 48 months, and the median DFS was 9.05 months (range, 3.99–12.01 months). The 1-, 3-, and 5-year DFS rates were 35%, 9%, and 0%, respectively (Table 3).

Complications and causes of death

Of the 48 patients with HCC, 34 (71%) died during supportive care or follow-up visits. The most common causes of death were HCC ($n = 27$), hepatic failure and hepatorenal syndrome ($n = 4$), and upper gastrointestinal bleeding ($n = 2$). One patient developed obstructive jaundice, and no patients developed post-treatment hepatic failure (within 4 weeks).

Multivariate Cox proportional hazards regression analysis

Cox hazards regression analysis revealed that the Child–Pugh class ($p = 0.000$), LMR ($p = 0.020$), platelet count ($p = 0.003$), and DFS ($p = 0.000$) were independent prognostic factors for patients with a solitary large HCC ranging from 5 to 7 cm. The LMR ($p = 0.029$) and platelet-to-lymphocyte (PLR) ($p = 0.001$) were independent prognostic factors for recurrence (Table 4).

In this study, the survival of patients with solitary HCC lesions ranging from 5 to 7 cm was not closely correlated with the degree of tumor differentiation ($p = 0.92$). We found no significant association of patient survival with the AFP level, age, ECOG status, neutrophil-to-lymphocyte ratio, HBV-DNA quantity, CLIP score (0–2), or cirrhosis.

Discussion

This prospective study was conducted to examine the prognosis and influencing factors of a solitary large HCC (5–7 cm) after TACE + RFA during an 8-year follow-up. Two main findings are of particular clinical significance. First, the study revealed the long-term prognosis of TACE + RFA for a single HCC of 5 to 7 cm. The median OS in this cohort was 47 months. The 1-, 3-, 5-, and 8-year OS rates were 73%, 57%, 53%, and 27%, respectively, while the 1-, 3-, and 5-year DFS rates were 35%, 9%, and 0%, respectively. The longest DFS was 48 months. These outcomes are satisfactory and show that TACE + RFA may serve as an effective treatment for a solitary large HCC ranging from 5 to 7 cm. At present, most guidelines for the treatment of HCC mention that the indication for HCC ablation is a single HCC with a diameter of ≤ 5 cm. Our findings are promising but require further verification by a prospective randomized controlled trial. Second, the multivariate regression analysis showed that the LMR was significantly correlated with OS (hazard ratio [HR], 3.859; $p = 0.020$), while the PLR and LMR had a close relationship with DFS (HR 3.964;

Table 2 Median survival and clinical characteristics of 48 patients with solitary large hepatocellular carcinoma ranging from 5 to 7 cm

Parameter	*n*	Median survival (month) (95% CI)	1-year survival,% (95% CI)	3-year survival,% (95% CI)	5-year survival,% (95% CI)	8-year survival,% (95% CI)	*p* value
Overall	48	47.00	0.73	0.57	0.53	0.27	
Male	36	44.00	0.69	0.53	0.42	0.25	0.327
Female	12	54.00	0.83	0.67	0.50	0.33	
Age distribution (year)							
< 50	12	34.00	0.83	0.50	0.33	0.33	0.646
50–60	16	62.00	0.69	0.63	0.56	0.16	
60–70	13	36.00	0.69	0.46	0.23	/	
> 70	7	88.00	0.71	0.71	0.71	0.57	
Child—Pugh							
A	44	64.00	0.83	0.67	0.52	0.33	0.046*
B	4	19.00	0.67	0.0	/	/	
CLIP score distribution							
0	22	54.00	0.73	0.55	0.41	0.36	0.123
1	18	68.00	0.78	0.72	0.61	0.33	
2	8	18.00	0.63	0.25	0.13	0	
ECOG status							
0	36	54.00	0.78	0.58	0.44	0.25	0.672
1	12	24.00	0.58	0.50	0.42	0.33	
Cirrhosis							
Yes	19	44.00	0.72	0.55	0.41	0.34	0.932
No	29	54.00	0.79	0.58	0.47	0.17	
NLR							
≤ 3.5	40	44.00	0.75	0.55	0.42	0.27	0.888
> 3.5	8	47.00	0.63	0.63	0.50	0.25	
AFP distribution (ng/mL)							
< 20	23	57.00	0.79	0.63	0.46	0.28	0.686
20–100	5	13.00	0.50	050	0.17	0	
> 100	20	26.00	0.70	0.50	0.40	0.28	
Pathology (differentiated)							
Well	10	39.00	0.70	0.60	0.40	0.29	0.64
Moderately	22	57.00	0.68	0.59	0.50	0.32	
Poorly	9	22.00	0.78	0.44	0.33	0	
HBV-DNA quantity							
< 100	24	44.00	0.71	0.58	0.46	0.29	0.866
100–1000	4	2.00	0.50	0.50	0.50	0.5	

