

Radiofrequency ablation combined with transarterial chemoembolization versus hepatectomy for patients with hepatocellular carcinoma within Milan criteria: a retrospective case–control study

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Abstract

Proposal To compare the effectiveness of TACE + RFA with hepatectomy in patients with HCC within Milan criteria.

Methods It is a retrospective matched case–control study from January 2006 to December 2010 in a tertiary cancer center. 74 patients with HCC within Milan criteria initially treated with TACE + RFA were identified and compared with 148 matched controls selected from a pool of 782 patients who received hepatectomy. Patients were matched with respect to age, gender, tumor size and number, AFP and liver function test.

Results The 1, 3, and 5 years overall survival (OS) was 94.6, 75.1 and 55.3%, respectively, in the combination group, and 91.2, 64.4, and 47.7%, respectively, in the hepatectomy group ($P = 0.488$). The 1, 3, and 5 years disease-free survival (DFS) in the combination group was 87.8, 48.3, and 33.5%, respectively, and 68.9, 49.2, and 40.9%, respectively, in the hepatectomy group ($P = 0.619$). In

subgroups analyses according to the tumor size and number, no significant difference was identified in either OS or DFS for patients with single tumor smaller than 3.0 cm, 3.0–5.0 cm, and multiple tumors. Multivariate analysis showed that tumor size, ALT, and CLIP score were significant prognostic factors for OS, and ALT and Child–Pugh class were significant prognostic factors for DFS.

Conclusion TACE + RFA is safe and as effective as hepatectomy for patients with HCC within Milan criteria.

Keywords Hepatocellular carcinoma · Hepatectomy · Radiofrequency ablation · Transarterial chemoembolization · Survival · Recurrence

Abbreviations

HCC	Hepatocellular carcinoma
TACE	Transarterial chemoembolization
RFA	Radiofrequency ablation
PEI	Percutaneous ethanol injection
IRB	Institutional review board
CT	Computed tomography
MRI	Magnetic resonance imaging
OS	Overall survival
DFS	Disease-free survival
MDT	Multidisciplinary team
WBC	White blood cell
HGB	Hemoglobin
PLT	Platelets
ALT	Alanine aminotransferase
ALB	Serum albumin
TBIL	Total bilirubin
AFP	α -Fetoprotein
HBV	Hepatitis B virus
HCV	Hepatitis C virus
CLIP	Cancer of Liver Italian Program

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Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer in the world [1] and the third most common cause of cancer-related deaths with about 600,000 patients dying from the disease annually [2]. The incidence of HCC has been on the rise and is associated with an increase in hepatitis B or C-associated cirrhosis [3]. Approximately 80% of patients with HCC develop the tumor from such chronic liver diseases [4]. The incidence of HCC in cirrhotic patients varies between 0.2 and 8.0% per year depending on the cause of cirrhosis [5]. Mortality rate of HCC associated with liver cirrhosis is rising in developed countries with HCC now being a major cause of death in patients with compensated cirrhosis [6]. Therefore, it is prominent to develop more researches and studies to find the best treatments and therapeutic approaches to help the wide population who is infected.

Therapeutic options for HCC include liver transplantation, resection, transarterial chemoembolization (TACE), and local ablative techniques, such as radiofrequency ablation (RFA) and alcohol injection. Among these, liver transplantation remains the ideal option at earlier stages, yet this choice is greatly limited by the shortage of organ donors and the advanced age of patients at diagnosis. Although surgical resection is considered the main curative treatment, many data have accumulated on the efficacy and safety of a wide array of local ablative therapies. RFA has emerged as a new treatment modality and has attracted great interest because of its effectiveness and safety for small HCC (≤ 5 cm) [7]. Its superiority over microwave coagulation therapy [8, 9] and percutaneous ethanol injection (PEI) [10–14] was reported. On the basis of the data from randomized controlled trials and systematic review, TACE is currently recommended only for large or multinodular HCC [15–18]. TACE prolongs survival by the arterial injection of anticancer drugs and embolizing agents, which subsequently induces ischemic necrosis.

