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ORIGINAL ARTICLE

Retrospective Study

Effectiveness and safety of sequential transarterial chemoembolization and microwave ablation for subphrenic hepatocellular carcinoma: A comprehensive evaluation

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Abstract

BACKGROUND

Subphrenic carcinoma has been identified as a significant risk factor for the thermal ablation of intrahepatic tumors, resulting in a high rate of residual tumor recurrence. Some studies have proposed that combination treatment with transarterial chemoembolization (TACE) followed by radiofrequency ablation is both feasible and safe for tumors in the subphrenic region. However, research specifically examining the therapeutic outcomes of combination therapy using TACE and microwave ablation (TACE-MWA) in subphrenic tumors is lacking.

AIM

To evaluate the efficacy and safety of TACE-MWA in patients with subphrenic hepatocellular carcinoma (HCC).

METHODS

Between December 2017 and December 2021, 49 patients diagnosed with HCC ≤ 6 cm, who received TACE-MWA, were included in this retrospective cohort study. These patients were classified into subphrenic and non-subphrenic groups based on the distance between the diaphragm and the tumor margin. The rates of local tumor progression (LTP), progression-free survival (PFS), and overall survival (OS) were compared between the two groups. Complications were evaluated by using a grading system developed by the Society of Interventional Radiology.

RESULTS

After a median follow-up time of 38 mo, there were no significant differences in LTP between the subphrenic and non-subphrenic groups (27.3% and 22.2% at 5 years, respectively; *P* = 0.66), PFS (55.5% at 5 years in both groups; *P* = 0.91), and OS (85.0% and 90.9% in the subphrenic and non-subphrenic groups at 5 years; *P* =

0.57). However, a significantly higher rate of LTP was observed in subphrenic HCC > 3 cm compared to those ≤ 3 cm (P = 0.085). The dosage of iodized oil [hazard ratio (HR): 1.52; 95% confidence interval (CI): 1.11-2.08; P = 0.009] and multiple tumors (HR: 13.22; 95%CI: 1.62-107.51; P = 0.016) were independent prognostic factors for LTP. There were no significant differences in complication rates between the two groups (P = 0.549).

CONCLUSION

Combined TACE and MWA was practical and safe for managing subphrenic HCC. The efficacy and safety levels did not vary significantly when tumors outside the subphrenic region were treated.

Key Words: Hepatocellular carcinoma; Transarterial chemoembolization; Microwave ablation; Prognosis; Subphrenic

Core Tip: Tumors located under the diaphragm present a challenge when it comes to percutaneous thermal ablation of liver tumors, as they have a higher likelihood of recurrence compared to resection and laparoscopic ablation. There is a solution that can enhance the accuracy of localization and increase the coverage of ablation: the combination of transarterial chemoembolization and percutaneous thermal ablation. In addition, the concurrent application of multiple antennas to create a confluent ablation zone has been successfully employed in recent years. Thus, we aim to investigate the effectiveness and safety of the combination therapy for tumors located under the diaphragm.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and the leading cause of death in patients with cirrhosis[1,2]. However, in clinical practice, only 20%-30% of patients diagnosed with HCC are considered ideal candidates for surgical treatment[3]. Among the various thermal ablation techniques, radiofrequency ablation (RFA) is the most well-studied, utilizing high-frequency alternating electric current to heat tissue[1,4].

Microwave ablation (MWA) is a recently widely used thermal ablation treatment that induces tissue coagulation using electromagnetic waves around a monopolar antenna. It offers several advantages over RFA, including higher temperature, shorter time, a more predictable ablation zone, and less susceptibility to heat sinks[5-7]. Many preclinical and clinical studies have shown that MWA is more suitable than RFA for treating high-risk tumors (adjacent to a large vessel, gallbladder, subcapsular, gastrointestinal tract, or subphrenic) or tumors > 3 cm[8-10].

Subphrenic tumors are commonly considered independent risk factors for incomplete ablation[11]. Ultrasound images often do not clearly show tumors near the diaphragm because the view is obscured by the lung and ribs[12]. Similarly, computed tomography (CT) images may not be able to visualize tumors after antenna placement because of overlapping metallic artifacts. Additionally, there are concerns about potential thermal injury to the adjacent diaphragm, leading to lower-power protocols for treating these tumors compared with those in non-subphrenic areas[13]. As a solution, artificial ascites has been used to decrease the temperature of the diaphragm near the ablation area and allow for more power to be applied to the target lesion by altering the relative distance between the cancer and the hepatic dome[14]. However, it is important to note that artificial ascites may not be successful in certain patients with abdominal adhesions, and there is an ongoing debate regarding its utilization, given the comparable technical success and complication rates observed in combined therapy in which artificial ascites has not been applied[15-17].

