

# Microwave Ablation and/or Transcatheter Arterial Chemo-embolization in the Treatment of Hepatocellular Carcinoma

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**Background and study aim:** Percutaneous microwave ablation (MWA) and trans-arterial chemo-embolization (TACE) are established therapies for treatment of HCC patients. Lower rates of complete response with mono-therapies have been reported. Therefore, combined treatment strategies, including combined TACE and MWA have been used. The study aimed at comparing the efficacy of MWA mono-therapy; TACE mono-therapy and combined TACE-MWA in the treatment of 3- 5 cm HCC.

**Patients and methods:** The study prospectively included 102 patients with 113 hepatic focal lesions (3-5 cm) diagnosed as HCC by contrast-enhanced triphasic CT or dynamic MRI. Thirty-five HCC in 34 patients were subjected to MWA mono-therapy; 41 HCC in 34 patients were subjected to TACE mono-therapy, while 37 HCC in 34 patients were subjected to combined TACE-MWA

therapy. Follow up by contrast-enhanced CT or MRI was done at one month, and every 3 months, up to one year after treatment. Therapeutic tumor response and local tumor progression were evaluated and compared among the groups.

**Results:** After one year follow up, the combined TACE-MWA group showed a higher rate of complete response (CR) (83.3%) when compared to MWA group (76.5%) and TACE group (66.6%) ( $P>0.05$ ). The local tumor progression (LTP) rate in the combined TACE-MWA group was lower (16.6%) than that in MWA group (23.5%) and TACE group (33.3%) ( $P=0.2$ ).

**Conclusion:** Combined TACE-MWA therapy appears to be non-significantly superior to MWA mono-therapy and TACE mono-therapy in terms of complete tumor response and local tumor progression in patients with 3-5 cm HCC.

## INTRODUCTION

Hepatocellular carcinoma (HCC) is a highly malignant tumor with elevated morbidity and mortality. HCC is the fifth among cancers and develops predominately in patients with liver cirrhosis [1,2]. Thermal ablation and trans-arterial chemo-embolization (TACE) are now well-established and widely used treatments for HCC [3-5].

According to the Barcelona Clinic Liver Cancer (BCLC) staging classification, liver resection, ablation, and transplantation are recommended treatments for early-stage HCC, while TACE is indicated in treatment of intermediate-stage HCC and multifocal tumors. However, this treatment classification in BCLC guidelines may be affected by other

factors like tumor size, location, infiltration and tumors bridging more than one liver segment which may decrease the rates of complete response with mono-therapies [6-9]. Therefore, alternative treatments as combination therapy of TACE and thermal ablation are of growing interest.

Combination of radiofrequency ablation (RFA) and TACE has been shown to be more effective for induction of local tumor control and improvement of disease-free and overall survival of both medium-sized and large HCC tumors [10-12]. Nevertheless, percutaneous microwave ablation (MWA) can produce larger ablation zones and acquire

faster ablations than RFA by preserving consistently higher temperatures inside the tumors [13,14]. Several studies, combining TACE and MWA were carried out for treatment of HCC. These studies either focused on treatment of small-sized (<3 cm) HCC or included a wide range of tumor size [15-18]. Therefore, this study aims at comparing the efficacy of MWA monotherapy; TACE mono-therapy and combined TACE-MWA in the treatment of 3-5 cm HCC.

## PATIENTS AND METHODS

### Patients

This prospective non-randomized study was carried out in Tropical Medicine and Radiology Departments, Zagazig University Hospitals, Egypt between March 2017 and November 2019. The study included 102 patients with 113 hepatic focal lesions (3-5 cm) diagnosed as HCC by contrast-enhanced triphasic CT or dynamic MRI.

**Inclusion criteria** were **a)** single hepatic focal lesion (3-5 cm) or multiple focal lesions (up to 3 tumors  $\leq$ 3 cm) with absence of vascular invasion or extra-hepatic metastasis; **b)** Child-Pugh A and B; **c)** performance status 0-2; **d)** creatinine <2 mg; **e)** bilirubin <2 mg; **f)** platelets count >50000 and **g)** prothrombin concentration >60%. **Exclusion criteria** were **a)** previous treatment of HCC, **b)** technical contraindications to percutaneous ablation or TACE, **c)** patients who did not fulfill the inclusion criteria.