The combination of TACE and RFA has also been reported to be an effective treatment for HCC. Studies have shown that the efficacy of TACE combined with RFA is better than that of RFA alone for medium sized HCCs (3–5 cm) and HCCs involving multiple tumors but not for small HCCs (≤ 3 cm) [19–21]. Although RFA combined with TACE is increasingly used in treating patients with HCCs, there have been relatively few studies on the outcome of this combined treatment in patients with early stage HCC in comparison with surgical resection, in which the disease-free and overall survival rates after treatment with either a combination of RFA and TACE or surgical resection were comparable in patients with early stage HCC [22–24].

Thus, the purpose of present study was to compare the effectiveness of RFA combined with TACE with surgical resection in patients with HCC within Milan criteria.

Materials and methods

Patients

This retrospective study was carried out at the Department of Hepatobiliary Surgery of Sun Yat-Sen University Cancer Center. The research was approved by the institutional review board (IRB) of Sun Yat-Sen University Cancer Center, and written informed consent was obtained from all patients before undergoing treatment. The records of patients who received TACE + RFA or hepatectomy as the initial curative treatment of HCC between January 2006 and December 2010 were reviewed.

The diagnosis of HCC for patients in the combination therapy group was based on the European Association for the Study of the Liver [5], as follows: demonstration of typical features of HCC with two imaging modalities, demonstration of typical features of HCC with one imaging modality together with an α -fetoprotein (AFP) level of more than 400 ng/mL, or demonstration of cytologic and/or histologic evidence of HCC, whereas that in the hepatectomy group was based on histological findings and pathology.

Inclusion criteria were as follows: (1) no previous treatment for HCC, (2) within Milan criteria (single HCC ≤ 5 cm or up to 3 HCCs ≤ 3 cm), (3) Child–Pugh class A and B defining cirrhosis, (4) no vascular invasion, and (5) no extrahepatic metastasis. Patients with incomplete medical records matching the inclusion criteria were excluded from the study. Since liver transplantation is not available in our cancer center, hepatectomy is the first-line recommendation for patients with HCC within Milan criteria, and the TACE + RFA is reserved as second-line option for those patients refused or unsuitable for surgery.

74 patients undergoing TACE + RFA and 782 patients undergoing hepatectomy meeting our inclusion criteria were identified. The cases were matched with a 1:2 ratio between the combination therapy group and the hepatectomy group as far as possible in the following order of matching: (a) age, (b) gender, (c) tumor size, (d) tumor number, (e) baseline serum albumin, (f) baseline serum bilirubin, (g) same period of enrollment, (h) baseline serum AFP. The selection was stopped once enough cases were identified. An investigator who was blinded to the outcome of each case (KQ P) performed the case matching.

TACE + RFA procedure

For patients in the combination therapy group, a 5-F catheter was inserted in the right femoral artery through to the abdominal aorta junction and a visceral angiography was performed to evaluate the arterial blood supply to the liver and confirm the patency of the portal vein. Then a 5-F microcatheter was introduced into the hepatic artery and fixed to the target tumor site. Hepatic artery infusion chemotherapy was performed using 50 mg epirubicin mixed with lipiodol. If the territory of the chemolipiodized artery did not show stagnant flow, pure lipiodol was then injected. In the end, embolization was then carried out with absorbable gelatin sponge particles. After embolization, angiography was carried out to determine the extent of vascular occlusion and assess blood flow in other arteries.

RFA was performed within 2 months after TACE. In this procedure, the patients were placed in a supine position. After conscious analgesic sedation was applied intravenously using remifentanyl and parecoxib, a local anesthetic (1% lidocaine) was injected from the insertion site in the skin down to the peritoneum along the planned puncture track. The skin was then incised with a small lancet. Two systems were used throughout the study. A 15-gage needle with ten expandable hook-shaped electrode tines that had a diameter of either 4 or 5 cm (LeVeen needle, Radiotherapeutics) or an open-perfused electrode of 15 cm, 14 gage, and a 15 mm active electrode tip with microbores (Elektrotom HiTT 106, Berchtold, Medizinelektronik, Germany) was used. The electrode needle was inserted along the planned track under the ultrasonographic guidance. This operation was performed by an experienced doctor (MS C). The tumor was ablated in one or several overlapping ablations as described by Chen et al. [25], depending on the tumor size and number of tumors present. After ablation was complete, the needle was withdrawn and track ablation was performed at the same time to prevent bleeding and tumor seeding. Contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) was performed about 1 month after treatment to assess the treatment response.