Previous studies have demonstrated that transarterial chemoembolization (TACE) combined with ablation therapy improves the accuracy of antenna placement and enlarges the ablation zone[18,19]. Yamakado *et al*[17] indicated that there was no difference between subphrenic and non-subphrenic tumors in terms of local tumor control and treatment safety using TACE followed by RFA without artificial ascites. However, there is a lack of literature that separately describes TACE followed by MWA for the treatment of subphrenic tumors. Additionally, with advancements in technology and protocols, the concurrent application of multiple antennae to create a confluent ablation zone has been successfully employed for medium-sized tumors in recent years[20]. Therefore, we aimed to explore the efficacy and safety of the combination of TACE and MWA in subphrenic HCC.

MATERIALS AND METHODS

Patient population

This retrospective study was approved by our institutional review board and conducted in accordance with the Declaration of Helsinki. A waiver of informed consent was granted. We examined the clinical records of 412 consecutive patients who received TACE-MWA treatment (TACE followed by MWA) between December 2017 and December 2021. HCC was diagnosed based on the American Association for Liver Disease guidelines, and a liver biopsy was performed if deemed necessary[21]. All patients who underwent TACE-MWA had been deemed ineligible for, or refused, surgical resection (SR) or liver transplantation (LT) after consultation with a multidisciplinary team (including hepatologists, radiologists, oncologists, and anesthesiologists) and were fully informed about the benefits and drawbacks of each approach. CT-guided MWA was performed 4-6 weeks after TACE, depending on the embolization syndrome and the recovery time of liver function.

All patients who received TACE-MWA and met the inclusion criteria were enrolled in this study (Table 1). Based on the tumor's location on axial or coronal images of preoperative enhanced CT or magnetic resonance imaging (MRI), 27 patients were assigned to the subphrenic group when the cancer was abutting the diaphragm (maximum distance from the tumor to the diaphragm ≤ 5 mm). Twenty-two patients were assigned to the non-subphrenic group when the cancer was distinct from that of the diaphragm (Figure 1).

TACE

TACE was performed 4-6 weeks before MWA, as reported in our previous study[22]. Briefly, a 5F RH catheter (Terumo, Tokyo, Japan) was introduced over a 0.035-inch hydrophilic guidewire (Terumo) to catheterize the celiac, superior mesenteric artery, and any suspected artery feeding the tumor. Digital subtraction angiography was performed to accurately determine the tumor location and size. After superselective catheterization of the distal target artery, chemoembolization was performed using a combination of epirubicin (20-40 mg; Pharmorubicin; Pfizer, Wuxi, China) and iodized oil (1-10 mL; Lipiodol Ultra Fluid; Hengrui, Jiangsu Province, China), depending on liver function, tumor size, and vascular supply. To achieve arterial flow stasis and prevent tumor staining, further embolization with precision-administered gelatin sponge particles (Hangzhou Alc, Hangzhou, Zhejiang Province, China) was performed until satisfactory results were obtained as evaluated by repeat angiography.

CT-guided MWA

The MWA procedure was conducted 4-6 weeks after the TACE. Two clinical MWA systems were used: KY-2000 (Canyou Medical Inc., Jiangsu Province, China) and ECO-100AI10 (ECO Medical Inc., Jiangsu Province, China). Both systems contained two autonomous microwave generators operating at a frequency of 2450 MHz and a power output range of 1-100 W. These systems can simultaneously propel microwave energy into tumor tissue *via* two water-cooled 15-gauge (1.9 cm) antennas through two flexible coaxial cables. Each CT-guided procedure was performed percutaneously by two board-certified operators with a minimum of 5 years of experience. Following conscious sedation and local anesthesia, a single antenna was placed at the tumor center if the diameter was 2 cm or less. In comparison, for tumors larger than 2 cm, two antennas were used and inserted simultaneously at a separation distance of 1.0-1.5 cm in the upper part of the tumor, with the energy application set at 45-55 W for 5-10 min per session. Subsequently, the antennae were removed and reinserted into the lower part of the tumor using the same protocol. The antenna inclination angle was considered when selecting either a transpulmonary or transhepatic route. A minimum of four ablation zones were required to attain an ablation zone overlap across the entire tumor surface in the 3D space. To reduce residual lesions near the diaphragm from excessive antenna tilt angles, the ablation antenna was maneuvered as close as possible to the diaphragm, utilizing the transpulmonary route. This effectively extended the ablation range to the upper part of the lesion. The outpower setting, ablation duration, and antenna placement were contingent on the tumor dimensions, shape, and location. After treatment, all patients underwent track ablation to prevent tumor bleeding and seeding.

