Am J Transl Res 2021;13(10):11908-11916
www.ajtr.org /ISSN:1943-8141/AJTR0132586

Original Article

Improvement in the condition of patients with primary liver cancer with transcatheter arterial chemoembolization before and after microwave ablation interventional therapy

Chenhong Zhu[1], Haibo Chen[1], Qian Fang[1], Yinghao Jiang[1], Honggen Xu[2]

Departments of [1]Emergency Surgery, [2]Hepatobiliary Surgery, The First People's Hospital of Wenling, Wenling 317500, Zhejiang, China

Received February 28, 2021; Accepted August 6, 2021; Epub October 15, 2021; Published October 30, 2021

Abstract: Background: We compared the clinical efficacy and safety of transcatheter arterial chemoembolization (TACE) combined with microwave ablation (MWA) and TACE alone for the treatment of patients with primary liver cancer (PLC). Materials and Methods: A total of 160 patients with PLC were enrolled and randomized into a study group (n=80) and a control group (n=80). Patients in the study group were treated with TACE combined with MWA, whereas those in the control group were treated with TACE alone. Treatment efficacy, changes in hepatic function indices after the treatment, incidence of adverse reactions, quality of life after treatment, and 3-year survival rates of the two groups were compared. Cox proportional hazards model was used for analyzing the patients' prognostic factors. Results: The total effective rate in the study group was higher than that in the control group (P<0.05). Patients in the study group had lower alanine aminotransferase and total bilirubin levels (P<0.05) and higher albumin levels (P<0.05) than those in the control group. The 1-, 2-, and 3-year overall survival rates in the study group were higher than those in the control group (P<0.05). Cox proportional hazards model showed that tumor size, extrahepatic metastasis, portal vein tumor thrombosis, severity of liver cirrhosis, and therapeutic methods were independent risk factors for patients with PLC. Conclusions: TACE combined with MWA is more effective than TACE alone in treating PLC, reducing the damage to the patients' cardiac function and prolonging survival.

Keywords: PLC, TACE, MWA, prognostic factors

Introduction

Primary liver cancer (PLC) is a common tumor type and it is the second-leading cause of cancer-related death worldwide; thus, it poses a serious public health issue [1]. PLC is presently treated with surgery, which is considered to be the most effective and a possibly radical treatment method. However, there are significant disadvantages to surgery, such as considerable trauma, high postoperative recurrence rate, and expensive treatment. Moreover, 80% of patients with PLC are not eligible for surgery because of tumor metastasis, lesions in special sites, and other causes [2]. Therefore, interventional therapy is suitable for those who are unwilling or ineligible for surgery. In recent years, with the promotion of interventional therapy and the improvement in patients' understanding of this therapy, more patients with PLC have undergone interventional therapy and achieved good results.

Transcatheter arterial chemoembolization (TACE) is the main nonsurgical treatment for patients with advanced liver cancer [3]. TACE is performed in the following stages: one or more chemotherapeutic agents are selectively injected; then, substances for embolization are injected into tumor-feeding arteries to temporarily block the blood from flowing to the tumor [4, 5]. Radiofrequency ablation (RFA) and microwave ablation (MWA), both of which are thermal ablation techniques, have been widely used in the treatment of liver cancer, with efficacy and limited trauma [6]. As per a report, the MWA

zone is easier to control than the RFA zone; therefore, MWA does easily damage the adjacent organs [7]. Moreover, MWA induces a larger ablation volume in a shorter duration and is more resistant to "the heat dissipation effect" [8]. Thermal ablation techniques combined with TACE exerts certain synergistic effects in the treatment of tumors because chemotherapeutic drugs for TACE and embolization of tumor-feeding arteries enhances the therapeutic effect of thermal ablation techniques [9]. In addition, computed tomography (CT) imaging shows that lipiodol, a vascular embolic agent, deposits in the arteries that feed tumors with a high density, contributing to the targeted process of CT-guided percutaneous ablation [10].

Therefore, in this study, the clinical efficacy and safety of TACE combined with MWA and TACE alone were compared for the treatment of patients with PLC; furthermore, prognosis-related factors for PLC were explored.