Table 2 (continued)

Parameter	*n*	Median survival (month) (95% CI)	1-year survival,% (95% CI)	3-year survival,% (95% CI)	5-year survival,% (95% CI)	8-year survival,% (95% CI)	*p* value
> 1000	20	47.00	0.80	0.55	0.40	0.23	
PLT ($\times 10^9$/L)							
< 150	28	67.0	0.86	0.71	0.54	0.35	0.024*
≥ 150	20	24.0	0.55	0.35	0.30	0.17	
LMR							
> 4	16	67.00	0.88	0.73	0.58	0.36	0.025*
≤ 4	32	24.00	0.60	0.40	0.30	0.19	
NMLR							
≤ 1.2	40	37.00	0.67	0.49	0.38	0.24	0.039*
> 1.2	8	76.80	1.00	0.89	0.67	0.42	
PLR							
> 100	27	25.00	0.63	0.41	0.30	0.17	0.017*
≤ 100	21	67.50	0.86	0.76	0.62	0.41	

ECOG eastern cooperative oncology group, *CLIP* cancer of the liver Italian program, *NLR* neutrophil-to-lymphocyte ratio, *PLR* platelet-to-lymphocyte ratio, *LMR* lymphocyte-to-monocyte ratio, *NMLR* neutrophil, monocyte, and lymphocyte ratio (product of the neutrophil count and monocyte count divided by the absolute lymphocyte count), *AFP* alpha fetoprotein, *HBV* hepatitis B virus, *PLT* platelet count, *CI* confidence interval

*$p < 0.05$

Table 3 Median disease-free survival and clinical characteristics of 48 patients with solitary large hepatocellular carcinoma ranging from 5 to 7 cm

Parameter	*n*	Median DFS (month) (95% CI)	1-year DFS,% (95% CI)	3-year DFS,% (95% CI)	5-year DFS,% (95% CI)	*p* value
Overall	48	9.05 (3.99–12.01)	0.35	0.09	0.00	/
Male	36	7.66 (1.67–12.33)	0.35	0.10	0.00	0.727
Female	12	10.00 (1.21–14.79)	0.33	0.08	0.00	/
Age distribution (year)						
< 50	12	18.00 (0.00–32.17)	0.50	0.29	0.00	0306
50–60	16	6.67 (3.61–10.39)	0.32	0.00	/	/
60–70	13	7.00 (0.53–13.47)	0.18	0.00	/	/
> 70	7	13.2 (2.22–21.78)	0.71	0.00	/	/
Child–Pugh						
A	44	10.00 (6.75–15.25)	0.35	0.10	0.00	0.984
B	4	7.00 (0.60–13.40)	0.33	0.00	/	
CLIP score distribution						
0	22	12.83 (10.98–13.02)	0.37	0.00	22	0.378
1	18	7.00 (2.87–11.13)	0.39	0.22	0.00	
2	8	5.80 (1.98–8.02)	0.16	0.00	/	
ECOG status						
0	36	12.36 (7.65–16.36)	0.40	0.12	0	0.166
1	12	4.93 (1.65–8.35)	0.30	0.00	/	
Cirrhosis						
Yes	19	13.09 (4.12–19.88)	0.44	0.12	0.00	0.622
No	29	7.34 (4.25–9.75)	0.22	0.06	0.00	
NLR						
≤ 3.5	40	7.87 (0.0–14.03)	0.30	0.08	0.00	0.171
> 3.5	8	15.25 (0.0–34.68)	0.59	0.15	0.00	
LMR						
> 4	16	15.30 (4.65–25.36)	0.55	0.16	0.00	0.046*
≤ 4	32	6.45 (3.95–10.05)	0.26	0.07	0.00	
NMLR						
≤ 1.2	40	7.84 (1.15–12.85)	0.33	0.08	0.00	0.162
> 1.2	8	13.08 (0.0–24.63)	0.43	0.14	0.00	
AFP distribution (ng/mL)						
≤ 20	24	11.24 (5.58–16.41)	0.31	0.00	/	0.545
> 20	24	7.92 (3.77–10.23)	0.40	0.20	0.00	
Pathology (differentiated)						
Well	10	30.38 (0.00–61.53)	0.52	0.13	0.00	0.222