Outcome assessment and follow-up

Primary technical success was determined by the disappearance of contrast enhancement within or abutting the ablation zone on imaging examination 1 mo after therapy. The primary outcomes were local tumor progression (LTP), progression-free survival (PFS), and overall survival (OS). LTP was defined as the recurrence of any tumor adjacent to the ablation zone that was previously considered completely ablated. PFS was defined as the follow-up time without any events, such as local tumor progression, intrahepatic distant recurrence, extrahepatic recurrence, or death. OS was defined as the interval between the first administration of the study treatment and either death or the end of the study, which in this case was March 2023. Complications were assessed by using the Society of Interventional Radiology grading system[23]. Enhanced liver CT/MRI scans and laboratory tests were performed to determine treatment outcomes at 1 mo and 3 mo after treatment. Follow-up scans were conducted at 3-mo intervals during the 1st year, and then at approximately 6-mo intervals. All follow-up images were thoroughly reviewed by two board-certified radiologists, who reached a consensus. Each radiologist had over 5 years of experience in abdominal imaging and thermal ablation to ensure the accuracy and reliability of the results.

Statistical analysis

The statistical software packages R (http://www.R-project.org, The R Foundation) and Free Statistics version 1.7 were used for all analyses, and a two-sided $P < 0.05$ was considered statistically significant. Categorical variables are presented as proportions (%), while continuous data are expressed as either the mean ± SD or the median and interquartile range

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Age range 18-75 years	Age < 18 years or > 75 years
HCC diagnosis according to AASLD guideline	No pathology or image evidence
Child-Pugh grade A or B	Child-Pugh grade C
BCLC grades A and B	BCLC grade C
ECOG score ≤ 2	ECOG score > 2
Tumor number ≤ 2	Tumor number > 2
Tumor diameter ≤ 6 cm	Tumor diameter > 6 cm
The nonsubphrenic tumor diameter ≤ 2 cm	The nonsubphrenic tumor diameter > 2 cm
No intrahepatic vascular invasion	Intrahepatic vascular invasion
PLT > 40 × 10^9	PLT ≤ 40 × 10^9

AASLD: American Association for Liver Disease; BCLC: Barcelona Clinic Liver Cancer; ECOG: Eastern Cooperative Oncology Group; PLT: Platelet; HCC: Hepatocellular carcinoma.

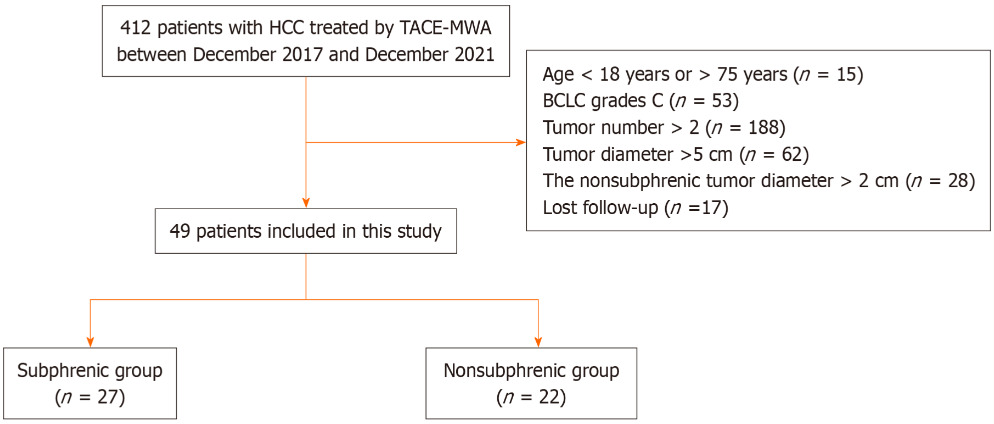

Figure 1 Flowchart of patient selection. BCLC: Barcelona Clinic Liver Cancer; HCC: Hepatocellular carcinoma; MWA: Microwave ablation; TACE: Transarterial chemoembolization.

(IQR), as appropriate. Univariate and multivariate Cox regression analyses were used to predict prognostic factors for LTP. Survival curves were plotted using Kaplan-Meier and log-rank analyses.

RESULTS

The baseline patient characteristics are presented in Table 2. The transpulmonary approach was more commonly used in the subphrenic group than in the non-subphrenic group, but the dose of doxorubicin administered per session was significantly higher in the non-subphrenic group. The two groups showed no significant difference in the number of patients with multiple tumors or the mean tumor size. Two patients with cirrhosis and subphrenic HCC were treated with TACE-MWA presented in Figure 2.

LTP

The median follow-up period for the subphrenic group was 37.5 mo (range: 13.0-64.0 mo) and 38.5 mo (range: 27.0-64.0 mo) for the non-subphrenic group. LTP was observed in six of 27 (22.2%) patients in the subphrenic group and 6 of 22 (27.3%) patients in the non-subphrenic group. The cumulative 1-, 2-, 3-, and 5-year LTP rates were 14.8%, 22.2%, 22.2%, and 22.2% in the subphrenic group and 18.2%, 27.3%, 27.3%, and 27.3% in the non-subphrenic group, respectively. No significant intergroup differences were observed (P = 0.66) (Figure 3A). Univariate and multivariate Cox regression analyses showed that the dose of iodized oil [hazard ratio (HR): 1.52; 95% confidence interval (CI): 1.11-2.08; P = 0.009] and multiple tumors (HR: 13.22; 95%CI: 1.62-107.51; P = 0.016) were independently associated with poorer LTP (Table 3).

