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Original Article

Drug-eluting beads-transarterial chemoembolization plus microwave ablation is an effective and safe treatment strategy in treating hepatocellular carcinoma adjacent to gallbladder

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Abstract: The present study aimed to compare the efficacy and safety of drug-eluting beads-transarterial chemoembolization (DEB-TACE) plus microwave ablation (MWA) versus (*vs.*) surgery in treating patients with hepatocellular carcinoma (HCC) adjacent to gallbladder. Totally 54 patients with HCC adjacent to gallbladder were included and divided into two groups: DEB-TACE plus MWA group (n = 24) and surgery group (n = 30). Treatment response, relapse-free survival (RFS), progression-free survival (PFS), overall survival (OS) and adverse events were assessed and documented. For DEB-TACE plus MWA group, complete response rate, objective response rate and disease control rate were 79.2%, 95.8% and 100.0% after one-month post treatment, respectively. In terms of survival profiles, DEB-TACE plus MWA group presented similar RFS (28.2 (95% CI: 12.5-43.9) months *vs.* 26.6 (95% CI: 19.2-34.1) months) (P = 0.930), PFS (21.2 (95% CI: 1.6-40.8) months *vs.* 26.6 (95% CI: 19.2-34.1) months) (P = 0.541), and OS (41.4 (95% CI: 35.0-47.9) months *vs.* 59.7 (95% CI: 51.7-67.7) months) (P = 0.138) compared with surgery group, and further multivariate Cox's regression analysis validated that, after adjustment of confounding factors, DEB-TACE plus MWA group exhibited no difference of RPS, PFS or OS compared with surgery group. Regarding safety, the intraoperative adverse event incidence was higher in DEB-TACE plus MWA group compared with surgery group (P = 0.008), while two groups exhibited no difference of postoperative adverse event incidence (P = 0.618). In conclusion, DEB-TACE plus MWA presents to be an optional treatment strategy in patients with HCC adjacent to gallbladder.

Keywords: Microwave ablation, drug-eluting beads-transarterial chemoembolization, hepatocellular carcinoma adjacent to gallbladder, survival profiles, adverse events

Introduction

Hepatocellular carcinoma (HCC) represents to be the most prevalent primary hepatic malignancy globally, comprising approximately 80% cases of primary liver cancer with its 5-year overall survival (OS) rate of under 12% [1]. HCC at anatomical challenging locations (including HCC adjacent to important organs, such as gallbladder, major vessels, diaphragm) is considered as a significant obstacle in HCC management, which is normally treated by surgical resection based on the guideline of HCC treatment [2, 3]. However, there are still large majority of patients with HCC adjacent to gallbladder who are inappropriate for surgery owing to the presence of liver cirrhosis or poor remaining liver function [2, 4, 5]. Therefore, it is essential to look for an alternative treatment approach for these patients.

Microwave ablation (MWA), as one type of thermal ablation methods, is recommended as an alternative curative treatment option and has been widely used in the current clinical practice for unresectable HCC patients [4, 5]. Furthermore, MWA for HCC adjacent to gallbladder (< 5 mm) is conducted in the previous several

studies, however, it has not been well accepted due to several principal challenges including (1) firstly, thermal injury to gallbladder, such as gallbladder penetrating and thermal trauma, may happen due to the failure to achieve a safe ablation range of over 5 mm; (2) secondly, since the adjacent bile serve as a "heat sink", the effectiveness of MWA may be limited, contributing to higher risk of HCC remnant or local HCC progression in long-term period [2, 3, 6, 7]. Therefore, it is essential to look for a treatment strategy, which could help to achieve a safe tumor margin and further facilitate the application of MWA in patients with HCC adjacent to gallbladder.

Transarterial chemoembolization (TACE) is an effective HCC treatment approach comprising selective tumor-feeding arterial obstruction and the chemotherapeutic drug injection for the management of intermediate stage HCC, meanwhile, TACE is also applied in order to meet acceptable criteria for curative treatments in unresectable patients [8]. For example, in one previous study, after tumor shrinks by the application of TACE, the MWA exhibits OS rate to be 100%, 79% and 73% at 1-, 3-, and 5-year follow-up, respectively in HCC patients [9]. Recently, drug-eluting beads (DEB)-TACE, as a novel drug-delivering device, is introduced to present more efficient treatment response and better safety profiles compared to conventional TACE (cTACE), which is supposed to present increased ability of bridging to curative MWA treatment compared with cTACE in HCC management [10-12].

