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Percutaneous microwave ablation combined with simultaneous transarterial chemoembolization for hepatocellular carcinoma with macrovascular invasion or extrahepatic metastases

Mengfei Wu [a], Shanshan Gao [a,b], Huadan Song [a], Zihan Zhang [a], Zhiyuan Zheng [a,b], Zhiping Yan [a,b], Xiaolin Wang [a,b], Jianhua Wang [a,b], Lingxiao Liu [a,b,*]

[a] Department of Interventional Radiology, Zhongshan Hospital, Fudan University, Shanghai, 200032, China
[b] Shanghai Institute of Medical Imaging, Shanghai, 200032, China

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ABSTRACT

Objective: To evaluate the safety and efficacy of percutaneous microwave ablation (MWA) combined with simultaneous transarterial chemoembolization (TACE) in patients with hepatocellular carcinoma (HCC) patients with microvascular invasion (MVI) or extrahepatic metastases (EHM).
Methods: Between August 2012 and April 2017, 101 patients with MVI/EHM of HCC underwent percutaneous MWA combined with simultaneous TACE at our center. The clinical data were collected and analyzed for survival and prognostic factors.
Results: The mean follow-up time was 23.6 ± 14.7 months. One patient had grade 3 complications, and the median overall survival was 12.0 months (95% confidence interval 9.7–14.3). Multivariate analysis showed that Child-Pugh class, serum alpha-fetoprotein level, and Eastern Cooperative Oncology Group performance status were independent factors of survival.
Conclusion: Our results suggest that percutaneous MWA combined with simultaneous TACE is a safe and effective treatment for HCC with MVI/EHM.

Introduction

Hepatocellular carcinoma (HCC) has a high incidence worldwide.[1] Although hepatology and oncology societies recommend regular monitoring of high-risk populations[2], most of the developing countries does not have a well-established HCC surveillance system. In that condition, 30–35% of patients are diagnosed at stage C HCC according to the Barcelona Clinic Liver Cancer (BCLC) staging system(3), which means the patients have macrovascular invasion (MVI), extrahepatic metastases (EHM), or poor performance status (PS).[4] Currently, the BCLC system is widely used in most clinical treatment decisions. Targeted drugs represented by sorafenib are recommended treatment for patients with stage C HCC. Although the use of sorafenib has been shown to prolonged the median overall survival (OS) of patients with stage C HCC, the high cost of this drug[5] has hindered the full implementation of the BCLC recommendation. Moreover, this recommendation does not adequately take into account the heterogeneity of patients with stage C HCC.[3] Researchers are making unceasing efforts to improve the treatment of patients with stage C HCC.[6,7] This study aimed to retrospectively analyzed the survival of HCC patients with MVI and/or EHM treated by percutaneous microwave ablation (MWA) combined with simultaneous transarterial chemoembolization (TACE) treatment at our center.

Materials and methods

Patients

A total of 101 HCC patients with description above between August 2011 and April 2017 were included in this retrospective study. All patients signed and consented their conditions to be used as analytical data.

The inclusion criteria were: (i) HCC diagnosed on the basis of pathologic evaluation or the diagnostic criteria of American Association for the Study of Liver Diseases(8), (ii) MVI (incomplete portal occlusion or presence of portal vein collateral circulation) or EHM on radiology, (iii) Child-Pugh class A/B, and (iv) Eastern Cooperative Oncology Group (ECOG) PS 0–2 score. The exclusion criteria were (i) uncorrectable

* Corresponding author. Department of Interventional Radiology, Zhongshan Hospital, Fudan University, Shanghai 200032, China.
E-mail address: liu.lingxiao@zs-hospital.sh.cn (L. Liu).

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coagulation abnormalities, (ii) hepatic encephalopathy, massive ascites, or other serious complications, and (iii) other malignant tumors.