Table 3 (continued)

Parameter	*n*	Median DFS (month) (95% CI)	1-year DFS,% (95% CI)	3-year DFS,% (95% CI)	5-year DFS,% (95% CI)	*p* value
Moderately	22	26.07 (9.28–44.72)	0.50	0.25	0.00	
Poorly	9	6.86 (2.39–11.61)	0.31	0.04	0.00	
HBV-DNA quantity						
< 100	24	12.13 (9.31–14.69)	0.28	0.09	0.00	0.73
100–1000	4	30.00 (0.00–5.92)	0.50	0.00	/	
> 1000	20	6.67 (4.14–12.01)	0.40	0.10	0.00	
PLT ($\times 10^9$/L)						
< 150	28	9.46 (0.63–15.37)	0.31	0.04	0.00	0.697
≥ 150	20	12.26 (5.10–18.90)	0.40	0.17	0.00	
PLR						
≤ 100	28	5.94 (2.29–7.72)	0.21	/	/	0.016*
> 100	20	24.65 (4.46–43.54)	0.53	0.00	/	

ECOG eastern cooperative oncology group, *CLIP* cancer of the liver Italian program, *NLR* neutrophil-to-lymphocyte ratio, *PLR* platelet-to-lymphocyte ratio, *LMR* lymphocyte-to-monocyte ratio, *NMLR* neutrophil, monocyte, and lymphocyte ratio, *DFS* disease-free survival, *PLT* platelet count, *HBV* hepatitis B virus, *AFP* alpha fetoprotein, *CI* confidence interval

*$p < 0.05$

$p = 0.001$ and HR 4.052; $p = 0.029$). This is the first study to investigate the prognosis of a solitary large HCC (5–7 cm) after TACE + RFA during an 8-year follow-up. The results suggest that the LMR may be a useful predictor for patients with a solitary large HCC ranging from 5 to 7 cm who have undergone TACE + RFA. However, this conclusion also requires verification in future research.

Effective treatments for patients with large HCC who are not candidates for surgical resection remain limited and controversial. Although surgical resection is the first-choice treatment for early-stage HCC, it is not necessarily suitable for intermediate-stage HCC. In previous studies, the 5-year OS of patients with solitary large HCC who underwent surgical resection ranged from 28.6 to 47.0% [8, 11, 12]. In their retrospective study, Yang et al. [9] found that the 1-, 3-, and 5-year OS rates for a solitary large HCC after surgical resection were 87.0%, 55.5%, and 38.2%, respectively. In the present study, the 5-year OS rate was 53%. Thus, the 5-year OS of patients with a single large HCC (5–7 cm) after surgical resection was similar between previous research and the present study. In a retrospective study of single large HCC (≤ 7 cm), TACE + RFA provided a longer median OS than did surgical resection (52.0 vs. 45.0 months, respectively; $p = 0.023$) [13]. In another retrospective study of TACE + RFA in 66 patients with a single large HCC (≥ 5 cm in diameter), Zuo et al. [14] reported that the OS was 18.3 months, progression-free survival was 14.2 ± 6.2 months, and the 3- and 5-year survival rates were 42.5% (17/40) and 27.2% (9/33), respectively. This study showed that TACE + RFA has long-term benefits for patients with a solitary large HCC ranging from 5 to 7 cm. Sharon W Kwan, et al. [15] reported that TACE for HCC, in 70% of the nodules, > 90% necrosis was achieved. In combination therapy, TACE could play an important role in the treatment of HCC, and the specific mechanism may be as follows. First, lipiodol can play a marker role in CT guided ablation by specific binding to HCC cells. Second, TACE can reduce the arterial blood supply within and around the tumor, which makes lesion more easily destroyed during ablation.