According to these aforementioned evidences, we hypothesized that the application of DEB-TACE might result in the decreased tumor size, allowing the safe ablation range around the lesion and further facilitating the curative MWA treatment in patients with HCC adjacent to gallbladder. Hence, we conducted the present study to compare the efficacy and safety profiles of DEB-TACE plus MWA versus (*vs.*) surgery in treating patients with HCC adjacent to gallbladder.

Materials and methods

Patients

From January 2015 to January 2020, 54 patients with HCC adjacent to gallbladder, who received surgery or DEB-TACE combined with MWA therapy in Beijing Ditan Hospital affiliated to Capital Medical University, were enrolled in this study. The inclusion criteria were: (1) diagnosed as primary HCC by biopsy; (2) tumor was adjacent to gallbladder with distance less than 5 mm revealed by Computed Tomography (CT) or ultrasound examination; (3) age ≥ 18 years old; (4) willing to receive surgical resection or DEB-TACE plus MWA therapy. The exclusion criteria were as follows: (1) contraindications to surgery or DEB-TACE plus MWA; (2) vascular invasion or bile duct invasion; (3) distant metastasis; (4) complicated with other cancers; (5) pregnant or lactating women. All patients provided the signed informed consents. The Ethic Committee of our hospital gave permission for the study.

Clinical data recording

Demographic and clinical characteristics of patients, including age, gender, tumor differentiation, Eastern Cooperative Oncology Group (ECOG) performance score, Child-Pugh stage, Barcelona Clinic Liver Cancer (BCLC) stage, tumor number, tumor capsule, tumor size, and preoperative alpha fetoprotein (AFP) level, were documented in a case report form (CRF).

Treatments

Among 54 HCC patients, 30 patients who selected to receive surgical resection were categorized into surgery group, and the surgical treatment was performed according to the guidelines [13]. The remaining 24 patients who selected to receive DEB-TACE combined with MWA therapy were categorized into DEB-TACE plus MWA group. The DEB-TACE was performed as described in previous study [14]. Briefly, Seldinger technique was used to intubate the femoral artery via percutaneous puncture, then the location, size, number and supplying arteries of tumors were identified by Digital Subtraction Angiography (DSA); following that, the hybrid emulsion of CalliSpheres® microspheres (Jiangsu Hengrui Medicine Co., Ltd., Jiangsu Province, China) loading with doxorubicin (60-80 mg) was infused into the supplying arteries of tumors, and all supplying arteries of tumors were embolized as much as possible. Four to six weeks after DEB-TACE, patients received MWA therapy, which was carried out as follows: conventional preoperative plain CT

and ultrasonography were used to determine the tumor location; with sterile towel and 1% lidocaine local anesthesia, the microwave ablation needle was punctured to the tumor center under CT and ultrasound guidance; after determining the ablation range and the safety of peripheral organs, the microwave power was set at 30-60 watts (W), and the ablation time was 3-6 minutes under ultrasonic real-time monitoring; when the MWA finished, plain CT was performed again to confirm whether the ablation area was safety or not, and intervention was adopted if not. The MWA procedures were guided by combination of CT and ultrasonography, which achieved complementary advantages. Because the CT scan had a certain advantage in determining the safe range of organs around the lesion and some lesions with restricted ultrasound (gas interference), while the real-time monitoring of ultrasound could better guarantee the safety of the surgical procedure and reduce the number of CT scans so as to minimize iatrogenic radiation damage in patients.