Preoperative examination

Abdominal enhanced computed tomography (CT)/magnetic resonance imaging (MRI) examination was performed within 2 weeks before treatment. Moreover, routine blood parameters, liver and kidney function, electrolytes, coagulation function, and levels of serum alpha-fetoprotein (AFP), carbohydrate antigen 199 (CA199), and carcinoembryonic antigen (CEA) were regularly measured. Patients with treatment contraindications were excluded to avoid fatal intraoperative or postoperative complications. All patients were deprived of fluid for at least 4 h before treatment.

Treatment procedure

All treatments were done in a single phase, under sedation or local anesthesia. The patients were placed supine on a digital subtraction angiography (DSA) bed.

Tumor confirmation

The right femoral artery was punctured by following the modified Seldinger method. Hepatic artery and superior mesenteric artery angiography was performed to observe the location, size, number, and staining of the tumors. The location, boundary, and visibility of the tumors were observed using ultrasound.

Ultrasound-guided percutaneous MWA

Taking into account the findings of preoperative abdominal enhanced CT/MRI, combined with intraoperative DSA, the ultrasound examination was performed to determine the ablation of the tumors and to establish a suitable puncture path (through 1 cm liver parenchyma and the shortest path avoiding large blood vessels, gallbladder, bile duct, and intestine). Under ultrasound guidance, the tumor was directly punctured with a 14G microwave antenna. To cover the target tumor with the ablation range and reach 0.5–1 cm beyond the tumor boundary, multipoint ablation was adopted. After the end of the ablation procedure, the needle was withdrawn while applying 50W to ablate the needle track.

TACE treatment

After the MWA procedure, hepatic angiography was performed again to observe the effect of ablation. Moreover, the blood supply and staining of residual lesions were also observed. At the same time, the presence of bleeding and signs of an arteriovenous fistula were checked. A microcatheter was superselected to the target artery, and a suspension oxaliplatin (50–150 mg) + epirubicin (20–50 mg) + ultra -liquefied Lipiodol (5–20 ml)+ contrast agent was injected. When blood flow was observed to be stagnant, the injection would be stopped. Angiography of the infraorbital artery or left gastric artery and embolization were performed if necessary.

Postoperative treatment

After the removal of the catheter and vascular sheath, a pressure bandage was applied to the puncture site. The patient was asked to keep the right lower limb straight and immobilized for 6 h. After 24 h, the pressure bandage was removed. Vital signs were monitored 24 h after treatment, and the patients were provided with liver protection, hydration, antiemetics, urine alkalization agents, and nutritional support treatments.

Postoperative follow-ups and evaluation

Abdominal enhanced CT/MRI was performed at 1, 3, 6, 9, and 12 months after treatment. Moreover, routine blood parameters, liver and kidney function, electrolytes, and levels of serum AFP, CA199, and CEA were also measured. According to the modified Response Evaluation Criteria in Solid Tumors (m-RECIST) standard[9], the therapeutic response of target tumors was divided into complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). If residual tumors, recurrences, or metastases were found during follow-up visits, the treatment was rescheduled based on the patient's condition. When there was no enhanced lesion on abdominal enhanced CT/MRI within 1 year, further follow-up imaging would be scheduled every 6 months. Complications were assessed according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Data and statistical analysis

All data were obtained from electronic medical records or via telephone follow-up. Data analysis was performed using SPSS24 (Chicago, IL, USA). Measurement data were expressed as mean ± standard deviation and analyzed using an independent sample *t*-test. Count data were expressed as percentages and analyzed using the chi-square test. Survival curves were plotted using the Kaplan-Meier method, and the log-rank test and Cox proportional hazards model were used to analyze risk factors that may affect survival. Values of $p < 0.05$ were considered statistically significant.