Materials and methods

General information

A total of 160 patients with PLC who were willing to undergo interventional therapy at our hospital from March 2014 to January 2016 were enrolled and randomized into the study and control groups. The study group consisted of 48 men and 32 women (average age, 45.75±8.41 years). According to pathological type, there were 68 cases of hepatocellular carcinoma (HCC), 6 cases of cholangiocellular carcinoma, and 6 cases of mixed HCC in the study group. The control group consisted of 42 men and 38 women (average age, 46.12±7.78 years). According to the pathological type, there were 71 cases of HCC, 5 cases of cholangiocellular carcinoma, and 4 cases of mixed HCC in the study group.

As per the inclusion criteria, patients with PLC confirmed on the basis of pathological histology and imaging, those with good compliance, and those with complete clinical data were included. Patients who received chemotherapy within the previous 6 months, those with survival duration of ≤6 months, those allergic to drugs used in this study, those with communication and mental disorders, those with hepatic and renal insufficiency, and those with coagulation disorders were excluded. This study was approved by the Ethics Committee of The First People's Hospital of Wenling. We provided written informed consent forms to the guardians. Patients and their families were informed, and they signed the informed consent form.

Therapeutic methods

Patients in both groups were treated with TACE. Celiac arteriography was performed using the Seldinger technique and digital subtraction angiography, to show the number, location, and size of tumors. A microcatheter was inserted into the appropriate hepatic artery (left or right hepatic artery). Gemcitabine (800-1,000 mg/m^2) and oxaliplatin (85-100 mg/m^2) were perfused into the microcatheter, and super-liquid lipiodol (10-30 mL) mixed with gemcitabine (10-20 mg) was used for chemoembolization. Gelatin sponge particles were additionally administrated to strengthen embolization according to the patients' conditions.

Patients in the study group were treated with MWA during the fourth week of treatment with TACE. CT-guided localization was used to localize ablation targets and select the puncture point and path; 2% lidocaine was used for local anesthesia from the puncture path. The puncture needle was advanced to the central position of the tumor tissue under the guidance of CT scan. The power of the microwave therapy apparatus was set at 55-60 W, and administration for a single time was 6-10 min. Single or multiple double needle treatments with MWA were adopted as per the patients' situations. CT re-examination was performed in the fourth week after the operation, and treatment with MWA was continued if the original lesion persisted.

Outcome measures

Efficacy evaluation was divided into four parts according to the revised Response Evaluation Criteria in Solid Tumors (RECIST) by the World Health Organization [11]. Complete response (CR) indicated that the tumor lesion had completely disappeared, and no new lesion was found. Partial response (PR) indicated that the volume of the tumor lesion reduced by >50%. Stable disease (SD) indicated that the volume of the tumor lesion reduced by <50%. Progressive disease (PD) indicated that the volume of the tumor lesion increased by >25%. The

Table 1. Comparison of general information [n (%)]/(x±SD)

Groups	Control group (n=80)	Study group (n=80)	χ^2	P
Age			0.231	0.631
<45 years old	32 (40.00)	35 (43.75)		
≥45 years old	48 (60.00)	45 (56.25)		
Sex			1.249	0.264
Male	42 (52.50)	49 (61.25)		
Female	38 (47.50)	31 (38.75)		
History of smoking			0.465	0.495
Yes	57 (71.25)	53 (66.25)		
No	23 (28.75)	27 (33.75)		
Exercise habits			3.029	0.082
Yes	36 (45.00)	47 (58.75)		
No	44 (55.00)	33 (41.25)		
Place of residence			3.249	0.072
City	56 (70.00)	45 (56.25)		
Countryside	24 (30.00)	35 (43.75)		
Educational level			2.331	0.127
< Senior high school	21 (26.25)	30 (37.50)		
≥Senior high school	59 (73.75)	50 (62.50)		
Body weight			0.905	0.341
<55 KG	34 (42.50)	40 (50.00)		
≥55 KG	46 (57.50)	40 (50.00)		
Food preference			1.290	0.256
Bland	59 (73.75)	65 (81.25)		
Spicy	21 (26.25)	15 (18.75)		
Drinking status			1.162	0.281
Never or rarely	18 (22.50)	24 (30.00)		
All the time	62 (77.50)	56 (70.00)		
Pathological type			0.556	0.757
Hepatocellular carcinoma	71 (88.75)	68 (85.00)		
Cholangiocellular carcinoma	5 (6.25)	6 (7.50)		
Mixed hepatocellular carcinoma	4 (5.00)	6 (7.50)		

overall response rate (ORR) = (CR + PR cases)/total number of cases ×100%.