Assessment and follow-up

For patients in DEB-TACE plus MWA group, treatment response was evaluated by abdominal enhanced Magnetic Resonance Imaging (MRI) examination at one month after DEB-TACE plus MWA therapy, meanwhile, the AFP level was also assessed. Response classification criteria (including complete response (CR), partial response (PR), stable disease (SD), or progression disease (PD)) were in line with the modified RECIST (mRECIST) for HCC [15]. Objective response rate (ORR) was defined as: CR+PR; disease control rate (DCR) was defined as CR+PR+SD. After DEB-TACE plus MWA therapy, patients underwent abdominal enhanced MRI every 1-3 months to monitor disease relapse or progression and determine subsequent therapy. As for patients in the surgery group, abdominal enhanced MRI was performed every 3 months after surgery. All patients were followed up to August 2020. Relapse-free survival (RFS), progression-free survival (PFS) and OS were evaluated according to the follow-up documents. In addition, intraoperative and postoperative adverse events were recorded in detail.

Statistical analysis

Data processing, graphs plotting, and statistical analysis were completed with SPSS 22.0 statistical software (IBM, Chicago, Illinois, USA) and GraphPad Prism 7.02 (GraphPad Software Inc., San Diego, California, USA). Clinical data comparison between two groups was determined by independent t test, Wilcoxon rank sum test, or Chi-square test. Comparison of preoperative and postoperative AFP level was determined by Wilcoxon signed rank test. RFS was calculated from the date of treatment to the date of disease relapse or patients' death. The RFS in the DEB-TACE plus MWA group was calculated only for patients who achieved CR after DEB-TACE plus MWA therapy. The PFS was calculated from the date of treatment to the date of disease relapse, disease progression or patients' death, whichever occurred first. The OS was calculated from the date of treatment to the date of patients' death. Patients, who lost to follow-up or did not suffer from disease relapse/progression or death, were censored at the date of the last available observation. The RFS, PFS, and OS were displayed using Kaplan-Meier curve. The comparison of RFS/PFS/OS between two groups was determined by Log-rank test. Correction for confounders in the analysis of RFS/PFS/OS was completed by univariate and multivariate Cox's regression model. Statistical significance level was set as $P < 0.05$.

Results

Clinical characteristics

For patients in DEB-TACE plus MWA group, the mean age was 60.0±9.0 years, and there were (25.0%) females and 18 (75.0%) males included (**Table 1**). As for patients in surgery group, the mean age was 55.8±9.7 years, and there were 7 (23.3%) females and 23 (76.7%) males. There was no difference of age, gender, tumor differentiation, ECOG score, BCLC stage, tumor number, tumor capsule or AFP between two groups (all $P > 0.05$). However, DEB-TACE plus MWA group presented increased child-Pugh stage ($P = 0.009$), but smaller tumor size ($P = 0.005$) compared with surgery group. More detailed information about the clinical characteristics of DEB-TACE plus MWA group and surgery group was displayed in **Table 1**, and the detailed information about the operating parameters of MWA was shown in Supplementary Table 1.

Treatment response and AFP level for patients in DEB-TACE plus MWA group

For patients in DEB-TACE plus MWA group, treatment response was evaluated at one

Table 1. Clinical characteristics of HCC patients

Items	DEB-TACE plus MWA (N = 24)	Surgery (N = 30)	$t/\chi^2/Z$	*P* value
Age (years), mean ± SD	60.0±9.0	55.8±9.7	1.646	0.106
Gender, No. (%)			0.020	0.887
Female	6 (25.0)	7 (23.3)		
Male	18 (75.0)	23 (76.7)		
Differentiation, No. (%)			-1.456	0.145
Poor/moderate	18 (75.0)	27 (90.0)		
Well	6 (25.0)	3 (10.0)		
ECOG score, No. (%)			0.565	0.565
0	22 (91.7)	26 (86.7)		
1	2 (8.3)	4 (13.3)		
Child-Pugh stage, No. (%)			-2.631	0.009
A	17 (70.8)	29 (96.7)		
B	7 (29.2)	1 (3.3)		
BCLC stage, No. (%)			-1.439	0.150
A	23 (95.8)	25 (83.3)		
B	1 (4.2)	5 (16.7)		
Tumor number, No. (%)			-1.456	0.145
1	14 (58.3)	23 (76.7)		
2	8 (33.3)	6 (20.0)		
3	2 (8.3)	1 (3.3)		
Tumor capsule, No. (%)			2.372	0.124
No	19 (79.2)	28 (93.3)		
Yes	5 (20.8)	2 (6.7)		
Tumor size (cm), mean ± SD	2.2±0.7	3.4±2.0	-2.965	0.005
AFP (ng/mL), median (IQR)	22.0 (6.9-93.4)	14.5 (3.8-45.4)	-0.740	0.495

Comparison was determined by Student's t test, Chi-square test or Wilcoxon rank sum test. HCC, hepatocellular carcinoma; DEB-TACE, drug-eluting bead transarterial arterial chemoembolization; MWA, microwave ablation; SD, standard deviation; ECOG, Eastern Cooperative Oncology Group; BCLC, Barcelona Clinic Liver Cancer; AFP, alpha fetoprotein; IQR, interquartile range.