Table 2 Baseline characteristics of study patients

Variables	Total, *n* = 49	Subphrenic HCC, *n* = 27	Nonsubphrenic HCC, *n* = 22	*P* value	Statistic
Sex				0.646	Fisher
Male	44 (89.8)	25 (92.6)	19 (86.4)		
Female	5 (10.2)	2 (7.4)	3 (13.6)		
Age in years	58.0 ± 9.3	58.7 ± 10.1	57.2 ± 8.4	0.595	0.287
Etiology				0.608	Fisher
HBV	41 (83.7)	24 (88.9)	17 (77.3)		
HCV	5 (10.2)	2 (7.4)	3 (13.6)		
Non-hepatitis virus	3 (6.1)	1 (3.7)	2 (9.1)		
Child-Pugh class				0.388	Fisher
A	43 (87.8)	25 (92.6)	18 (81.8)		
B	6 (12.2)	2 (7.4)	4 (18.2)		
AFP				0.646	Fisher
< 200 ng/mL	44 (89.8)	25 (92.6)	19 (86.4)		
≥ 200 ng/mL	5 (10.2)	2 (7.4)	3 (13.6)		
PLT as 10^9/L	105.5 ± 70.9	119.1 ± 87.6	88.9 ± 38.3	0.139	2.264
Undergone hepatectomy				0.146	2.112
No	35 (71.4)	17 (63.0)	18 (81.8)		
Yes	14 (28.6)	10 (37.0)	4 (18.2)		
Amount of iodized oil in mL	4.4 ± 2.6	4.6 ± 3.1	4.2 ± 1.8	0.597	0.283
Amount of epirubicin in mg	26.9 ± 7.1	24.8 ± 8.0	29.5 ± 4.9	0.019	5.877
Tumor number				0.617	Fisher
Single	45 (91.8)	24 (88.9)	21 (95.5)		
Multiple	4 (8.2)	3 (11.1)	1 (4.5)		
Tumor size in cm	3.2 ± 1.2	3.4 ± 1.1	3.0 ± 1.2	0.255	1.327
Transpulmonary				< 0.001	19.958
No	25 (51.0)	6 (22.2)	19 (86.4)		
Yes	24 (49.0)	21 (77.8)	3 (13.6)		

Data are *n* (%) or mean ± SD. AFP: Alpha-fetoprotein; HBV: Hepatic B virus; HCV: Hepatic C virus; PLT: Platelet; HCC: Hepatocellular carcinoma.

Five patients from the subphrenic and non-subphrenic groups were treated with secondary MWA to manage local tumor progression. Subsequently, contrast-enhanced CT/MRI was performed, which revealed complete ablation of the residual tumor. After a multidisciplinary team discussion, one patient in the subphrenic group underwent surgical resection 3 mo after combination treatment, because MWA was having little effect on the residual tumor.

PFS and OS

The 1-, 3-, and 5-year PFS rates were 85.2%, 55.5%, and 55.5%, respectively, in the subphrenic group and 73.0%, 55.5%, and 55.5%, respectively, in the non-subphrenic group (P = 0.91) (Figure 3B). Four of 27 patients (14.8%) in the subphrenic group and two of 22 patients (9.1%) in the non-subphrenic group died. The cumulative OS rates in the subphrenic group were 100%, 88.8%, and 85.0% at 1-, 3-, and 5-years respectively. In the non-subphrenic group, the corresponding cumulative survival rates were 100.0%, 95.4%, and 90.9%, respectively. Despite the observed differences, the statistical analysis did not reveal any significant differences between the two groups (P = 0.57) (Figure 3C).

Subgroup analysis of the subphrenic group

To examine the relationship between tumor diameter and the LTP rate, 27 patients in the subphrenic group were divided into two groups according to the tumor diameter; ≤ 3 cm and > 3 cm (small and medium groups). The mean maximum tumor diameter was 2.1 cm ± 0.5 cm in the small group and 3.9 cm ± 0.9 cm in the medium group. In the medium group,

Table 3 Univariate and multivariate analysis of local tumor progression using Cox regression model