Surgical resection

Hepatectomy was carried out using the techniques we described previously. In brief, hepatectomy was carried out under general anesthesia using a right subcostal incision with a midline extension. Intraoperative ultrasonography was routinely performed to confirm resectability and major vascular structures. Pringle's maneuver was routinely used with a clamp/unclamp time of 10/5 min. The liver parenchyma was divided with clamp-crushing technique or ultrasonic dissector (CUSA) according to the surgeon's

preference. Anatomic resection was our preferred surgical method in hepatic resection for multiple nodules in one segment or in neighboring segments. For anatomic resection, the hepatic parenchyma was transected at the intersegmental plane as described by Couinaud. For multiple bilobar nodules, anatomic resection was preferred for the main tumor, while satellite nodules were resected nonanatomically with intent for a negative resection margin. When an inadequate liver remnant was suspected, nonanatomic resection was performed with intent for a negative resection margin. Hemostasis on the raw liver surface was done with suturing and fibrin glue.

Follow-up

Computed tomography (and/or magnetic resonance imaging) was performed within 1 month after treatment to assess the response to the combination therapy or hepatectomy. After the first month, these radiological examinations were performed every 3 months for the first 2 years. Thereafter, it was extended to once every 6 months from 2 to 5 years and extended to every 12 months after 5 years. At each of these follow-up visits, blood tests including serum liver and AFP tests were performed. All patients with HBV or HCV infection received antiviral treatment according to the guidelines. A complete response to the combination therapy was achieved when no enhancement or a thin peripheral enhancement rim (representative of an inflammatory response) was observed, while an incomplete response to the combination therapy was defined as persistent nodular enhancement. If enhancement areas were observed, additional RFA ablation was performed.

Causes of death and sites of recurrence were determined from death certificates, medical interviews, and radiological findings. Overall survival (OS) was defined as the interval between surgery and time of either death or last follow-up. Disease-free survival (DFS) was defined as the length of time after liver resection for HCC to detectable intrahepatic and/or extrahepatic recurrence. The treatment for recurrent tumors was determined by our multidisciplinary team (MDT) including surgeons, oncologists, radiologists, hepatologists, and pathologists.

Statistical analysis

The baseline characteristics of patients were expressed in mean \pm SD. Comparisons between two groups were done using the student's *t* test for continuous data and the Chi-square test for categorical data. The OS was calculated by Kaplan–Meier method and compared by log-rank test. The prognostic variables in predicting OS were assessed by multivariate Cox proportional hazards regression analysis. Variables that proved to be significant in the univariate

analysis were tested subsequently with the multivariate Cox proportional hazard model. The forward selection method was used for multivariate Cox proportional analysis. All statistical tests were two-sided, and a significant difference was considered when $P < 0.05$. All the statistical were performed using the SPSS 13.0 statistical software (SPSS Company, Chicago, IL, USA).

Results

Baseline characteristics

After the matching process, 222 patients (74 in the combination therapy group and 148 in the hepatectomy group) were enrolled in this study. The demographic data of these two groups of patients are shown in Table 1. There was no significant difference between two groups in any of the clinicopathologic characteristics.

The median tumor size in the hepatectomy group was 3.0 ± 1.1 cm and the combination therapy group was 2.9 ± 1.1 cm ($P = 0.71$). According to the tumor number, the combination therapy group had 58 (78.4%) patients with one tumor and 16 (21.6%) patients with more than one tumor whereas the hepatectomy group had 116 (78.4%) patients with one tumor and 32 (21.6%) patients with more than one tumor ($P = 1.0$). Most patients, 70 (94.6%) in the combination therapy group and 144 (97.3%) in the hepatectomy group, had a good liver functional reserve with Child–Pugh A.