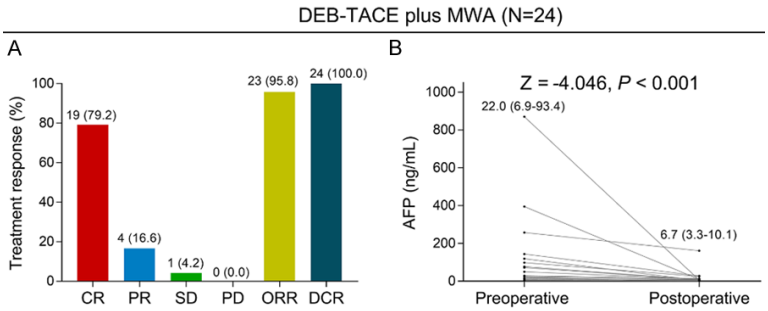

Figure 1. Assessment of treatment response and AFP level. CR, PR, SD, PD, ORR and DCR in patients with HCC adjacent to gallbladder after the treatment of MWA plus DEB-TACE (A). The longitudinal change of AFP from preoperation to post-operation (B). DEB-TACE, drug-eluting beads-transarterial chemoembolization; MWA, microwave ablation; CR, complete response; PR, partial response; SD, stable disease; PD, progression disease; ORR, objective response rate; DCR, disease control rate; AFP, alpha fetoprotein.

month after DEB-TACE plus MWA therapy, which observed that CR, PR, SD, PD, ORR and DCR were 79.2%, 16.6%, 4.2%, 0.0%, 95.8% and 100.0%, respectively (**Figure 1A**). Meanwhile, the AFP level was also assessed, which found that AFP was decreased at postoperative period compared with preoperative period ($P < 0.001$) (**Figure 1B**). However, the assessment of treatment response was not necessary in surgery group, which led to the lack of treatment response comparison between two groups.

Comparison of prognosis between DEB-TACE plus MWA group and surgery group

According to the follow-up documents, DEB-TACE plus MWA group presented similar RFS (median: 28.2 months (95% CI: 12.5-43.9

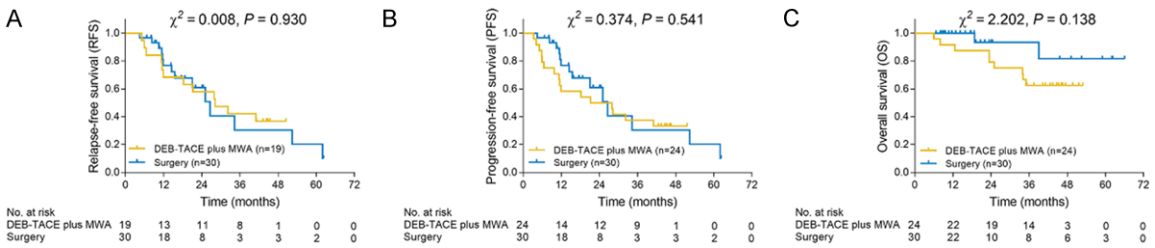

Figure 2. Comparison of RFS, PFS and OS. Comparison of RFS (A), PFS (B) and OS (C) between DEB-TACE plus MWA group and surgery group. DEB-TACE, drug-eluting beads-transarterial chemoembolization; MWA, microwave ablation; RFS, relapse-free survival; PFS, progression-free survival; OS, overall survival.