Our multivariate analysis demonstrated that the Child–Pugh class, LMR, platelet count, and DFS were independent prognostic factors for long-term survival, while the degree of tumor differentiation, LMR, and PLR significantly affected DFS. Patients who have HCC with Child–Pugh class A liver function are more likely to receive effective treatment, achieve a CR at the first treatment, and have better OS. Previous studies have shown that platelets can promote tumor metastasis by interacting directly with cancer cells [16, 17]. The PLR is the ratio of platelets to lymphocytes and represents the balance between the promotion and inhibition of tumor recurrence. In the present study, we verified that the inflammation index is closely related to the prognosis of HCC. Recently, increasing evidence has shown that systemic

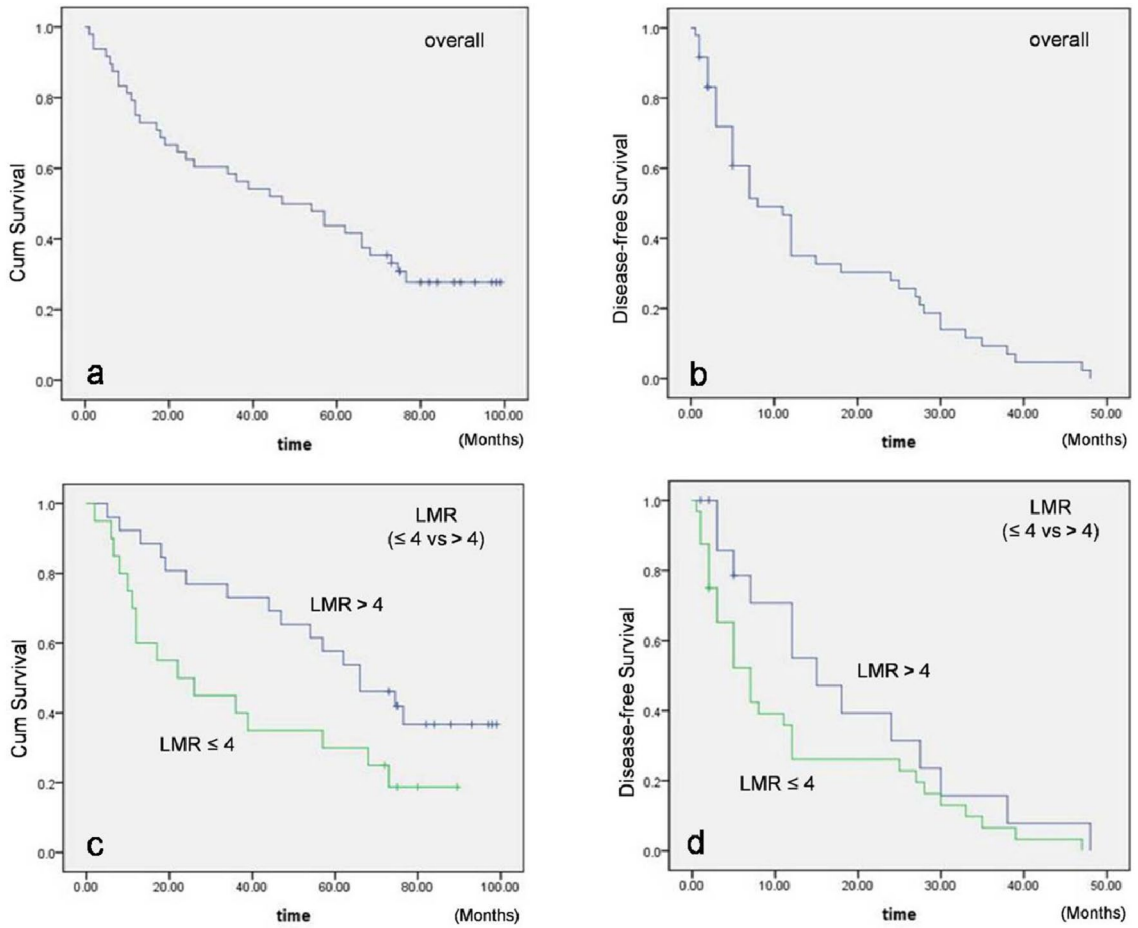

Fig. 2 **a** Overall survival curve of 48 patients with solitary large (5–7 cm) HCC. **b** DFS of 48 patients with solitary large (5–7 cm) HCC. **c** Survival according to LMR (> 4 vs. ≤ 4) of 48 patients with solitary large (5–7 cm) HCC. **d** DFS according to LMR (> 4 vs. ≤ 4) for 48 patients with solitary large (5–7 cm) HCC. *HCC* hepatocellular carcinoma, *DFS* disease-free survival, *LMR* lymphocyte-to-monocyte ratio, *Cum* cumulative

inflammation is correlated with poorer cancer-specific survival in patients with certain cancers. Various markers of the systemic inflammatory response, including cytokines, C-reactive protein, and the peripheral blood neutrophil or lymphocyte count as well as their ratios (such as the LMR), have been investigated for their prognostic roles in patients with certain tumors [18–20].