Variable	Local tumor pregression			
	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Female sex	0 (0-Inf)	0.086	ND	ND
Age	1.02 (0.96-1.09)	0.487	ND	ND
Etiology		0.407	ND	ND
HCV	Reference		ND	ND
HBV	1.31 (0.17-10.11)		ND	ND
Non-viral	0 (0-Inf)		ND	ND
CP B	0.66 (0.08-5.08)	0.668	ND	ND
AFP ≥ 200 ng/mL	2.07 (0.45-9.46)	0.388	ND	ND
PLT	1.0031 (0.9966-1.0096)	0.381	ND	ND
Non-undergone hepatectomy	0.46 (0.10-2.08)	0.271	ND	ND
Amount of iodized oil in mL	1.34 (1.15-1.57)	0.001	1.52 (1.11-2.08)	0.009
Amount of epirubicin in mg	1.07 (0.96-1.19)	0.174	ND	ND
Tumor number of 2	3.23 (0.70-14.80)	0.186	13.22 (1.62-107.51)	0.016
Tumor size in cm	2.59 (1.48-4.52)	< 0.001	ND	ND
Transpulmanory: 1 *vs* 0	1.50 (0.48-4.72)	0.487	ND	ND
Nonsubphrenic *vs* subphrenic	1.29 (0.42-4.00)	0.661	ND	ND

AFP: Alpha-fetoprotein; CI: Confidence interval; CP: Child-Pugh classification; HBV: Hepatic B virus; HCV: Hepatic C virus; HR: Hazard ratio; ND: Not done; PLT: Platelet.

the cumulative 1-, 3-, and 5-year LTP rates were 15.0%, 22.2%, and 22.2%, respectively. However, no LTP was observed in the small group (P = 0.085). The cumulative LTP rate of patients with medium tumors significantly increased with tumor diameter.

Complications

No treatment-related mortality was observed in either group. However, one patient (3.7%) in the subphrenic group, experienced a major Class C complication of pneumonia and received closed thoracic drainage treatment. In contrast, one patient (4.5%) in the non-subphrenic group experienced a major Class D complication, with a bacterial lung infection that necessitated anti-infective therapy. Minor complications, such as vomiting, fever, nausea, and puncture point or right shoulder pain, were observed in 6 of 27 patients (22.2%) in the subphrenic group and 2 of 22 patients (9.1%) in the non-subphrenic group (P = 0.549). All minor complications were transient and resolved before discharge.

The transpulmonary approach was used in 21 patients in the subphrenic group and 3 from the non-subphrenic group. Among these patients, pneumothorax occurred in six individuals (28.5%) in the subphrenic group compared to none in the non-subphrenic group. One patient (4.7%) with a pneumothorax underwent closed chest drainage to alleviate breathing difficulties. Following a chest CT scan that confirmed the disappearance of the pneumothorax, the drain was removed the following day.

DISCUSSION

Our study is the first to explore the therapeutic outcomes of the TACE followed by MWA under CT guidance, comparing subphrenic HCC to non-subphrenic HCC. We observed comparable LTP, PFS, and OS outcomes between the subphrenic and non-subphrenic groups. In addition, no LTP was found in the subphrenic subgroup with small (≤ 3 cm) tumors. However, for medium-sized subphrenic HCC (> 3 cm), the 5-year LTP rate was only 22.5%.

Subphrenic or subdiaphragmatic tumor ablation is associated with a high incidence of local tumor progression and treatment-related complications[11,24,25]. The main challenge for complete ablation may be the accuracy of tumor targeting due to obscuration by the pulmonary tissue. Although some studies have reported the use of auxiliary techniques (artificial pleural effusion, artificial ascites, artificial pneumothorax, or artificial ventilation) to improve tumor visibility, some small nodules in patients with severe cirrhosis may remain undetected. Two recent studies compared