Table 2. Cox's regression analysis for RFS

Items	Univariate Cox's regression		Multivariate Cox's regression	
	P value	HR (95% CI)	*P* value	HR (95% CI)
DEB-TACE plus MWA vs. surgery	0.930	0.963 (0.420-2.208)	0.935	1.048 (0.341-3.218)
Age (> 60 years vs. ≤ 60 years)	0.787	0.899 (0.414-1.949)	0.724	1.181 (0.468-2.980)
Gender (male vs. female)	0.572	1.328 (0.497-3.547)	0.380	1.599 (0.560-4.561)
Differentiation (poor/moderate vs. well)	0.750	1.266 (0.296-5.424)	0.497	1.718 (0.360-8.209)
ECOG score (1 vs. 0)	0.915	0.936 (0.278-3.149)	0.921	1.073 (0.265-4.339)
Child-Pugh stage (B vs. A)	0.298	1.771 (0.604-5.194)	0.033	5.498 (1.143-26.446)
BCLC stage (B vs. A)	0.045	3.299 (1.028-10.585)	0.537	1.562 (0.379-6.433)
Tumor number (multifocal vs. unifocal)	0.030	2.452 (1.093-5.501)	0.052	2.853 (0.990-8.223)
Tumor capsule (yes vs. no)	0.460	1.503 (0.510-4.430)	0.694	1.315 (0.336-5.155)
Tumor size (> 2 cm vs. ≤ 2 cm)	0.022	2.807 (1.160-6.793)	0.016	3.910 (1.286-11.892)
AFP (> 25 ng/mL vs. ≤ 25 ng/mL)	0.617	0.817 (0.370-1.805)	0.160	0.512 (0.201-1.301)

RFS, relapse-free survival; HR, hazard ratio; CI, confidence interval; DEB-TACE, drug-eluting bead transarterial arterial chemoembolization; MWA, microwave ablation; ECOG, Eastern Cooperative Oncology Group; BCLC, Barcelona Clinic Liver Cancer; AFP, alpha fetoprotein.

months) *vs.* median: 26.6 months (95% CI: 19.2-34.1 months)) (*P* = 0.930) (**Figure 2A**), PFS (median: 21.2 months (95% CI: 1.6-40.8 months) *vs.* median: 26.6 months (95% CI: 19.2-34.1 months)) (*P* = 0.541) (**Figure 2B**), and OS (median: 41.4 months (95% CI: 35.0-47.9 months) *vs.* median: 59.7 months (95% CI: 51.7-67.7 months)) (*P* = 0.138) (**Figure 2C**) compared with surgery group.

Factors affecting RFS, PFS and OS

Univariate Cox's regression analysis indicated that DEB-TACE plus MWA vs. surgery was not correlated with RFS (*P* = 0.930) (**Table 2**), PFS (*P* = 0.542) (**Table 3**) or OS (*P* = 0.158) (**Table 4**). Further multivariate Cox's regression exhibited that, after adjustment of confounding factors, DEB-TACE plus MWA vs. surgery was still not correlated with RFS (*P* = 0.935), PFS (*P* = 0.333) or OS (*P* = 0.189), which suggested that these two treatments presented similar survival profiles. As for other predictive factors for survival, child-Pugh stage (B vs. A) (*P* = 0.033), tumor size (> 2 cm vs. ≤ 2 cm) (*P* = 0.016), tumor number (multifocal vs. unifocal) (*P* = 0.024) could predict decreased RFS, PFS or OS independently.

Comparison of adverse events between DEB-TACE plus MWA group and surgery group

During the treatment, there was higher adverse event incidence in DEB-TACE plus MWA group (7 (29.2%)) compared with surgery group (1 (3.3%)) (*P* = 0.008). In detail, the incidences of hemobilia (*P* = 0.444), bleeding of gallbladder (*P* = 0.444), gallbladder cardiac reflex (*P* = 0.082), heart rate decline (*P* = 1.000) and elevation of blood pressure (*P* = 0.444) were similar between two groups (**Table 5**). As for adverse events after treatment, there was no difference of adverse event incidence between DEB-TACE plus MWA group and surgery group (*P* = 0.618).