To prevent changes in peripheral blood cells caused by fever or infection, we excluded patients with HCC who had manifestations of fever or acute infection. Immune cells from peripheral blood are important elements in the tumor microenvironment. Monocytes may promote tumorigenesis through immunosuppression and tumor-promoting chemokines/cytokines [21]. Lymphocytes play an important role in tumor immunomodulation by releasing cytokines and chemokines to attract monocytes, dendritic cells, and endothelial cells to the tumor [22]. Thus, the complex interaction between inflammation and the immune cell population may affect tumor growth. The LMR is the result of the interaction between the immune state and inflammatory response in the tumor microenvironment and its reflection in peripheral blood. Tumor cell necrosis can produce permanent tumor-associated antigens that do not require antigen loading and can play an immune role directly through dendritic cells [23]. The peripheral blood LMR has been identified as an outcome predictor in various tumors [24, 25]. To the best of our knowledge, few studies have demonstrated an association between the LMR and prognosis of a single large HCC (5–7 cm) treated by TACE + RFA. Our study results suggest that a high LMR (> 4) is associated with better OS and longer DFS for patients with a single large HCC (5–7 cm). We consider several possible mechanisms underlying this correlation based on the results of several previous experiments. First, the LMR is based on measurement of lymphocytes and monocytes, which play an important role in the immune system. In solid tumors,

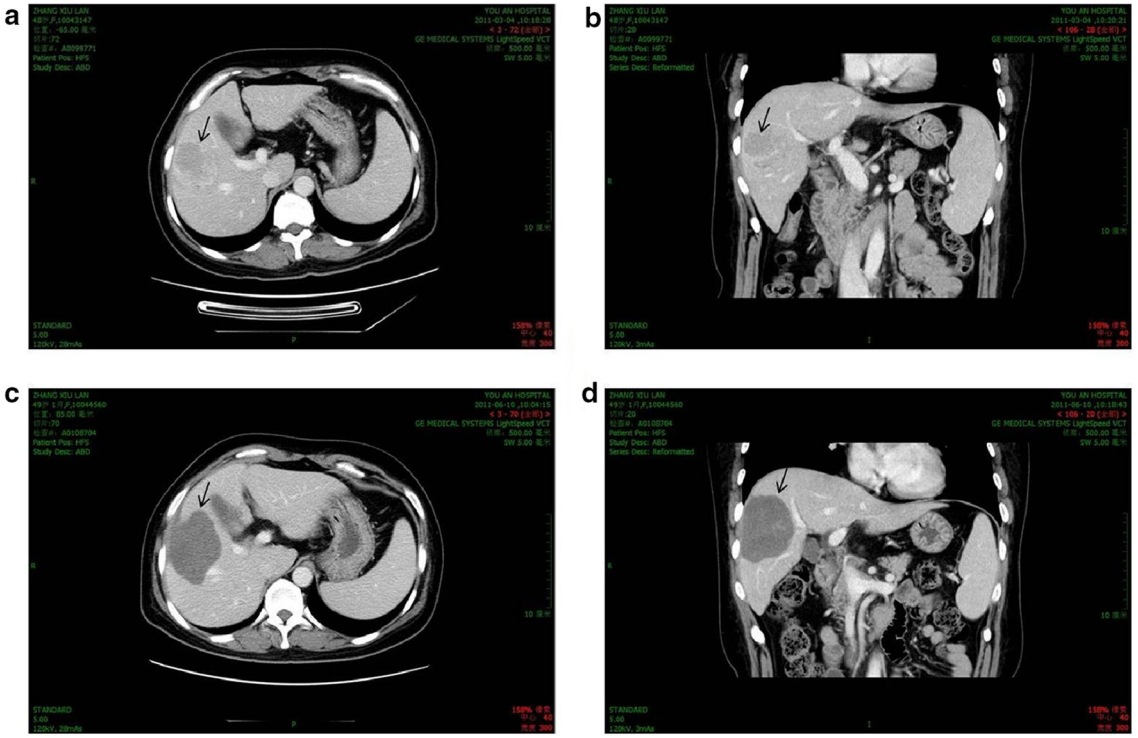

Fig. 3 Diagnostic and follow-up images from a 48-year-old woman with a solitary large HCC. **a** Venous-phase pretreatment axial CT image shows the tumor in the right lobe of the liver. **b** Venous-phase pretreatment coronal CT image shows the tumor in the right lobe of the liver. **c** Axial CT scan 3 months after ablation shows the complete ablation zone. **d** Coronal CT scan 3 months after ablation shows the complete ablation zone. *CT* computed tomography