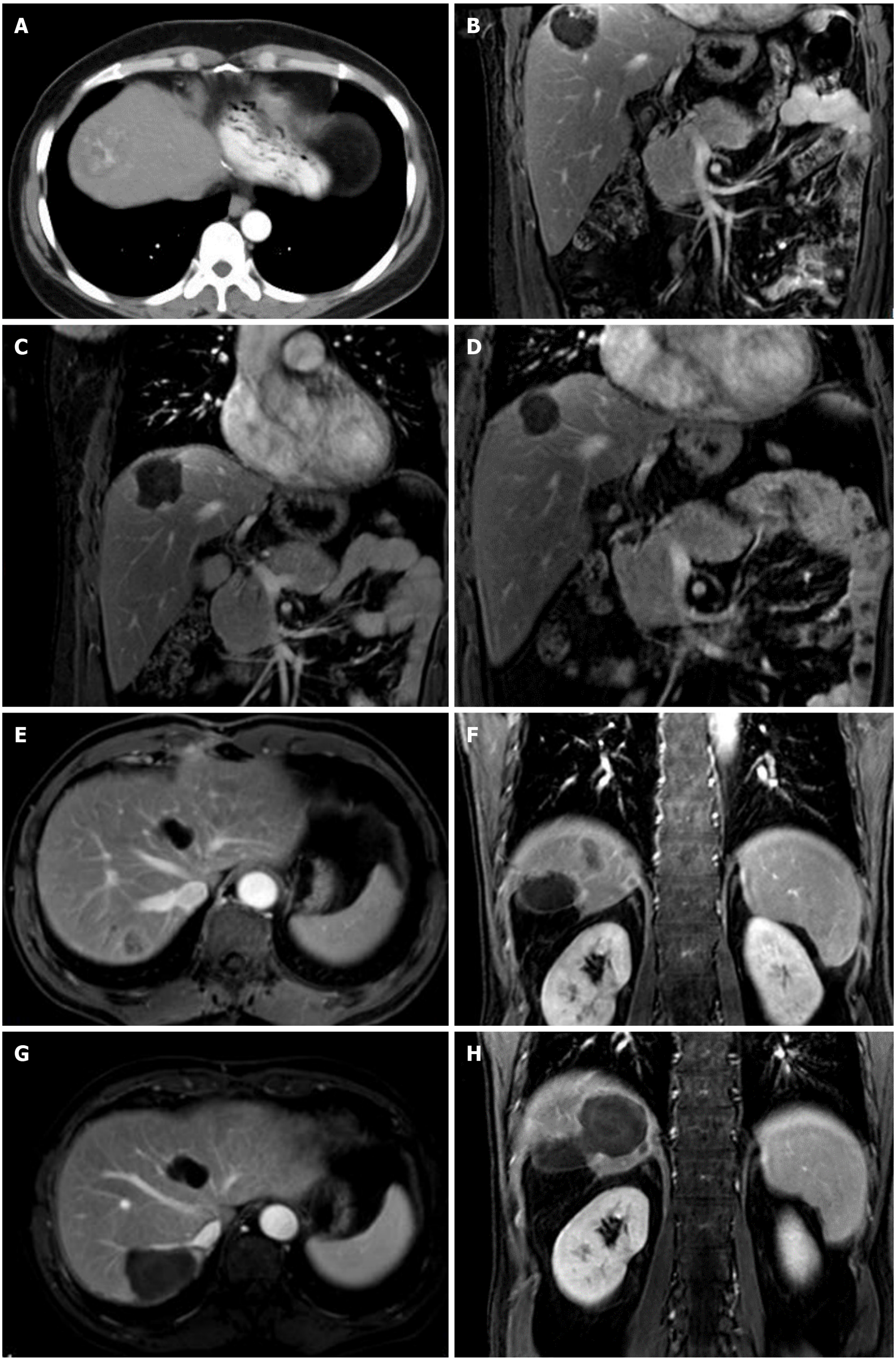

Figure 2 Two patients with cirrhosis and subphrenic hepatocellular carcinoma were treated with transarterial chemoembolization-microwave ablation. A-D: 50-year-old female with cirrhosis and subphrenic hepatocellular carcinoma measuring 5.0 cm in maximum diameter in segment 8 of the liver. Preprocedure axial contrast computed tomography shows a hypervascular tumor in the liver dome (A); coronal enhanced magnetic resonance imaging (MRI)

showing suspicious residues within the upper part of the tumor after transarterial chemotherapy with a combination of 30 mg of epirubicin and 5 mL iodized oil (B); 1 mo after the combination treatment, coronal contrast MRI showed that the ablation area encompassed the tumor and was close to the diaphragm (C); 4 years after the combination treatment, coronal contrast MRI showed no residual tumor and significant shrinkage of the ablation area compared with 1-mo postprocedure (D); E-H: 65-year-male with cirrhosis and subphrenic hepatocellular carcinoma measuring 3.2 cm in maximum diameter in segment 7 of the liver. Preoperative axial and coronal contrast MRI showing a hypervascular tumor in the liver dome (E and F); 1 mo after combination treatment, axial and coronal contrast MRI showed that the ablation area encompassed the tumor and was close to the diaphragm and right hepatic vein (G and H).