According to multidisciplinary team decision, patients were enrolled in 3 groups according to technical eligibility and/or anticipated response to thermal ablation:

- **Microwave ablation (MWA) group:** included 34 patients with 35 HCC lesions. The focal lesions received percutaneous MWA.
- **Transarterial chemoembolization (TACE) group:** included 34 patients with 41 HCC lesions. The focal lesions were deemed appropriate for TACE if thermal ablation is contraindicated as subcapsular lesions and lesions adjacent to main biliary branches. The focal lesions received maximum 3 sessions of TACE.
- **Combined TACE-MWA group:** included 34 patients with 37 focal lesions. The focal lesions were deemed appropriate for combined TACE-MWA therapy if the lesion was not

well visualized by ultrasound or located in areas of higher recurrence rates. The focal lesion received MWA 2 weeks after TACE.

**Patients were subjected to:** **a) medical history** taking; **b) physical examination** including the ECOG scale of performance status [19]; **c) laboratory tests-** complete blood count- liver and kidney function tests- coagulation profile- alphafetoprotein [AFP] and viral markers (anti-HCV antibodies and HBsAg); **d)** modified Child – Pugh score [20]; **e)** pelvi-abdominal ultrasonography and **f)** abdominal contrast-enhanced triphasic CT-scan or enhanced dynamic MRI.

### Diagnosis of HCC:

Triphasic CT-scan or dynamic MRI was done for all patients to confirm the diagnosis. The typical hallmark is the combination of arterial phase hyperenhancement and washout on the portal venous and/or delayed phases [21].

### Patient management

**Microwave ablation (MWA):** All patients were fasting (at least 6 hours) and under conscious sedation with propofol and midazolam. MTC-3 microwave generator (**Amica**, 2450 MHz) was used for MWA. The ultrasound examination (using a 3.5 MHz probe; Esaote MyLab20Plus) was performed to determine the shortest puncture path and to refrain from the large blood vessels, the bile ducts, the gall bladder and the intestines. Ultrasound-guided puncture of the tumor was done by 14G MWA-antenna and the needle was withdrawn with applying 20-100 W to ablate the needle track and get 0.5-1 cm target ablation beyond the tumor boundary. MWA was performed once for patients of both MWA group and combined TACE-MWA group.

**Trans-arterial Chemo-embolization (TACE):** A 5F catheter was introduced through the femoral artery by Seldinger technique and the angiogram of abdominal vessels was performed to visualize the arterial supply of the tumor. Then, the catheter was inserted into the artery supplying the tumor with injection of lipiodol (10 ml), and doxorubicin (30 mg) into the tumor followed by gelatin sponge particles embolization. At the end of the procedure, another angiogram was performed to ensure full embolization of the supplying artery. TACE was performed once for patients of combined TACE-MWA group and repeated for non-chemoembolized cases with maximum of

three sessions for patients of TACE mono-therapy group.

#### Follow-up and evaluation of therapeutic response:

Abdominal contrast-enhanced triphasic CT-scan or enhanced dynamic MRI was performed at one month, and every 3 months, up to one year after treatment. Images were evaluated for the therapeutic tumor response and local tumor progression. The therapeutic tumor response was classified into complete response (CR); partial response (PR); stable disease (SD) and; progressive disease (PD). Disappearance of all target lesion(s) is considered **complete response**; decrease by 30% or more in the sum of longest diameter of target lesion(s) is considered **partial response**; while increase by 20% or more in the sum of the longest diameter of target lesion(s) is considered **progressive disease**. **Stable disease** is neither partial response nor progressive disease [22]. **Local tumor progression** (LTP) is defined as new nodular enhancement along the ablation margin or growth of the ablation zone on follow up imaging examination [23]. And, **overall survival (OS)** rate is the percentage of people in a study or treatment group who are still alive for a certain period of time after they were diagnosed with or started treatment for a disease. In this study, the OS is the percentage of patients who were still alive at the end of one year post treatment.

Moreover, post-treatment laboratory parameters and AFP level were measured. Procedure-related complications were assessed according to Society of Interventional Radiology (SIR) classification [24].

#### Study endpoints:

The primary endpoint was complete response and local tumor progression at the end of follow up period of 12 months after treatment. The secondary endpoints were adverse events and overall survival rate.

#### STATISTICAL ANALYSIS

Data were checked, entered and analyzed using SPSS statistical package. Data were expressed as mean  $\pm$  SD for quantitative variable, number and percentage for qualitative one. Chi-squared ( $X^2$ ), ANOVA (F-test), and paired t test were used when appropriate. P value  $< 0.05$  was considered significant.