Changes in hepatic function indices after treatment were measured and mainly included alanine aminotransferase (ALT), total bilirubin (Tbil), and albumin levels. Adverse reactions, including nausea, vomiting, fever, abdominal pain, bone marrow suppression, diarrhea, and hepatic injury, were observed during the treatment.

The patients' quality of life (QOL) after treatment was assessed according to the Karnofsky Performance Score (KPS) [12]. After treatment, increase in the KPS by >10 points indicated improvement, decrease in KPS or increase by ≤10 points indicated stability, and decrease in KPS by >10 points indicated worsening condition. Improvement rate of QOL = (improved + stable cases)/total number of cases ×100%.

Follow-up

All patients were followed up via telephone calls and outpatient service for 3 years, once every 3 months. The study period ended in January 2019. The overall survival rate (OSR) was from the day of treatment to patient death or the last follow-up.

Statistical methods

SPSS 21.0 was used for statistical analysis. The chi-square test was used for comparisons between groups. Measurement data were expressed as mean ± SD, and the paired t test was used for comparisons within groups before and after the treatment. The log-rank test was used to assess the differences in survival curves between two groups. The Cox proportional hazards model was used to test independent prognostic factors for PLC. P<0.05 indicated a statistically significant difference.

Results

Comparison of general information

No significant differences were noted between the study and control groups with respect to age, sex, history of smoking, exercise habits, educational level, body weight, food preference, drinking status, and pathological type (P> 0.05) (**Table 1**).

Table 2. Comparison of clinical efficacy [n (%)]

Groups	Control group (n=80)	Study group (n=80)	χ^2	P
CR	28 (35.00)	44 (55.00)	-	-
PR	20 (25.00)	26 (32.50)	-	-
SD	21 (26.25)	7 (8.75)	-	-
PD	11 (14.75)	3 (3.75)	-	-
ORR	48 (60.00)	70 (87.50)	15.626	<0.001

Comparison of clinical efficacy

After treatment, the control group had 28 (35.00%) cases of CR, 20 (25.00%) cases of PR, 21 (26.25%) cases of SD, and 11 (14.75%) cases of PD, with an ORR of 60.00%. The study group had 44 (55.00%) cases of CR, 26 (32.50%) cases of PR, 7 (8.75%) cases of SD, and 3 (3.75%) cases of PD, with an ORR of 87.50%. After treatment, the ORR in the study group was higher than that in the control group (P<0.05) (**Table 2**).

Comparison of changes in hepatic function indices after treatment

After treatment, the ALT and TBIL levels in the two groups significantly decreased (P<0.05); however, the albumin levels increased (P<0.05). After treatment, patients in the study group had lower ALT and TBIL levels (P<0.05), but higher albumin levels (P<0.05) than those in the control group (**Figure 1** and **Table 3**).

Comparison of QOL

Thirty days after discharge, 26 (32.50%) cases had improved QOL, 32 (40.00%) had stable QOL, and 22 (27.50%) had worse QOL in the control group, with an improvement rate of 72.50% for QOL. However, 45 (56.25%) cases had improved QOL, 29 (36.25%) had stable QOL, and 22 (7.50%) had worse QOL in the study group, with an improvement rate of 92.50% for QOL. The improvement rate of QOL in the study group was higher than that in the control group (P<0.05) (**Table 4**).

Comparison of adverse reactions

In the control group, there were 11 (13.75%) cases of nausea, 8 (10.00%) of vomiting, 4 (5.00%) of fever, 6 (7.50%) of abdominal pain, 2 (2.50%) of bone marrow suppression, 7 (8.75%) of diarrhea, and 3 (3.75%) of hepatic injury. The total incidence of adverse reactions was 51.25%. In the study group, there were 8 (10.00%) cases of nausea, 10 (12.50%) of vomiting, 2 (2.50%) of fever, 7 (8.75%) of abdominal pain, 2 (2.50%) of bone marrow suppression, 9 (11.25%) of diarrhea, and none of hepatic injury. The total incidence of adverse reactions was 47.50% (**Table 5**).