Results

Basic clinical characteristics of the patients

A total of 101 patients with HCC with MVI or/and EHM were included in this study. HCC was diagnosed pathologically in 27 patients and according to the diagnostic criteria of American Association for the Study of Liver Diseases[8] in the remaining patients. A total of 140 percutaneous MWA combined with simultaneous TACE treatments were performed, which meant an average of 1.4 times per patient. The cohort comprised 93 men and 8 women, with an average age of 54.2 ± 12.1 years (range, 22–81 years). Among the patients with MVI, 7 had portal vein invasion or tumor thrombosis, 38 had portal vein branch invasion, and 38 had both portal vein invasion and branch invasion or tumor thrombosis. There were also 21 patients with vena cava invasion or tumor thrombosis. There were 16 patients with EHM, including 1 patient with multiple organ metastases. The clinical characteristics of the patients are shown in Table 1.

Complications

The commonly observed complications were post-embolic syndrome, including fever, abdominal pain, nausea, and vomiting. These symptoms were usually were resolved 3–10 days after symptomatic treatment. Biloma (CTCAE grade 3) was detected on 1 patient at 11 month after treatment, which was CTCAE grade 3. There were no complications such as bleeding, adjacent organ damage, and other grade 3 complications that prolonged the hospital stays or caused disability or death.

Local efficacy evaluation

Two radiologists with >10 years of experience in abdominal diagnosis evaluated the efficacy of the treatment of target tumors according to the m-RECIST criteria. There were 13 patients with CR, 59 patients with PR, 25 patients with SD, and 4 patients with PD based on abdominal enhanced CT/MRI scans 1 month after treatment. 3 months after treatment, there were 13 patients with CR, 60 patients with PR, 14 patients with SD, and 14 patients with PD.

Table 1
Basic clinical and tumor characteristics of patients.

Characteristics	MVI (n = 85, 84.2%)	EHM (n = 12, 11.9%)	MVI + EHM (n = 4, 3.9%)	p-Value
Age (years)				0.301
<65	69	9	2	
≥65	16	3	2	
Sex				0.188
Male	80	10	3	
Female	5	2	1	
Pre-session serum AFP (ng/mL)				0.501
<400	45	7	1	
≥400	40	5	3	
ECOG-PS				0.265
0–1	70	10	2	
2	15	2	2	
Child-Pugh class				0.288
A	72	12	3	
B	13	0	1	
Recurrence after surgical resection				0.088
Yes	6	3	1	
No	79	9	3	
No. of tumors				0.547
<3	45	6	1	
≥3	40	6	3	
Tumor size (cm)				0.109
<5	16	5	0	
≥5	69	7	4	

MVI: Microvascular Invasion; EHM: Extrahepatic Metastases; AFP: Alpha Fetoprotein; ECOG-PS: Eastern Cooperative Oncology Group Performance Status.

Survival

The mean follow-up time was 23.6 ± 14.7 months. The OS rates at 0.5, 1, 1.5, 2, and 3 years were 81.2%, 50%, 28.1%, 18.6%, and 12.4%, respectively. The median OS was 12.0 months (95% confidence interval [CI] 9.7–14.3). The median OS of MVI, EHM, and MVI + EHM was 11.7 months (95% CI 8.55–14.9), 14.8 months (95% CI 11.2–18.5), and 4.8 months (95% CI 2.4–7.3), respectively. EHM had a longer median OS than MVI (p = 0.375) and MVI had a longer median OS than MVI + EHM, with no statistical difference (p = 0.087). The median OS of EHM was longer than that of MVI + EHM, and the difference was statistically significant (p = 0.042) (Fig. 1) (see Fig. 2).

Prognostic factors

We analyzed the prognostic factors (sex, age, recurrence, number of tumors, tumor size, Child-Pugh class, and AFP level) that may affect the survival of patients with HCC with MVI or/and EHM treated with MWA combined with simultaneous TACE. Univariate analysis revealed that tumor size, Child-Pugh class, serum AFP, and ECOG-PS were associated with survival. Furthermore, multivariate analysis showed that Child-Pugh class, serum AFP level, and ECOG-PS were independent factors affecting the survival of patients (Table 2). Patients with Child-Pugh B, serum AFP ≥400 ng/ml, and ECOG-PS = 2 had shorter survival period.