When patients were classified by the Cancer of Liver Italian Program (CLIP) score [26], 42 (56.8%), 25 (33.9%), and 7 (9.3%) patients in the combination therapy group had scores of 0, 1, and 2, respectively, whereas 76 (51.4%), 55 (37.2%), and 17 (11.4%) patients in the hepatectomy group had scores of 0, 1, and 2, respectively. The proportion of patients with particular CLIP scores did not differ significantly between two groups.

Technical success was achieved in all 74 patients treated with TACE + RFA. It was achieved after one RFA treatment in 70 patients (94.6%), after two RFA treatments in 4 (5.4%). Hepatectomy was performed in all 148 patients successfully and all procedures were considered to be curative.

Mortality and morbidity

Major complications occurred in seven patients: four patients with ascites and two patients with pleural effusion in the hepatectomy group and one patient with ascites in the combination therapy group. There was no significant difference between two groups ($P = 0.170$). There was no needle-track seeding in the combination therapy group.

There was no treatment-related death in this study.

Overall survival and recurrence

The follow-up period was 56.9 ± 33.5 and 50.2 ± 32.3 months for each group, respectively. During follow-up, 38 patients in the combination therapy group

Table 1 Baseline patient characteristics

Characteristic	Combination therapy group ($n = 74$)	Hepatectomy group ($n = 148$)	P value
Age	54.9 ± 10.8	52.2 ± 11.2	0.504
Gender (M/F)	68/6	136/12	1.000
Tumor diameter (cm)	2.9 ± 1.1	3.0 ± 1.1	0.710
Number of tumor (1/>1)	58/16	116/32	1.000
WBC ($\times 10^9/L$)	5.6 ± 2.3	6.0 ± 1.9	0.175
HGB (g/L)	135.0 ± 24.2	140.8 ± 15.4	0.061
PLT ($\times 10^9/L$)	129.0 ± 63.6	145.9 ± 72.5	0.091
ALB (g/L)	40.8 ± 4.1	41.6 ± 4.1	0.173
TBil ($\mu\text{mol/L}$)	19.7 ± 10.9	17.7 ± 7.8	0.122
ALT (ng/mL)	47.8 ± 26.9	42.6 ± 24.9	0.147
AFP ($\leq 400/\gt 400$ ng/mL)	55/19	93/55	0.087
HBV infection (yes/no)	70/4	135/13	0.372
HCV infection (yes/no)	4/70	2/146	0.079
Child–Pugh (A/B)	70/4	144/4	0.308
CLIP score (0/1/2)	42/25/7	76/55/17	0.735
Follow-up period (months)	56.9 ± 33.5	50.2 ± 32.3	0.760

WBC white blood cell, HGB hemoglobin, PLT platelets, ALT alanine aminotransferase, ALB serum albumin, TBIL total bilirubin, AFP α -fetoprotein, HBV hepatitis B virus, HCV hepatitis C virus, CLIP Cancer of Liver Italian Program

and 79 patients in the hepatectomy group died. At the time of censoring, there was tumor recurrence in 54 patients in the combination group and 96 patients in the hepatectomy group. For the recurrences, 28 patients received RFA, 14 received hepatectomy, and 12 received TACE in the combination therapy group. In the hepatectomy group, 20 patients received re-hepatectomy, 32 patients received RFA, 36 patients received TACE, 5 patients received systemic treatment, and 3 patients received conservative treatment.

The 1, 3, and 5 year overall survival (OS) in the combination group was 94.6, 75.1, and 55.3% respectively, and 91.2, 64.4 and 47.7%, respectively, in the hepatectomy group. The survival curve for the combination therapy group was slightly better than that for the hepatectomy group (Fig. 1a), but there was no significant difference ($P = 0.488$). The 1, 3, and 5 year disease-free survival (DFS) in the combination group was 87.8, 48.3, and 33.5%, respectively, and 68.9, 49.2, and 40.9%, respectively, in the hepatectomy group. The survival curve for the combination therapy group at the 1 year interval was better than that for the combination therapy group; however, at the 3 and 5 years interval, the survival curve for the hepatectomy group was better than that for the combination therapy group (Fig. 2a; $P = 0.619$).