Comparison of 3-year survival rate

The follow-up results showed that the 1-, 2-, and 3-year OSRs in the study group were 82.50% (66/80), 51.25% (41/80), and 27.50 (22/80), respectively, whereas those in the control group were 63.75 (51/80), 25.00 (20/80), and 5.00 (4/80), respectively. The 1-, 2-, and 3-year OSRs in the study group were higher than those in the control group (P<0.05) (**Figure 2**).

Univariate analysis of prognosis in patients with PLC

Univariate analysis was conducted for the general and clinical pathological factors of the patients in the two groups. The results showed that age, sex, presence/absence of hepatitis, and pathological type were not prognostic factors affecting the OSR of patients with PLC (P>0.05). Tumor size, extrahepatic metastasis, portal vein tumor thrombosis, severity of liver cirrhosis, and therapeutic methods may be prognostic factors (P<0.05) (**Table 6**).

Multivariate analysis of prognosis in patients with PLC

The analysis of Cox proportional hazards model showed that tumor size, extrahepatic metastasis, portal vein tumor thrombosis, severity of liver cirrhosis, and therapeutic methods were independent risk factors for patients with PLC (**Table 7**).

Discussion

PLC is the sixth most common malignant type of tumor in the world, with 782,000 new cases and 745,000 deaths every year [13]. At present, PLC can be treated through surgery, interventional therapy, radiotherapy, and biotherapy. TACE is the most common treatment method in interventional therapy, but it is also a main therapeutic scheme which may not be

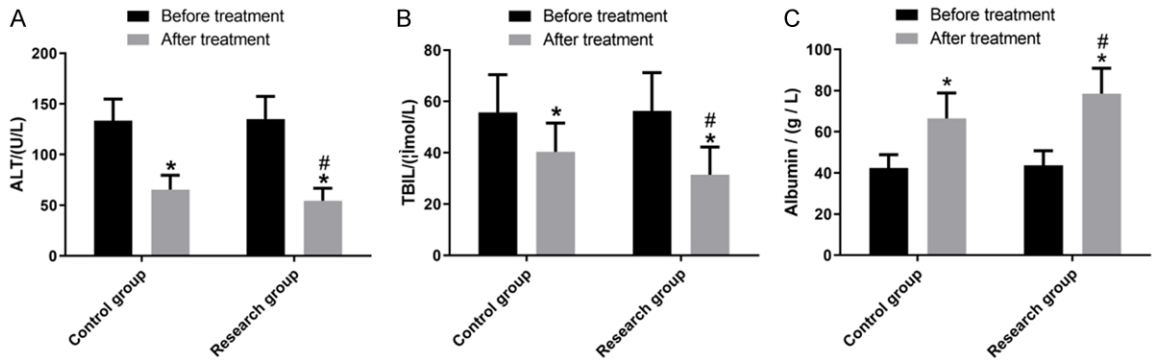

Figure 1. Comparison of changes in hepatic function indices before and after treatment. A. The comparison of alanine aminotransferase (ALT) level between the study and control groups before and after treatment. B. The comparison of total bilirubin (TBIL) level between the study and control groups before and after treatment. C. The comparison of albumin level between the study and control groups before and after treatment. Note: *P<0.05 compared with before treatment within groups. #P<0.05 compared with the control group after treatment.

Table 3. Comparison of changes in hepatic function indices before and after treatment (x±SD)

Groups	Control group (n=80)		Study group (n=80)	
	Before treatment	After treatment	Before treatment	After treatment
ALT (U/L)	133.46±21.35	65.35±14.26*	135.12±22.31	54.45±12.22*,#
TBIL/(μmol/L)	55.78±14.67	40.37±11.17*	56.34±14.89	31.42±10.78*,#
Albumin/(g/L)	42.45±6.46	66.52±12.35*	43.67±7.16	78.52±12.35*,#

Note: *indicates P<0.05 compared with before treatment within groups. #indicates P<0.05 compared with the control group after treatment.