## RESULTS

#### Patient and tumor characteristics

Demographic and baseline characteristics of MWA, TACE, and TACE-MWA groups are presented in (Table 1). Thirty five focal lesions in 34 patients were treated by MWA ablation; 41 focal lesions in 34 patients were treated by TACE; while combined TACE-MWA therapy was performed on 37 focal lesions in 34 patients.

No statistically significant differences ( $P > 0.05$ ) were seen among all studied groups regarding age, sex, viral markers, Child-Pugh Score, laboratory parameters and size of focal lesion. The representative images of the treatment procedures are shown in (Figures 1 and 2)

#### Complications and safety

All patients successfully received MWA mono-therapy, TACE mono-therapy or combined TACE-MWA. There were no procedure-related deaths or major complications in all groups. Hospital stay was not necessary as all of the observed complications were mild, transient and self-limiting. No statistically significant differences ( $P > 0.05$ ) were noted among all studied groups regarding procedure-related complications (fever, vomiting, ascites, pleural effusion and bleeding) apart from transient abdominal pain which was significantly higher in MWA group (32.4%,  $P = 0.02$ ). One patient (2.9%) had minor bleed related to the ablation procedure in the combined TACE-MWA group. Furthermore, there was no statistically significant differences among all studied groups regarding values of bilirubin ( $P = 0.6$ ) and alanine aminotransferase (ALT) ( $P = 0.2$ ) which indicate that any of the treatment procedure has no significant effect on hepatic function. AFP levels showed improvement but the results were non-significant among the studied groups ( $P = 0.9$ ) (Table 2).

#### Therapeutic tumor response and progression

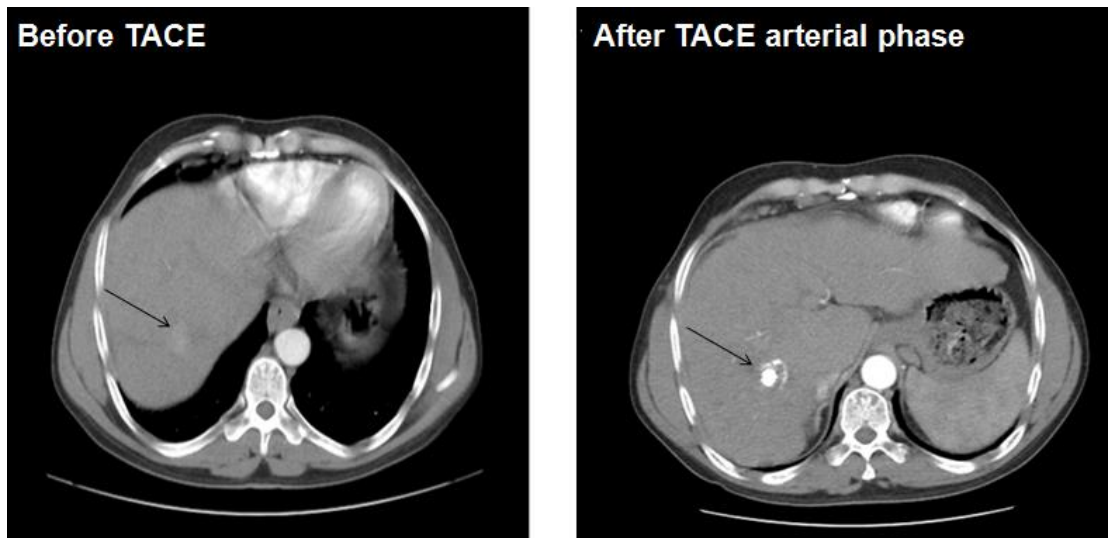
The therapeutic tumor response was followed at one month, and every 3 months, up to one year after treatment. Before the end point of the study, 4 patients were died in all groups. All deaths resulted from cirrhosis-related complications (repeated attacks of bleeding (one patient); terminal hepatic failure and hepatorenal syndrome in 3 patients).