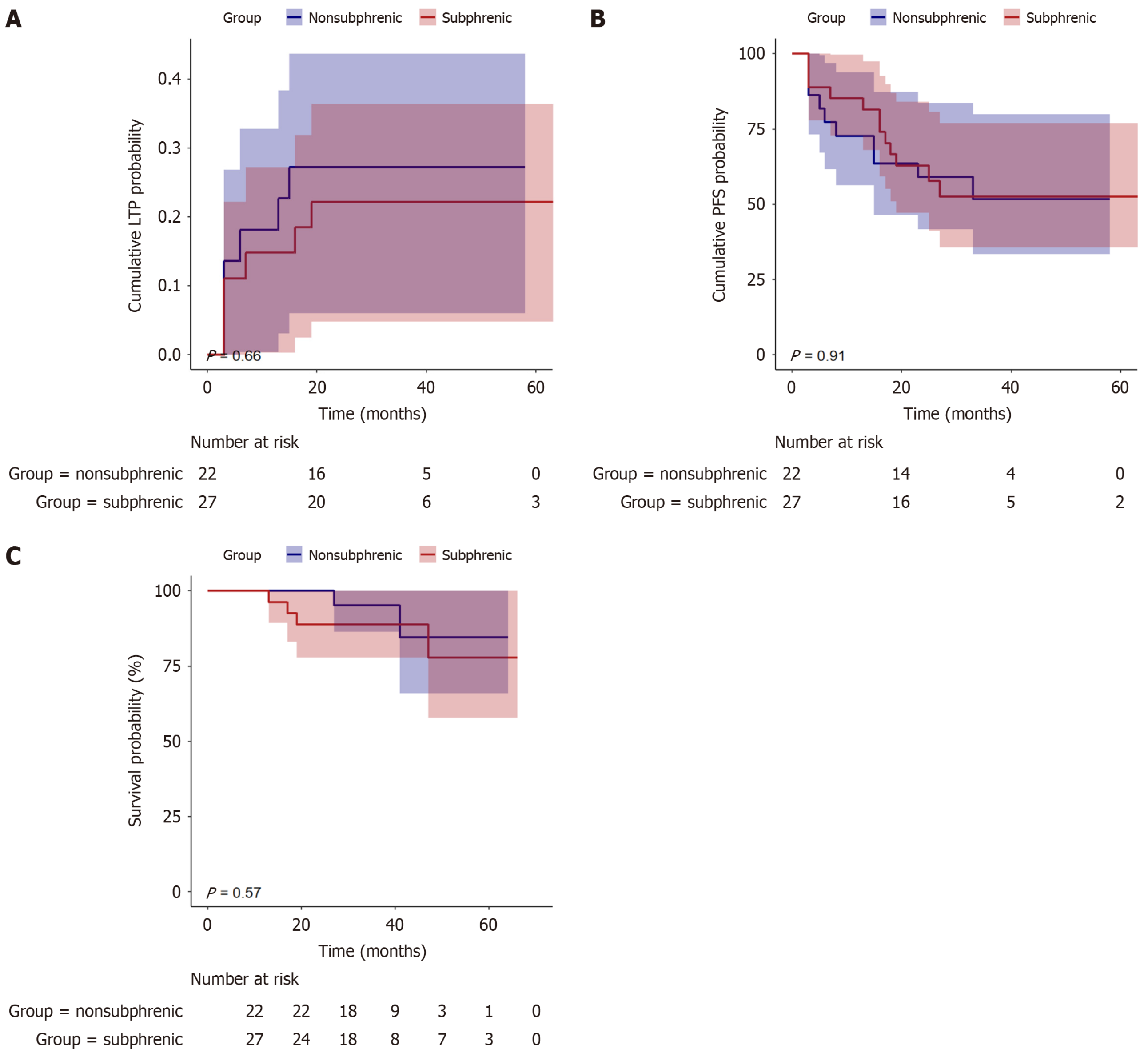

Figure 3 Cumulative local tumor progression rate, the cumulative progression-free survival, and the cumulative overall survival were not significantly different between the subphrenic and non-subphrenic groups. A: Local tumor progression (LTP) rate; B: Cumulative progression-free survival (PFS); C: Cumulative overall survival (OS).

ultrasonography-guided RFA with laparoscopic RFA or hepatic resection and reported 5-year LTP rates of 23.4% and 46.0%, respectively, in the ultrasonography group[11,26]. Therefore, some interventional radiologists prefer CT guidance for the treatment of tumors abutting the diaphragm. During TACE followed by thermal ablation, tumor visualization can be improved by injecting iodized oil into the feeding artery, especially for HCC characterized by vascularity. Kim *et al*[27] performed TACE combined with RFA for subphrenic HCC ≤ 3 cm using a transhepatic route and reported a 5-year LTP rate of 12.1%, similar to our findings. In our center, although the transhepatic route is preferred, the transpulmonary route is sometimes required to place the antennas parallel to the long axis of the lesion, even at the cost of an increased incidence of pneumothorax. This study used the transpulmonary route in 21 patients with subphrenic tumors (77.8%). Six patients (28.5%) had pneumothorax at the end of the session, and one patient (4.7%) required closed chest drainage, which is inferior to the results of Yamakado *et al*[17] using TACE-RFA combination treatment for subphrenic HCC of < 5 cm.

Compared to the treatment of HCC of ≤ 2 cm using only one antenna, tumors ranging between 2-5 cm require the application of multiple antennas to create a nearly spherical ablation zone with a sufficient safety margin[20,28-31]. In our center, we typically perform TACE before MWA to reduce vascularity in the treated area and increase the size of the ablation zone. Additionally, the intrahepatic marker induced by iodized oil deposited during TACE assists in calculating the distance between the tumor margin and the antenna, allowing us to determine whether the tailored ablation zone adequately covers the tumor with a safe margin. In our subgroup study focusing on tumors > 3 cm in size, the local tumor control rate was comparable to that reported by Andresciani *et al*[20] and Cazzato *et al*[29], but the 5-year LTP rate was not as good as that reported by Yamakado *et al*[17]. However, the mean tumor diameter in our subgroup study was larger than in the latter study.