Table 4. Comparison of QOL [n (%)]

Groups	n	Improved	Stable	Worsen	Improvement rate (%)
Control group	80	26 (32.50)	32 (40.00)	22 (27.50)	72.50
Study group	80	45 (56.25)	29 (36.25)	6 (7.50)	92.50
χ^2	-	-	-	-	11.082
P	-	-	-	-	<0.001

suitable for patients with PLC undergoing surgical resection. The long-term efficacy of TACE remains unsatisfactory owing to incomplete embolization, hepatic artery variation, and multiple blood supplies to the liver, as well as collateral circulation [3]. The tumor necrosis rate in patients treated with TACE is only 10%-20% [14]. Therefore, it is crucial to select more effective and safer therapeutic methods for patients with PLC.

TACE is a locally used chemotherapeutic drug. Although its dosage concentration is high, it does prevent adverse reactions caused by the large-scale and large-dose systemic use of chemotherapeutic drugs, and it greatly relieves patients' discomfort. Its method for vascular embolization also enhances the therapeutic effect on blood vessels. Therefore, TACE is presently widely used for treating liver cancer [15]. As a thermal ablation technique, MWA, in the absence of current, rapidly and uniformly heats, coagulates, and necrotizes the tumor tissue using electromagnetic energy generated by electromagnetic fields, thus treating tumors. It has been used for treating various cancers, such as HCC [7, 16]. MWA is a relatively new technique and has more substantial advantages than RFA. For example, it necrotizes more cells, shortens the operative time, and relieves pain, as well as arrests bleeding. It also has a faster temperature rise rate, high thermal efficiency, and a stable and controllable thermal field, suitable for medium sized tumors measuring 3-5 cm [17, 18]. Li et al. compared TACE combined with MWA with TACE alone in the treatment of middle and advanced HCC. The results showed that the ORR of MWA combined with TACE was

Table 5. Comparison of adverse reactions [cases (%)]

Groups	Control group (n=80)	Study group (n=80)	X^2	P
Nausea	11 (13.75)	8 (10.00)	-	-
Vomiting	8 (10.00)	10 (12.50)	-	-
Fever	4 (5.00)	2 (2.50)	-	-
Abdominal pain	6 (7.50)	7 (8.75)	-	-
Bone marrow suppression	2 (2.50)	2 (2.50)	-	-
Diarrhea	7 (8.75)	9 (11.25)	-	-
Hepatic injury	3 (3.75)	0	-	-
Total incidence of adverse reactions	41 (51.25)	38 (47.50)	0.225	0.625

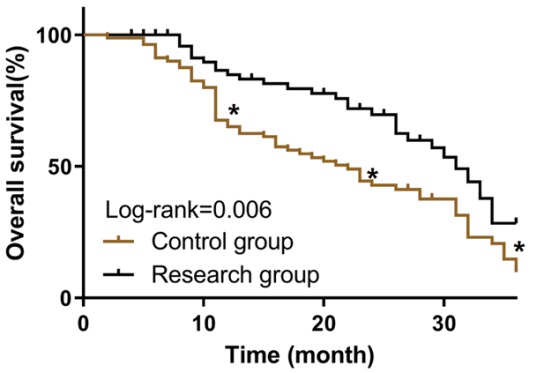

Figure 2. Comparison of 3-year survival rate. *P<0.05 compared with the control group after treatment.