Table 3. Cox's regression analysis for PFS

Items	Univariate Cox's regression		Multivariate Cox's regression	
	P value	HR (95% CI)	*P* value	HR (95% CI)
DEB-TACE plus MWA vs. surgery	0.542	1.271 (0.588-2.750)	0.333	1.635 (0.604-4.428)
Age (> 60 years vs. ≤ 60 years)	0.754	1.123 (0.543-2.324)	0.466	1.361 (0.593-3.122)
Gender (male vs. female)	0.432	1.435 (0.583-3.530)	0.266	1.756 (0.651-4.738)
Differentiation (poor/moderate vs. well)	0.613	0.778 (0.295-2.053)	0.735	0.827 (0.275-2.488)
ECOG score (1 vs. 0)	0.765	0.832 (0.251-2.765)	0.628	0.711 (0.179-2.826)
Child-Pugh stage (B vs. A)	0.552	1.342 (0.509-3.536)	0.105	2.988 (0.795-11.233)
BCLC stage (B vs. A)	0.127	2.384 (0.782-7.271)	0.950	1.044 (0.278-3.914)
Tumor number (multifocal vs. unifocal)	0.016	2.510 (1.187-5.309)	0.024	3.127 (1.162-8.414)
Tumor capsule (yes vs. no)	0.280	1.710 (0.646-4.523)	0.288	1.930 (0.573-6.493)
Tumor size (> 2 cm vs. ≤ 2 cm)	0.005	3.407 (1.434-8.091)	0.002	5.583 (1.869-16.676)
AFP (> 25 ng/mL vs. ≤ 25 ng/mL)	0.800	0.910 (0.437-1.892)	0.072	0.443 (0.182-1.077)

PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; DEB-TACE, drug-eluting bead transarterial arterial chemoembolization; MWA, microwave ablation; ECOG, Eastern Cooperative Oncology Group; BCLC, Barcelona Clinic Liver Cancer; AFP, alpha fetoprotein.

Table 4. Cox's regression analysis for OS

Items	Univariate Cox's regression		Multivariate Cox's regression	
	P value	HR (95% CI)	*P* value	HR (95% CI)
DEB-TACE plus MWA vs. surgery	0.158	3.057 (0.648-14.434)	0.189	4.228 (0.493-36.262)
Age (> 60 years vs. ≤ 60 years)	0.381	0.586 (0.177-1.937)	0.919	1.104 (0.164-7.455)
Gender (male vs. female)	0.547	1.601 (0.346-7.419)	0.234	4.229 (0.394-45.375)
Differentiation (poor/moderate vs. well)	0.199	0.418 (0.110-1.584)	0.302	0.351 (0.048-2.562)
ECOG score (1 vs. 0)	0.493	0.043 (0.000-353.910)	0.983	0.000 (0.000-0.000)
Child-Pugh stage (B vs. A)	0.085	2.948 (0.860-10.102)	0.076	7.024 (0.815-60.547)
BCLC stage (B vs. A)	0.143	3.261 (0.671-15.843)	0.454	2.581 (0.216-30.867)
Tumor number (multifocal vs. unifocal)	0.124	2.547 (0.775-8.374)	0.184	4.171 (0.506-34.354)
Tumor capsule (yes vs. no)	0.605	1.500 (0.323-6.963)	0.719	0.633 (0.052-7.631)
Tumor size (> 2 cm vs. ≤ 2 cm)	0.036	9.086 (1.155-71.478)	0.039	13.440 (1.135-159.125)
AFP (> 25 ng/mL vs. ≤ 25 ng/mL)	0.740	0.812 (0.237-2.783)	0.148	0.217 (0.027-1.722)

OS, overall survival; HR, hazard ratio; CI, confidence interval; DEB-TACE, drug-eluting bead transarterial arterial chemoembolization; MWA, microwave ablation; ECOG, Eastern Cooperative Oncology Group; BCLC, Barcelona Clinic Liver Cancer; AFP, alpha fetoprotein.

In detail, the incidence of biliary infection was increased in DEB-TACE plus MWA group (5 (20.8%)) compared with surgery group (0 (0.0%)) (P = 0.013), however, there was no difference of ascites (P = 0.245), abdominal infection (P = 0.245), or hepatic failure (P = 0.497) incidence between two groups. More detailed information of adverse events between two groups were shown in **Table 5**.