Subgroup analyses

For patients with single tumor smaller than 3.0 cm, the 1, 3, and 5 year OS was 97.7, 76.5, and 57.3%, respectively, in the combination therapy group and 90.0, 66.4, and 51.6%, respectively, in the hepatectomy group. There was no significant difference between these two groups (Fig. 1b; $P = 0.963$). The corresponding DFS was 90.9, 47.0, and 33.4%, respectively, in the combination therapy group, and 71.1, 52.1, and 44.7%, respectively, in the hepatectomy group (Fig. 2b; $P = 0.430$).

For patients with single tumor 3.0–5.0 cm, the 1, 3, and 5 years OS was 90.0, 73.0, and 52.2%, respectively, in the combination therapy group, and 93.1, 61.3, and 41.6%, respectively, in the hepatectomy group (Fig. 1c; $P = 0.193$). The corresponding DFS was 83.3, 50.0, and 33.3%, respectively, in the combination therapy group, and 67.5, 44.6, and 34.9%, respectively, in the hepatectomy group (Fig. 2c; $P = 0.719$).

For patients with multiple tumors, the 1, 3, and 5 years OS was 93.8, 87.5, and 74.0%, respectively, in the combination therapy group and 81.3, 55.7, and 48.8%, respectively, in the hepatectomy group (Fig. 1d; $P = 0.816$). The corresponding DFS was 81.3, 25.0, and 18.8%, respectively, in the combination therapy group, and 59.4, 50.0, and 43.3%, respectively, in the hepatectomy group (Fig. 2d; $P = 0.254$).

Prognostic factors

Multivariate analysis showed that tumor size (HR 1.535, 95% CI 1.021–2.308, $P = 0.040$), ALT (HR 1.792, 95% CI 1.245–2.578, $P = 0.040$), and CLIP score (HR 0.606, 95% CI 0.413–0.888, $P = 0.010$) were significant prognostic factors for OS (Table 2).

For DFS, multivariate analysis showed that ALT (HR 2.004, 95% CI 1.430–2.810, $P < 0.001$) and Child–Pugh class (HR 0.184, 95% CI 0.039–0.875, $P = 0.033$) were significant prognostic factors (Table 3).

Discussion

The present retrospective matched case–control study aimed to compare the safety and effectiveness of TACE + RFA with those of surgical resection in patients with early HCC, and our results demonstrated that the combination therapy of TACE + RFA is a feasible, safe and efficient treatment modality bearing comparable long-term OS and DFS to those of hepatectomy.

There were several studies comparing TACE + RFA with hepatectomy had been reported. Yamakado et al. [23] first reported their study compared TACE + RFA with hepatectomy for patients with HCC within Milan criteria and liver function Child A. For 104 patients in TACE + RFA group and 62 in hepatectomy group, the 5 year OS and DFS in TACE + RFA group (75 and 27%, respectively,) were similar to those of hepatectomy group (81 and 26%, respectively), and there were no significant differences in either major or minor complication rates between groups. After that, Kagawa et al. [22] also reported similar results with a 5 year OS of 64.6% in the TACE + RFA group (62 patients) and 76.9% in the resection group (55 patients) for the same patient population. More recently, Kim et al. [27] from Korea reported their study comparing 37 patients in TACE + RFA group and 47 patients in hepatectomy group with single HCC ranging from 2 to 5 cm, and their results demonstrated that the 4 year OS and DFS in TACE + RFA group (78.4 and 69.4%, respectively,) were similar to those of hepatectomy group (80.3 and 65%, respectively), but major complications occurred more frequently in the hepatectomy group (14.9%) than in the TACE + RFA group (2.7%). In the present study, we conducted a retrospective matched case–control study, 74 patients undergoing TACE + RFA were matched with 148 patients from a pool of 782 patients undergoing hepatectomy during the same treatment period. Although we included some patients with liver function Child–Pugh B and more patients with 2–3 tumors, we got the similar results to the previous studies, showing that the 5 year OS and DFS in TACE + RFA group (55.3 and