Rates of complete response (CR), partial response (PR) and progressive disease (PR) among the study groups were summarized in (Table 2). After one year follow up; the combined TACE-MWA group showed a non-significant higher rate of complete response (CR) (83.3%) when compared to MWA group (76.5%) and TACE group (66.6%) ( $P>0.05$ ); furthermore, there was a non-significant lower rate of the local tumor progression (LTP) in the combined TACE-MWA

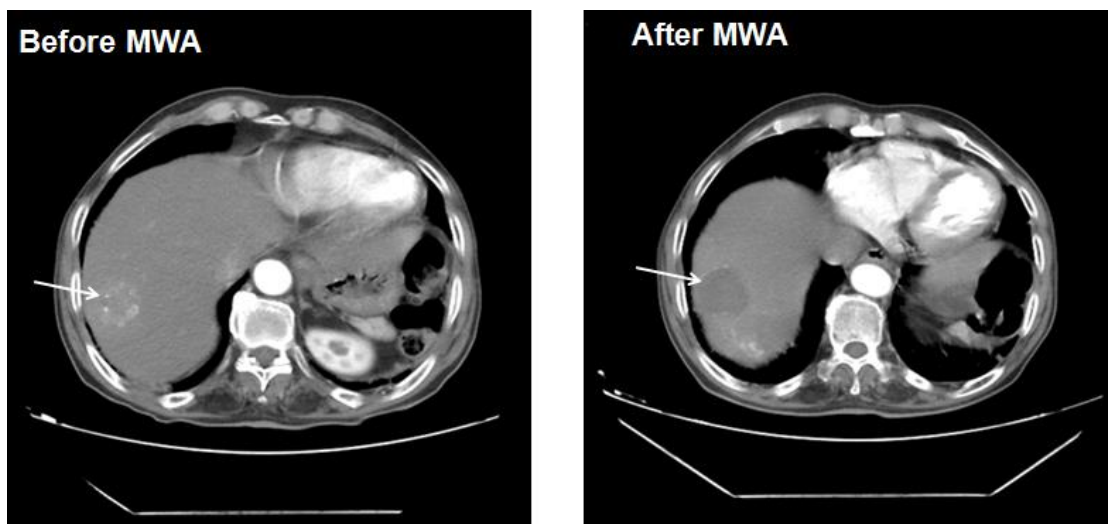
group (16.6%) when compared to MWA group (23.5%) and TACE group (33.3%) ( $P=0.2$ ).

#### Overall survival rate (OS rate)

There was no statistically significant difference ( $P=0.4$ ) among all studied groups regarding OS rate. Both MWA group and combined TACE-MWA group had same OS rate (97.1%), while TACE group had 94.1% OS rate.



**Figure (1):** A 50-year old male presented with 4.8 cm HCC, TACE mono-therapy was performed with complete lipiodol uptake after one month.



**Figure (2):** A 67-year old male presented with 4.5 cm HCC, MWA mono-therapy was performed with complete ablation of the tumor after one month.



**Table (1):** Demographic and baseline characteristics of all studied groups.

Factor	MWA (n. = 34)	TACE (n. = 34)	TACE+MWA (n. = 34)	P value
<b>Total number of FL</b>	35	41	37	
<b>Number of FL/Patient</b>				
1	97.1% (33/34)	88.2% (30/34)	94.1% (32/34)	0.4
2	2.9% (1/34)	2.9% (1/34)	2.9% (1/34)	
3	0.0	8.8% (3/34)	2.9% (1/34)	
<b>Age (years)</b>				
Mean±SD	58.7±5.9	56.3±6.7	59.4±7.4	0.08
Range	(49-71)	(45-70)	(47-73)	
<b>Sex</b>				
Male	79.4% (27/34)	91.2% (31/34)	85.3% (29/34)	0.9
Female	20.6% (7/34)	8.8% (3/34)	14.7% (5/34)	
<b>Viral markers</b>				
Positive HCV	91.2% (31/34)	85.3% (29/34)	94.1% (32/34)	
Positive HBV	8.8% (3/34)	11.8% (4/34)	0.0	0.2
HBV and HCV	0.0	2.9% (1/34)	5.9% (2/34)	
<b>Child-Pugh Score</b>				
A	55.9% (19/34)	52.9% (18/34)	58.8% (20/34)	0.9
B	44.1% (15/34)	47.1% (16/34)	41.2% (14/34)	
<b>AFP (ng/mL)</b>	206.1±248.8	208.1±259	203±248.3	0.9
<b>Bilirubin (mg/dL)</b>	1.16±0.55	1.04±0.28	1.14±0.46	0.5
<b>ALT (IU/L)</b>	39.5±17.5	34.6±24.1	38.2±25.2	0.2
<b>Size of FL (cm)</b>	3.9±0.6	4.1±1	4.3±0.7	0.21

n. = number of patients

FL= focal lesion

No statistical significant difference (P&gt;0.05)