higher than that of TACE alone, and the survival rate of patients treated with MWA combined with TACE was higher than that of patients treated with TACE alone during the 24-month postoperative follow-up [19]. Chen et al. compared TACE combined with MWA with TACE alone in treating HCC tumors measuring ≤5 cm. The results showed that after the initial treatment, the tumor necrosis rate in the TACE-MWA group (TACE combined with MWA) was higher than that in the TACE group (TACE alone); patients in the TACE-MWA group had better tumor responses and better time to tumor regression during the 6-month follow-up than those in the TACE group [20]. The findings of Zheng et al. were similar to these results. Their results showed that compared with TACE alone, TACE combined with MWA more effectively prolonged the OSR of hospitalized patients with large isolated or multinodular HCC, with better time to tumor progression [21]. The results of this study showed that after treatment, patients in the study group had higher ORR and 1-, 2-, and 3-year OSRs than those in the control group, similar to the above results. This indicates that TACE combined with MWA is more effective than TACE alone in treating PLC. MWA guided by CT and other imaging equipment accurately localizes and removes the residual tumor tissue after TACE through thermal ablation, controls tumor recurrence and metastasis *in situ*, prolongs patients' survival time, and improves their prognoses [22]. During TACE, chemotherapeutic drugs and iodine are infused, and these drugs can cause cytotoxicity and local ischemia in the tumor tissue. TACE combined with MWA reduces the use of TACE, thus reducing the damage to patients during TACE [9, 23]. In this study, hepatic function indices, such as the ALT, TBIL, and albumin levels were detected. The results showed that after treatment, ALT and TBIL levels in the two groups decreased, but albumin level increased. After treatment, patients in the study group had lower ALT and TBIL levels, but higher albumin level than those in the control group. In this study, the patients' QOL and adverse reactions after treatment were evaluated. The results showed that the improvement rate of QOL in the study group was higher than that in the control group, and TACE combined with MWA did not increase the incidence of adverse reactions. This suggests that compared with TACE alone, TACE combined with MWA can more effectively reduce damage to patients' cardiac function and enable them to obtain better QOL.

There are currently few studies on prognostic factors for patients with PLC undergoing interventional therapy. In this study, univariate analysis was conducted on the general and clinical pathological factors in the study group. The results showed that tumor size, extrahepatic metastasis, portal vein tumor thrombosis, the severity of liver cirrhosis, and therapeutic methods may be prognostic factors affecting the

Table 6. Univariate analysis of prognosis in patients with PLC

Groups	Number of investigation cases (cases)	Number of 3-year survival cases (cases)	χ^2	P
Age (years)			3.145	0.370
<35	18	5		
35-45	58	8		
45-55	56	7		
≥56	28	6		
Sex			1.227	0.268
Male	91	18		
Female	69	8		
Tumor size			10.570	0.001
<5 cm	89	22		
≥5 cm	71	4		
Hepatitis			2.331	0.127
Yes	58	6		
No	102	20		
Extrahepatic metastasis			10.478	0.001
Yes	64	3		
No	96	23		
Portal vein tumor thrombosis			9.053	0.003
Yes	45	1		
No	115	25		
Severity of liver cirrhosis			17.625	<0.001
Child A	56	18		
Child B	35	5		
Child C	69	3		
Pathological type			5.340	0.069
Hepatocellular carcinoma	139	19		
Cholangiocellular carcinoma	11	4		
Mixed hepatocellular carcinoma	10	3		
Therapeutic methods			14.879	<0.001
TACE combined with MWA	80	22		
TACE	80	4		

Table 7. Multivariate analysis of prognosis in patients with PLC

Variables	B	SE	P	EXP (B)	Wald	Lower	Upper
Tumor size	1.038	0.288	0.000	2.824	13.039	1.608	4.962
Extrahepatic metastasis	0.618	0.172	0.000	3.856	12.994	1.326	5.598
Portal vein tumor thrombosis	0.118	0.055	0.031	4.125	4.669	1.011	6.252
Severity of liver cirrhosis	0.579	0.188	0.002	4.785	9.548	1.236	7.578
Therapeutic methods	0.481	0.235	0.001	1.722	9.792	1.141	2.601

"Lower/Upper" mean 95% or 99% confidence intervals.

OSR of patients with PLC. Cox proportional hazards model was further used for analysis. The results showed that tumor size, extrahepatic metastasis, portal vein tumor thrombosis, severity of liver cirrhosis, and therapeutic methods were independent risk factors for patients with PLC. Tumor size is the main factor affecting early recurrence of liver cancer. Chen et al. have shown that tumor size is an important related factor for the early recurrence of liver

cancer [24]. Portal vein tumor thrombosis is a common complication in patients with liver cancer, and this complication usually predicts poor prognosis and difficult treatment of the patients. According to Ni et al., tumor size and portal vein tumor thrombosis are prognostic factors for patients with middle and advanced PLC [25]. Extrahepatic metastasis and the aggravation of liver cirrhosis in patients with PLC indicate the progression of the disease. Furthermore, Child-Pugh classification and extrahepatic metastasis before operation are related factors affecting the OSR of patients with PLC [10]. The results of this study were similar to those of previous similar studies, indicating that TACE combined with MWA has a positive effect on the prognosis of patients; thus, it can be widely popularized in clinical practice.