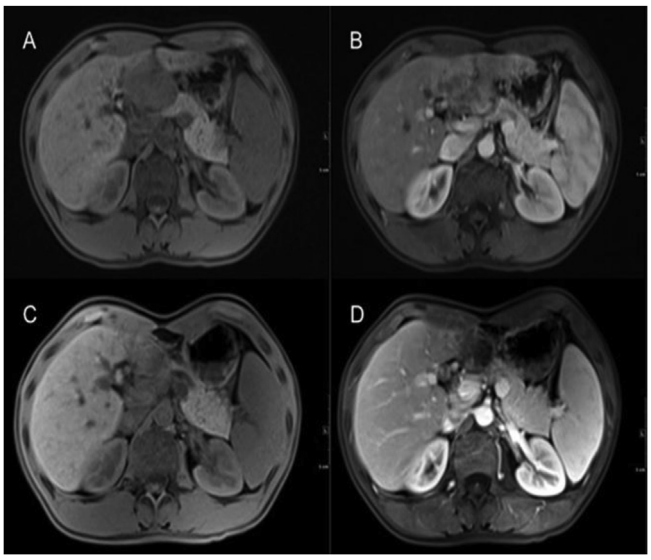

Fig. 2. Hepatocellular carcinoma in the left hepatic lobe with thoracic spine metastasis in a 28-year-old man. A and B: Preoperative enhanced magnetic resonance images showing large left-lobe lesions. C and D: Enhanced magnetic resonance images showing tumor necrosis at 1 month after surgery.

Discussion

Till now, there have been many attempts to find therapy strategies for HCC with stage C, include sorafenib, TACE, TACE combined with sorafenib, portal vein stent placement plus 125I seed strand combined with TACE, and radioembolization.[5–7,10] Currently, targeted drugs represented by sorafenib are BCLC-recommended method for treating patients with BCLC stage C HCC.[4] The SHARP (Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol)[11,9] and Asia Pacific trials[12] have also confirmed that sorafenib confers a longer survival time than does placebo, thus support the recommendation for BCLC stage C patients to use sorafenib. However, in most of the developing countries, sorafenib is not universally applicable because of its expenses. Besides, some patients have concerns about the adverse effects of sorafenib and the impact on the quality of life. Considering the high incidence and the late diagnosis of HCC in China[13], the Chinese guideline recommends that patients with BCLC stage C HCC to choose TACE (in the absence of TACE contraindications) and/or receive sorafenib. The effect of thermal ablation in the treatment of HCC is counted into the consideration. MWA is being increasingly applied owing to its fast heating and large ablation range. At

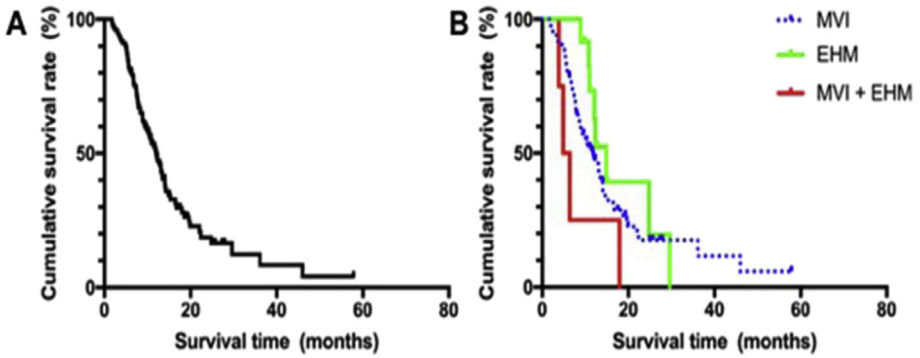

Fig. 1. A: Survival curve for the entire cohort. B: Survival curves for MVI, EHM, and MVI + EHM. MVI, microvascular invasion; EHM, extrahepatic metastases.

Table 2
Results of univariate and multivariate analyses.