The occurrence of diaphragmatic hernias during thermal ablation has been documented in literature, with most studies focusing on the use of deployable radiofrequency electrodes[13,26,32,33]. Only one study utilized MWA[34]. In the absence of large-scale prospective randomized controlled studies, it is difficult to definitively conclude that MWA is safer than RFA for subphrenic tumor ablation. However, MWA has inherent advantages over RFA. This technique employs electromagnetic waves to generate heat and does not require close contact with the diaphragm. Furthermore, the diameter of the charred ablation zone around the antenna, which has the potential to cause diaphragmatic hernias, remains relatively constant. Therefore, maintaining a consistent distance between the diaphragm and the microwave antenna could theoretically reduce the occurrence of diaphragmatic hernias[17,33].

Artificial pleural fluid, or ascites, is another auxiliary technique that protects the diaphragm from thermal injury. However, there is ongoing debate regarding the success rate of this technique and its associated complications[32]. While artificial pleural fluid and ascites can enhance tumor visibility under ultrasound guidance and reduce thermal injury to the diaphragm, our study found no significant differences in effectiveness and safety compared to previous studies, even without artificial ascites[9,25-27,29]. This finding aligns with that of Yamakado *et al*[17]. We hypothesized that although combination therapy might increase the extent of ablation, it primarily extends the non-charred area at the periphery. Consequently, the temperature in these areas could potentially cause discomfort to the patient but is unlikely to result in perforation. When ablating subphrenic tumors at our center, the antennas were parallel to the diaphragm, and placed at least 1 cm away from the diaphragm. We carefully monitored for right shoulder pain syndrome during the session and maintained a low power for a long time. In this study, only a few patients experienced right shoulder pain that resolved within a few days.

Several studies have highlighted the benefits of combination treatments. However, little research has been conducted on the ideal time interval between TACE and thermal ablation. The main advantage of the combination treatment lies in its ability to expand the ablation zone, which is influenced by the level of blockage of the tumor feeder artery through TACE. However, the feeder artery tends to recanalize shortly after embolization. As a result, a shorter interval between TACE and ablation leads to a larger ablation zone in combination treatment. Several studies have demonstrated that shorter intervals can improve the local tumor control rate by enlarging the ablation zone. However, it is essential to note that shorter time intervals may also cause acute liver function deterioration and complications due to excessive tissue heating. In an animal study by Lee *et al*[35], RFA performed immediately after TACE resulted in severe acute hepatic damage compared to RFA performed five days after TACE. Similarly, in a retrospective study by Kim *et al*[27], five patients experienced subsegmental hepatic infarction after RFA immediately following TACE treatment. Another retrospective study, by Feng *et al*[36], investigated the impact of varying time intervals on treatment outcomes and found that a time interval of 3-5 weeks was optimal, providing the longest survival time and minimal effect on liver function when compared with intervals of 1-2 weeks or 6-7 weeks. In this study, MWA was performed 4-6 weeks after TACE. Of all the patients, only six (12.2%) had a Child-Pugh score of B, and none experienced an upgrade in their Child-Pugh score due to chemoembolization. This can possibly be attributed to better liver function reserve, which may explain why the study did not show significant superiority in local tumor control rate but did observe a comparable 5-year survival rate.

Our study has several limitations. Owing to its retrospective design and relatively small sample size, the scope of this study was limited. Additionally, a significant proportion of patients in our study were postoperative and infected with hepatitis B virus, both of which are known to increase recurrence and decrease survival rates[37]. Therefore, the therapeutic outcomes may not be generalizable to other populations. Two different microwave devices were used in this study, and the primary parameters were similar to those in the manufacturer's protocol. However, there is the possibility of potential confounding factors affecting the results. Our multivariate analysis suggested that the dose of iodized oil used in TACE may be positively associated with local tumor progression. However, the amount of iodized oil utilized intraoperatively may not equate to the amount deposited in the tumor. There is no precise method for measuring the amount of iodized oil deposited in tumors. Therefore, animal experiments are necessary to determine the relationship between the amount of iodized oil deposited in the tumor and size of the ablation area.

CONCLUSION

In conclusion, our study demonstrates that the combination of TACE and MWA is an effective and safe method for treating subphrenic HCC. Furthermore, the therapeutic outcomes were comparable to those observed in non-subphrenic HCC.

FOOTNOTES

Author contributions: Yuan M contributed to the conception and design; Qian Z, Qin ZQ, Xie B, Wei JZ, and Yang PP are responsible for the provision of the study materials and data collection; Zhu ZY and Yuan M contributed to the data analysis and interpretation; Zhu ZY contributed to the manuscript writing; All authors read and approved the final manuscript.

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