In summary, TACE combined with MWA is more effective than TACE alone in treating PLC, reducing the damage to patients' cardiac function and prolonging their survival time. Tumor size, extrahepatic metastasis, portal vein tumor thrombosis, severity of liver cirrhosis, and therapeutic methods are independent risk factors for patients with PLC.

Disclosure of conflict of interest

None.

Address correspondence to: Honggen Xu, Department of Hepatobiliary Surgery, The First People's Hospital of Wenling, No. 333, Chuanan South Road, Chengxi Street, Wenling 317500, Zhejiang, China. Tel: +86-13586248566; E-mail: baijtta7@163.com

References

[1] Broutier L, Mastrogiovanni G, Verstegen MM, Francies HE, Gavarró LM, Bradshaw CR, Allen GE, Arnes-Benito R, Sidorova O, Gaspersz MP, Georgakopoulos N, Koo BK, Dietmann S, Davies SE, Praseedom RK, Lieshout R, IJzermans JNM, Wigmore SJ, Saeb-Parsy K, Garnett MJ, van der Laan LJ and Huch M. Human primary liver cancer-derived organoid cultures for disease modeling and drug screening. Nature medicine 2017; 23: 1424.

[2] Pan F, Ni H, Zheng Y, Yao L, Huang X, Ru L and Li Z. Combination therapy of hepatic arterial chemoembolization and radiofrequency ablation for primary liver cancer. Int J Clin Exp Med 2018; 11: 224-230.

[3] Jin W, Han H, Zhou S, Wang Y, Dong T and Zhao C. Therapeutic efficacy of brucea javanica oil emulsion (BJOE) combined with transcatheter hepatic arterial chemoembolization (TACE) in patients with primary liver cancer. Int J Clin Exp Med 2015; 8: 18954.

[4] Lv XH, Wang CH and Xie Y. Arsenic trioxide combined with transarterial chemoembolization for primary liver cancer: a meta-analysis. J Gastroenterol Hepatol 2017; 32: 1540-1547.

[5] Kim YS, Lim HK, Rhim H and Lee MW. Ablation of hepatocellular carcinoma. Best Pract Res Clin Gastroenterol 2014; 28: 897-908.

[6] Li J, Liu W, Zhu W, Wu Y and Wu B. Transcatheter hepatic arterial chemoembolization and sorafenib for hepatocellular carcinoma: a meta-analysis of randomized, double-blind controlled trials. Oncotarget 2017; 8: 59601-59608.

[7] Poulou LS, Botsa E, Thanou I, Ziakas PD and Thanos L. Percutaneous microwave ablation vs radiofrequency ablation in the treatment of hepatocellular carcinoma. World J Hepatol 2015; 7: 1054-63.

[8] Poch FG, Rieder C, Ballhausen H, Knappe V, Ritz J-P, Gemeinhardt O, Kreis ME and Lehmann KS. The vascular cooling effect in hepatic multipolar radiofrequency ablation leads to incomplete ablation ex vivo. Int J Hyperthermia 2016; 32: 749-756.

[9] Guo W, He X, Li Z and Li Y. Combination of transarterial chemoembolization (TACE) and radiofrequency ablation (RFA) vs. surgical resection (SR) on survival outcome of early hepatocellular carcinoma: a meta-analysis. Hepatogastroenterology 2015; 62: 710-4.

[10] Wang Y, Ma L, Yuan Z, Zheng J and Li W. Percutaneous thermal ablation combined with TACE versus TACE monotherapy in the treatment for liver cancer with hepatic vein tumor thrombus: a retrospective study. PLoS One 2018; 13: e0201525.

[11] Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S and Mooney M. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45: 228-247.