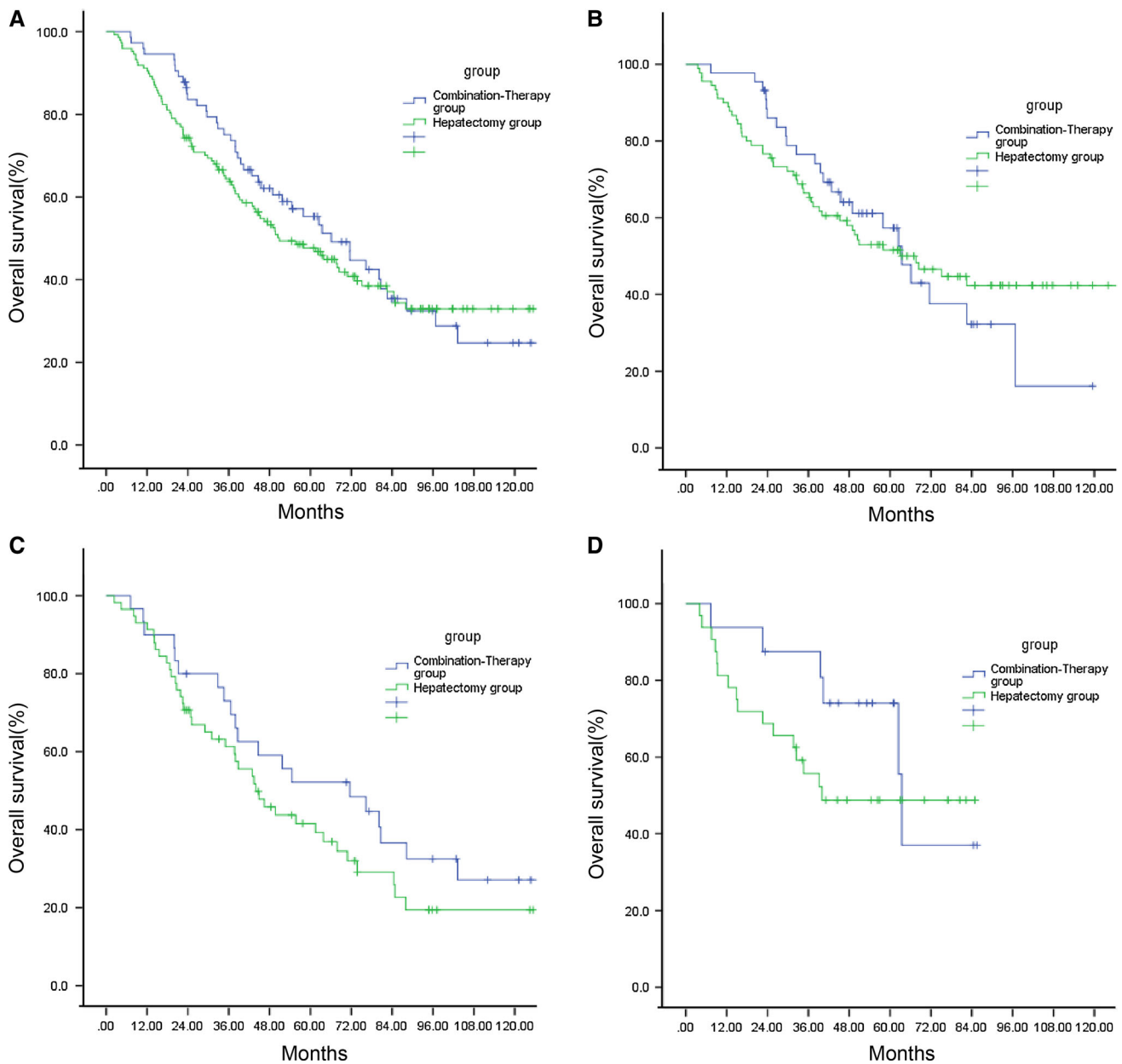


Fig. 1 Kaplan–Meier survival curves for overall survival (OS) in all patients (a), patients with single tumor smaller than 3.0 cm (b), patients with single tumor 3.0–5.0 cm (c), and patients with multiple tumors (d) undergoing the combination therapy and hepatectomy

33.5%, respectively,) were similar to those of hepatectomy group (47.7 and 40.9%, respectively). Our 5 year OS was poorer than previous studies'; it might be due to that we included eight patients with liver function Child–Pugh B and more patients with 2–3 tumors.