Table 4 Multivariate Cox proportional hazards regression analysis (survival and recurrence)

Variable	Survival (month)			Recurrence (month)		
	p value	HR	95% CI	*p* value	HR	95% CI
Sex (female/ male)	0.266	2.712	0.468–15.725	0.840	0.896	0.311–2.588
Pathology (well/ moderately / poorly differentiated)	0.023*	0.302	0.081–1.131	0.038*	0.410	0.071–2.379
Age (years)	0.977	0.978	0.21–4.470	0.207	0.507	0.177–1.456
Child–Pugh grading (A/ B)	0.000*	0.032	0.005–0.189	0.620	0.607	0.084–4.366
CLIP score (0/ 1/ 2)	0.048*	0.220	0.060–0.812	0.250	0.135	0.014–1.280
Cirrhosis (yes/ no)	0.048*	0.364	0.133–0.992	0.063	0.307	0.088–1.066
ECOG status (0/ 1)	0.662	1.374	0.331–5.703	0.005	0.219	0.075–0.636
HBV-DNA quantity (< 100 / 100–1000/ > 1000)	0.899	0.357	0.085–1.495	0.483	11.206	2.051–61.215
NLR	0.808	0.773	0.097–6.160	0.483	20.790	0.150–2879.656
PLR	0.164	2.228	0.721–6.886	0.001*	3.964	1.748–8.988
PLT ($< 150/\geq 150\times 10^9$/L)	0.003*	0.131	0.035–0.491	0.425	0.672	0.253–1.785
AFP distribution (ng/mL)	0.556	0.717	0.237–2.167	0.134	1.886	0.823–4.323
NMLR	0.637	1.341	0.396–4.541	0.755	1.298	0.252–6.699
LMR	0.020*	3.859	1.234–12.066	0.029*	4.052	1.156–14.204
Disease-free survival time (mon)	0.000*	0.886	0.838–0.937	/	/	/

HR hazard ratio, *CI* confidence interval, *CLIP* cancer of the liver Italian program, *ECOG* eastern cooperative oncology group, *HBV* hepatitis B virus, *PLT* platelet count, *PLR* platelet-to-lymphocyte ratio, *AFP* alpha fetoprotein, *NLR* neutrophil-to-lymphocyte ratio, *LMR* lymphocyte-to-monocyte ratio, *NMLR* neutrophil, monocyte, and lymphocyte ratio

*$p < 0.05$

tumor-infiltrating lymphocytes play an anti-tumor role by inhibiting the proliferation of tumor cells. A decrease in the lymphocyte count may indicate that the anti-tumor response is weak and the clinical prognosis is poor [26]. Second, monocytes can promote tumor growth and help tumor cells escape immune monitoring [27]. Tumor-associated macrophages reportedly come from monocytes and infiltrate into the tumor matrix to promote tumor proliferation, metastasis, angiogenesis, and immunosuppression [21, 22]. Again, a high percentage of monocytes decreases the LMR, inducing the effect of tumor-associated macrophages on tumor recurrence and metastasis [28]. Because a higher LMR (>4) and lower PLR (≤ 100) in peripheral blood before the operation can predict a lower recurrence rate and longer OS for a solitary large HCC (5–7 cm) treated by TACE + RFA, it can be used to identify patients who are suitable candidates for TACE + RFA. However, the specific mechanism of the correlation between inflammatory cells and post-ablative relapse remains uncertain and requires further study.

Limitation

All patients in this study had hepatitis B, which presumably reflects the patient population at the center but not necessarily patient populations elsewhere. The sample size of this study is small and belongs to a single center study.

Conclusion

TACE + RFA may be a safe and effective treatment for selected solitary large HCC ranging from 5 to 7 cm.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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