Discussion

In the present study, we found that (1) In patients with HCC adjacent to gallbladder, DEB-TACE plus MWA therapy presented CR, ORR and DCR to be 79.2%, 95.8% and 100.0%, respectively; (2) DEB-TACE plus MWA therapy displayed similar survival profiles to the treatment of surgery; (3) DEB-TACE plus MWA therapy exhibited increased incidence of adverse events during the treatment, but the similar incidence of adverse events after the treatment compared to the treatment of surgery.

MWA, as one type of ablation techniques, is a minimally invasive treatment approach frequently used for unresectable HCC patients in clinical practice, and in terms of mechanism, it causes the rotation of water molecules using

Table 5. Adverse events

Items	DEB-TACE plus MWA (N = 24)	Surgery (N = 30)	χ^2	*P* value
Adverse events during treatment, No. (%)	7 (29.2)	1 (3.3)	7.051	0.008
Hemobilia	1 (4.2)	0 (0.0)	-	0.444
Bleeding of gallbladder	1 (4.2)	0 (0.0)	-	0.444
Gallbladder cardiac reflex	3 (12.5)	0 (0.0)	-	0.082
Heart rate decline	1 (4.2)	1 (3.3)	-	1.000
Elevation of blood pressure	1 (4.2)	0 (0.0)	-	0.444
Adverse events after treatment, No. (%)	5 (20.8)	8 (26.7)	0.248	0.618
Biliary infection	5 (20.8)	0 (0.0)	-	0.013
Ascites	0 (0.0)	3 (10.0)	-	0.245
Abdominal infection	0 (0.0)	3 (10.0)	-	0.245
Hepatic failure	0 (0.0)	2 (6.7)	-	0.497

Comparison was determined by Chi-square test or Fisher's exact test. DEB-TACE, drug-eluting bead transarterial arterial chemoembolization; MWA, microwave ablation.

electromagnetic energy and further produces frictional heat to target lesion, leading to coagulation necrosis of tumor [5, 16]. Compared with other energy sources (such as radiofrequency), MWA presents with various advantages due to its larger power outputs, such as high thermal efficiency, increased capability of coagulating blood vessels, less risk of heat-sink effect, however, the increased power outputs of MWA also leads to the hesitation for its application in certain tumor locations (such as HCC adjacent to gallbladder) [2, 5, 17, 18]. Therefore, for MWA, a 5 mm-10 mm safety spherical ablation zone is needed to avoid the thermal injury, or the limited ablation volume of MWA is applied in which cases the risk of tumor remnant and local tumor progression is increased [3]. DEB-TACE is one type of arteria-targeted treatment methods with drug-eluting beads which effectively control the tumor growth and reduce the tumor size [10, 11]. Previous several studies reveal that the combination of DEB-TACE and MWA presents better treatment efficiency and safety profiles compared with monotherapy (TACE alone) in the treatment of HCC non-adjacent to gallbladder (including: large solitary HCC or multinodular HCC) [19-21]. For example, for treatment of 3 cm to 5 cm HCC, MWA plus TACE exhibits trends to reduced rate of local tumor progression and increased rate of treatment response compared with TACE monotherapy [22]. However, the potential of DEB-TACE plus MWA as an alternative treatment approach in management of HCC adjacent to gallbladder has not been explored before. According to the evidence above, we speculated that, after the achievement of safe ablation range using DEB-TACE, MWA could be effective and feasible in improving treatment response and further survival profiles, which was explored in our study.

In current study, 54 patients with HCC adjacent to gallbladder were included and divided into two groups: the group of 30 patients receiving surgical resection and the other group of 24 patients receiving DEB-TACE plus MWA therapy. In terms of treatment response, we observed that CR, PR, SD, PD, ORR and DCR were 79.2%, 16.6%, 4.2%, 0.0%, 95.8% and 100.0%, respectively in patients treated with DEB-TACE plus MWA, suggesting that MWA was effective and feasible in HCC adjacent to gallbladder after the application of DEB-TACE, which was numerically higher compared to the treatment of MWA or DEB-TACE alone in HCC patients [18, 23]. The possible reasons might include that (1) the application of DEB-TACE effectively prolonged drug retention duration and enhanced the directed and localized drug concentration towards the lesions, successfully reducing tumor size and further facilitating the application of ablation in HCC patients with lesions adjacent to gallbladder [10, 11]. (2) Furthermore, apart from the tumor-targeted drug delivery, DEB-TACE presented the capacity of embolizing effect, leading to the synergistic effect of ischemia and local cytotoxic concentration in the tumor-feeding arteries, thereby achieving the safe ablation range and making the MWA treatment feasible [10, 17]. (3) Except for the DEB-TACE, ablation volume of MWA without consideration of possible thermal injury to gallbladder