Subgroup analyses according to tumor size and number were also performed in the present study. Our results demonstrated that there were no significant differences between the two groups either for patients with single tumor smaller than 3 cm, 3–5 cm, or patients with 2–3 tumors. Recently, studies have shown that the efficacy of TACE + RFA is better than that of RFA alone for medium

HCC and HCC involving multiple tumors. As compared with small HCC, medium HCC was reported to be significantly correlated with a higher local tumor progression after RFA. Furthermore, during follow-up period after treatment, local tumor progression was more frequently observed in patients with medium HCC than small HCC. Our previous randomized controlled trial [28] had demonstrated that the TACE + RFA group achieved better OS and DFS than the RFA group regardless of tumor size and tumor number. TACE before RFA is beneficial because it enables better ablation than that achieved with RFA alone and possibly facilitates the effective treatment

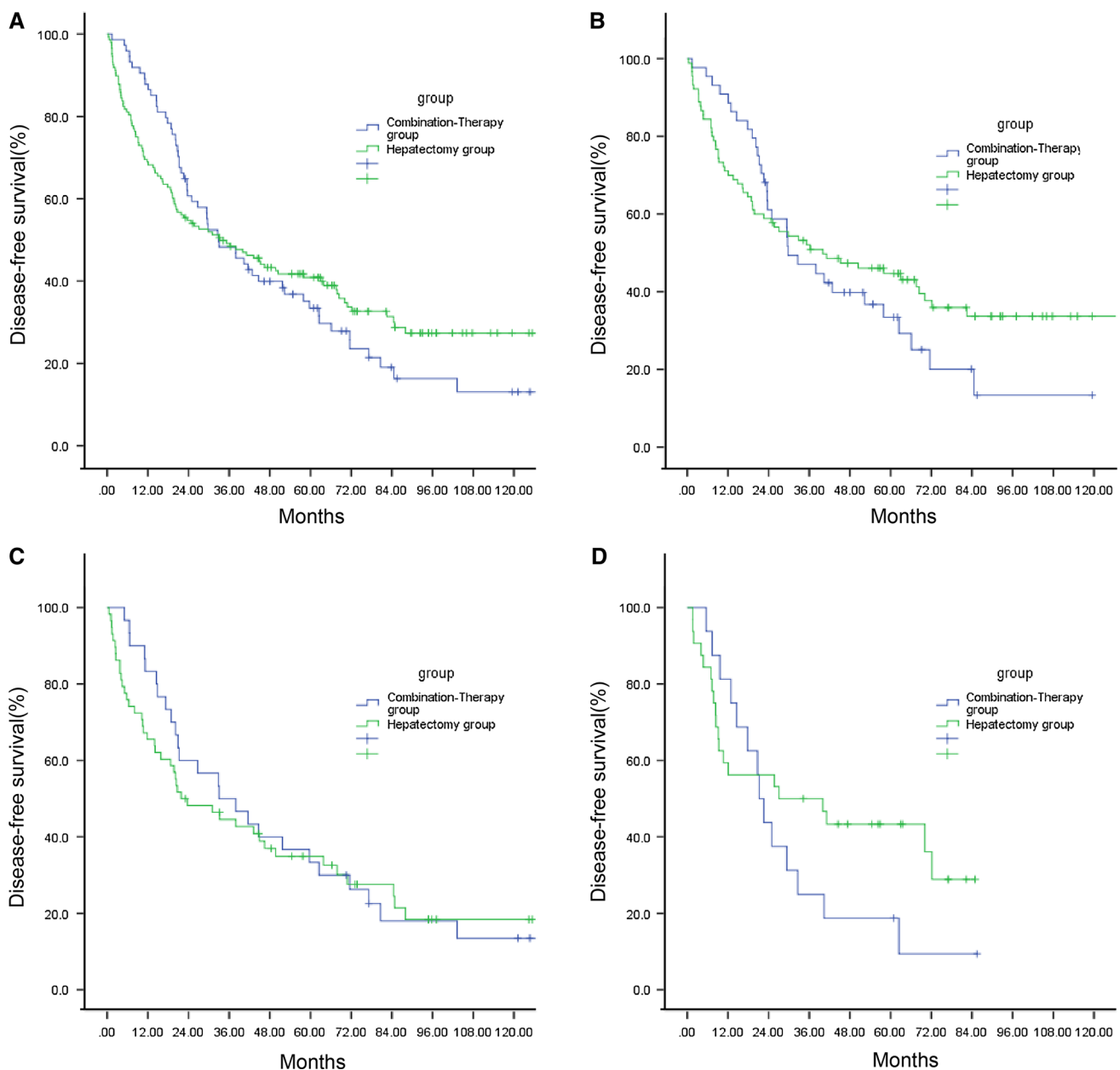


Fig. 2 Kaplan–Meier survival curves for disease-free survival (DFS) in all patients (a), patients with single tumor smaller than 3.0 cm (b), patients with single tumor 3.0–5.0 cm (c), and patients with multiple tumors (d) undergoing the combination therapy and hepatectomy

of patients with larger tumor. Our results re-confirmed that the combination of TACE with RFA seems to efficiently and safely control tumor burden locally.

The presence of an elevated AST level was also revealed as one of the prognostic factors for poor outcome, as it had been reported in previous studies [29]. In patients with chronic hepatitis and cirrhosis, an increase in AST/ALT ratio is associated with progressive liver functional impairment.

Major complications after TACE and RFA are uncommon. In previous studies [19–23], TACE + RFA had been shown to be safe, with major complication rate ranging

from 0 to 2.2%. In present study, there was only one patient (1.4%) with major complications in the TACE + RFA group.