Clinical characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-Value	HR (95% CI)	p-Value
Sex				
Male	0.975	0.961	NA	NA
Female	0.351–2.709			
Age (years)				
<65	1.155	0.614	NA	NA
≥65	0.659–2.023			
Child-Pugh classification				
A	5.196	<0.001	4.656	**<0.001**
B	2.724–9.911		2.333–9.291	
Serum AFP (ng/mL)				
<400	1.886	0.010	2.173	**0.002**
≥400	1.167–3.048		1.326–3.560	
ECOG-PS				
0–1	4.384	<0.001	3.719	**<0.001**
2	2.523–7.616		2.086–6.628	
Recurrence after surgical resection				
No	1.304	0.459	NA	NA
Yes	0.646–2.630			
Tumor size (cm)				
<5.0	2.055	0.023	1.408	0.294
≥5	1.106–3.819		0.743–2.669	
No. of tumors				
<3	1.193	0.465	NA	NA
≥3	0.743–1.915			

HR: hazard ratio; CI: confidence interval; MVI: microvascular invasion; EHM: extrahepatic metastases; AFP: alpha fetoprotein; ECOG-PS: Eastern Cooperative Oncology Group performance status; NA: not applicable.
Bold indicates that the data is statistically significant.

our center, we perform percutaneous MWA combined with simultaneous TACE on patients with BCLC stage C HCC who were unwilling to take sorafenib.

In our study, HCC patients with EHM had longer median OS than those with MVI or MVI + EHM, and patients with MVI had longer median OS than those with MVI + EHM, which is consistent with the trends reported in another study.[3] However, there was a difference in the existence of a statistical significance, which may be related to the proportionality of the cases. The proportion of HCC with MVI cases in our study (84.2%) was much higher than that of the other cases, whereas the proportion of MVI + EHM cases was only 3.9% (n = 4).

Our study concluded that the median OS of percutaneous MWA combined with simultaneous TACE for HCC with MVI and EHM reached 11.7 and 14.8 months, respectively. According to the results of existing studies, the median OS of sorafenib and TACE in the treatment of HCC with MVI was 3.0 and 4.1 months[5], respectively. The median OS of HCC with EHM was 7 and 8 months, respectively.[14] Percutaneous MWA, a localized radical treatment, combined with TACE can result in larger necrosis areas in tumors. Most patients with stage C HCC have large tumors and a large tumor burden. In our study, patients with tumors >5 cm in size accounted for 79.2%.Because of the complicated blood supply of large tumors, the effect of TACE alone is poor and the tumor necrosis rate is also low.[15] In simultaneous therapy, MWA first inactivates most tumors, which reduces the tumor burden, then TACE embolizes residual tumors and injects chemotherapy drugs. This method not only greatly reduces the amount of Lipiodol and chemotherapeutic drugs[16], but also allows observations of the ablation effect of MWA through DSA during TACE. At the same time, bleeding and arteriovenous fistula can be detected and treated in timely with TACE.[17]

Our study found that Child-Pugh class, serum AFP level, and ECOG-PS were independent prognostic factors of survival in patients with MVI or EHM HCC. This is consistent with previous studies.[18] The role of serum AFP levels in the prognosis of patients with HCC is well known. Patients with Child-Pugh class A had a longer survival than those with Child-Pugh class B, which has been confirmed in many studies, meaning that good liver function status is beneficial to the prognosis.[19] The prognostic role of ECOG-PS is also evident. Patients with PS 1–2 HCC are classified into BCLC stage C even if there is no MVI or EHM.

Limitations

This is a retrospective study with limitations such as selection bias, recall bias, and limited data. Prospective clinical trials are needed to further investigate the benefits of concurrent therapy for patients with BCLC stage C HCC. Randomized controlled trials are needed to compare the efficacy of concurrent therapy with combination therapy and other replacement therapy therapies to sorafenib.

Conclusion

Our data suggests that percutaneous MWA combined with simultaneous TACE is a safe and effective treatment for patients with MVI or EHM HCC. However, prospective clinical studies are still needed to validate our recommendations.

Conflict of interest

No conflict of interest to declare.

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