could be applied when a more aggressive volume was needed, thereby leading to more favorable treatment response and less risk of tumor progression in patients with HCC adjacent to gallbladder. In addition, in our study, AFP level presented an obvious decreased trend from pre-operation to post-operation, which might be explained as follows: existing numerous evidence exhibited that high serum AFP level was correlated with larger tumor size and regarded as an important index for predicting HCC progression in HCC, meanwhile, considering the favorable treatment response after the ablation, AFP level therefore underwent a decreased trend [24, 25].

In addition, we compared the survival profiles between patients treated with DEB-TACE plus MWA and patients treated with surgical resection, and observed that there was no difference of RFS, PFS and OS between them. After further adjustment of confounders by multivariate Cox's regression analysis, we found that DEB-TACE plus MWA *vs.* surgery did not affect the survival profiles (RFS, PFS and OS) in patients with HCC adjacent to gallbladder, which might be explained as follows: patients with HCC adjacent to gallbladder presented safe ablation range after DEB-TACE, facilitating the complete encompassment by the ablation zone and the entire necrosis of the tumor lesions, thereby achieving the similar survival profiles as the traditional surgical resection in patients with lesions adjacent to gallbladder [3, 12]. Therefore, the results in our study implied that DEB-TACE plus MWA presented to be an alternative treatment option comparable to the traditional surgical resection in patients with HCC adjacent to gallbladder.

Subsequently, the safety assessment was conducted in our study, which observed that increased incidence of adverse events during the treatment in patients receiving DEB-TACE plus MWA compared with patients receiving surgery. The detailed adverse events in patients treated with DEB-TACE plus MWA involved hemobilia, bleeding of gallbladder, gallbladder cardiac reflex and heart rate decline which were common complications owing to collateral thermal injury to non-target organ of gallbladder from MWA [5, 26]. In terms of adverse events after treatment, the incidence of biliary infection was increased in patients receiving DEB-TACE plus MWA, which might be explained as follows: postprocedural gallbladder changes (including gallbladder wall edema and pericholecystic fluid) were common and might lead to the symptoms of biliary infection [6]. However, notably, there was no difference of adverse event incidence rates between patients receiving DEB-TACE plus MWA and patients receiving surgical resection, the possible reasons might involve that (1) the prescribed distance from the gallbladder was obtained after the DEB-TACE treatment, which decreasing the thermal injury to the gallbladder. (2) Furthermore, in patients receiving DEB-TACE plus MWA, warm bile might serve as a source of heat convection, which protected the gallbladder wall from permanent thermal damage and avoided the gallbladder-related complications [7]. All the reported adverse events were moderate and relievable spontaneously in the present study.

There were several limitations in our study: (1) the data were from a single center, and samples from multiple regions were required for further validation. (2) the present study was retrospective, and selection bias might therefore exist affecting the results. (3) as our study was a cohort study, there existed some difference of baseline clinical characteristics between two groups, which might lead to the existence of confounding factors, and given this, we have conducted multivariate Cox's regression analysis to remove their interference as possible.

In conclusion, DEB-TACE plus MWA presents to be an alternative treatment option in the management of HCC adjacent to gallbladder.

Disclosure of conflict of interest

None.

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Supplementary Table 1. Operating parameters of MWA

Items	DEB-TACE plus MWA (N = 24)
Type of anesthesia, No. (%)	
Local anesthesia	19 (79.2)
General anesthesia	5 (20.8)
Ablation power (W), No. (%)	
40	2 (8.3)
50	20 (83.3)
60	2 (8.3)
Ablation time (min), No. (%)	
3	5 (20.8)
4	12 (50.0)
5	4 (16.7)
6	3 (12.5)

MWA, microwave ablation; DEB-TACE, drug-eluting bead transarterial arterial chemoembolization.