[12] Chang JY, Verma V, Li M, Zhang W, Komaki R, Lu C, Allen PK, Liao Z, Welsh J and Lin SH. Proton beam radiotherapy and concurrent chemotherapy for unresectable stage III non-small cell lung cancer: final results of a phase 2 study. JAMA Oncol 2017; 3: e172032.

[13] Meloni MF, Chiang J, Laeseke PF, Dietrich CF, Sannino A, Solbiati M, Nocerino E, Brace CL and Lee Jr FT. Microwave ablation in primary and secondary liver tumours: technical and

clinical approaches. Int J Hyperthermia 2017; 33: 15-24.
[14] Burrel M, Reig M, Forner A, Barrufet M, de Lope CR, Tremosini S, Ayuso C, Llovet JM, Real MI and Bruix J. Survival of patients with hepatocellular carcinoma treated by transarterial chemoembolisation (TACE) using drug eluting beads. Implications for clinical practice and trial design. J Hepatol 2012; 56: 1330-1335.
[15] Lencioni R, de Baere T, Soulen MC, Rilling WS and Geschwind JF. Lipiodol transarterial chemoembolization for hepatocellular carcinoma: a systematic review of efficacy and safety data. Hepatology 2016; 64: 106-116.
[16] Duan X, Chen P, Han X, Ren J, Wang Z, Zhao G and Li H. The influence of liposomal quercetin on liver damage induced by microwave ablation. Sci Rep 2017; 7: 12677.
[17] Lucchina N, Tsetis D, Ierardi AM, Giorlando F, Macchi E, Kehagias E, Duka E, Fontana F, Livraghi L and Carrafiello G. Current role of microwave ablation in the treatment of small hepatocellular carcinomas. Ann Gastroenterol 2016; 29: 460-465.
[18] Thamtorawat S, Hicks RM, Yu J, Siripongsakun S, Lin WC, Raman SS, McWilliams JP, Douek M, Bahrami S and Lu DS. Preliminary outcome of microwave ablation of hepatocellular carcinoma: breaking the 3-cm barrier? J Vasc Interv Radiol 2016; 27: 623-630.
[19] Li W, Man W, Guo H and Yang P. Clinical study of transcatheter arterial chemoembolization combined with microwave ablation in the treatment of advanced hepatocellular carcinoma. J Cancer Res Ther 2016; 12 Suppl: C217-C220.
[20] Chen QF, Jia ZY, Yang ZQ, Fan WL and Shi HB. Transarterial chemoembolization monotherapy versus combined transarterial chemoembolization-microwave ablation therapy for hepatocellular carcinoma tumors ≤5 cm: a propensity analysis at a single center. Cardiovasc Intervent Radiol 2017; 40: 1748-1755.
[21] Zheng L, Li HL, Guo CY and Luo SX. Comparison of the efficacy and prognostic factors of transarterial chemoembolization plus microwave ablation versus transarterial chemoembolization alone in patients with a large solitary or multinodular hepatocellular carcinomas. Korean J Radiol 2018; 19: 237-246.
[22] McWilliams JP, Yamamoto S, Raman SS, Loh CT, Lee EW, Liu DM and Kee ST. Percutaneous ablation of hepatocellular carcinoma: current status. J Vasc Interv Radiol 2010; 21 Suppl: S204-S213.
[23] Zhang R, Shen L, Zhao L, Guan Z, Chen Q and Li W. Combined transarterial chemoembolization and microwave ablation versus transarterial chemoembolization in BCLC stage B hepatocellular carcinoma. Diagn Interv Radiol 2018; 24: 219-224.
[24] Chan AW, Zhong J, Berhane S, Toyoda H, Cucchetti A, Shi K, Tada T, Chong CC, Xiang BD and Li LQ. Development of pre and post-operative models to predict early recurrence of hepatocellular carcinoma after surgical resection. J Hepatol 2018; 69: 1284-1293.
[25] Ni JY, Sun HL, Chen YT, Luo JH, Chen D, Jiang XY and Xu LF. Prognostic factors for survival after transarterial chemoembolization combined with microwave ablation for hepatocellular carcinoma. World J Gastroenterol 2014; 20: 17483-90.