There are some limitations in this study. First, it was a retrospective matched case–control study. There may be an inherent selection bias because of its nonrandomized design. A large-scale randomized controlled trial would be ideal but might be difficult to perform, because in general practice, factors such as tumor location and body constitution affect the choice of treatment. Second, our study included a relatively small number of patients; however, the follow-up periods were relatively long enough. Third,

Table 2 Multivariate analysis of prognostic factors for overall survival

	Cox proportional hazard analysis		
	HR	95.0% CI	P value
Treatment	1.308	0.880–1.944	0.184
Gender	0.357	0.142–1.896	0.280
Age	0.997	0.680–1.462	0.986
Tumor number	1.598	0.146–17.436	0.701
Maximum tumor size	1.535	1.021–2.308	0.040
Hepatitis B	0.726	0.342–1.537	0.402
Hepatitis C	0.762	0.226–2.563	0.660
PLT	0.701	0.061–8.086	0.776
ALB	1.088	0.555–2.132	0.807
ALT	1.792	1.245–2.578	0.002
TBil	0.631	0.098–4.061	0.628
Child–Pugh (A/B)	0.170	0.029–1.001	0.050
AFP	1.860	0.164–21.049	0.616
CLIP	0.606	0.413–0.888	0.010

Table 3 Multivariate analysis of prognostic factors for disease-free survival

	Cox proportional hazard analysis		
	HR	95.0% CI	P value
Treatment	0.990	0.698–1.405	0.957
Gender	0.651	0.327–1.296	0.222
Age	0.898	0.634–1.272	0.546
Tumor number	7.774	0.806–75.012	0.077
Maximum tumor size	1.372	0.939–2.004	0.102
Hepatitis B	1.116	0.590–2.111	0.736
Hepatitis C	1.274	0.426–3.807	0.665
PLT	0.709	0.495–1.014	0.059
ALB	0.967	0.518–1.805	0.917
ALT	2.004	1.430–2.810	<0.001
TBil	1.259	0.251–6.371	0.779
Child–Pugh (A/B)	0.184	0.039–0.875	0.033
AFP	5.483	0.550–54.683	0.147
CLIP	0.195	0.019–1.990	0.168

this study has been conducted in single center only. At last, some patients who underwent the combination therapy did not have a histological diagnosis. Nevertheless, our results indicated that the combination therapy of TACE + RFA can be reserved as an alternative for those patients refused or unsuitable for surgery.

In conclusion, the results of present study showed that the combination therapy of TACE + RFA is a feasible, safe, and efficient treatment achieving long-term survival rates comparable to those of hepatectomy.

Compliance with ethical standards

Ethics approval and consent to participate All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent for publication Publication consent was obtained from all authors.

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

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