**Table (2):** Follow up data and tumor response in all studied groups.

Factor	MWA (n.= 34)	TACE (n.= 34)	TACE+MWA (n.= 34)	P value
<b>Procedure-related complications</b>				
Abdominal Pain	32.4% (11/34)	5.9% (2/34)	20.6% (7/34)	0.02*
Fever	11.8% (4/34)	20.6% (7/34)	23.5% (8/34)	0.4
Vomiting	2.9% (1/34)	11.8% (4/34)	14.7% (5/34)	0.2
Ascites	5.9% (2/34)	0.0	2.9% (1/34)	0.3
Pleural effusion	2.9% (1/34)	2.9% (1/34)	5.9% (2/34)	0.8
Bleeding	0.0	0.0	2.9% (1/34)	0.3
<b>AFP (ng/mL)</b>	199.1±238.4	200.5±235.8	197.4±231.4	0.9
<b>Bilirubin (mg/dL)</b>	1.09±68	1.02±0.42	0.9±0.43	0.6
<b>ALT (IU/L)</b>	32.1±26.1	22.3±13.1	34.6±19.4	0.2
<b>Total number of deaths</b>	2.9% (1/34)	5.9% (2/34)	2.9% (1/34)	0.8
<b>Tumor response (at one year/end point)**</b>				
CR	76.5% (26/34)	66.6% (26/39)	83.3% (30/36)	0.4
PR	17.6% (6/34)	23.1% (9/39)	8.3% (3/36)	
PD	5.9% (2/34)	10.3% (4/39)	8.3% (3/36)	
<b>LTP rate (at one year/end point)</b>	23.5% (8/34)	33.3% (13/39)	16.6% (6/36)	0.2
<b>OS rate (%) at 1 year</b>	97.1% (33/34)	94.1% (32/34)	97.1% (33/34)	0.4

No statistical significant difference (P&gt;0.05)

CR= complete response

\* Statistical significant difference (P≤0.05)

PR= partial response

n. = number of patients

PD= progressive disease

LTP= local tumor progression

OS = overall survival

\*\* The number of focal lesion in MWA group=34, TACE group= 39, Combined TACE-MWA= 36; after subtracting the cases of deaths.

## DISCUSSION

MWA and TACE are established therapies for the treatment of HCC patients. TACE is one of the therapies used for the treatment of un-resectable large-sized HCC as well as treatment of intermediate stage and multifocal tumors [21,25,26]. However, complete response is difficult to be achieved by TACE for medium, large or multiple tumors. TACE may result in incomplete occlusion of the tumor-supplying artery with generation of small new collaterals for tumor remnants, or may result in complete occlusion of the tumor-supplying arteries with regeneration of various arterioles from other sites (gastric, superior mesenteric, phrenic, and intercostal arteries) [27,28] making it difficult to selectively catheterize tumor-feeding arteries to control residual tumor cells. On the other hand, MWA is an effective local thermal ablation technique which has been widely used for treatment of HCC [29-31] with a 5-year survival rate comparable to that of hepatectomy for small hepatic tumors [32]. Microwave ablation produces higher temperature in a shorter period and achieves larger ablation zones when compared with radiofrequency ablation [33,34].

The present study revealed that using MWA after TACE shows increased rate of CR and low rate of LTP when compared to MWA mono-therapy or TACE mono-therapy in the treatment of 3-5 cm HCC although the differences were not statistically significant.

Regarding tumor response to different therapeutic techniques, this study revealed that the combined TACE-MWA group has a non-significant higher rate of CR (83.3%) for 3-5 cm HCC when compared to MWA mono-therapy group (76.5%) and TACE mono-therapy group (66.6%) ( $P = 0.4$ ). These results compare favorably with **Smolock et al.**, who included same range of tumor sizes, from 3-5 cm, and reported higher CR rate in the combined TACE-MWA (65%; 15/23) versus TACE mono-therapy (38%; 9/24) ( $P = 0.12$ ) [35]. Furthermore, our study had a higher CR rate than that reported by **Li et al.**, who included larger tumors (mean size approximately 7cm) treated with TACE+MWA (65% CR) versus TACE mono-therapy (45% CR) [18].

The increased CR that was noted in the combined TACE-MWA group may be resulting from the complementary effect of both procedures. Prior

studies revealed that chemotherapeutic agents may cause a heat-sensitizing effect and thermal injury may sensitize tumors to these agents. In addition, larger necrotic zones have been demonstrated when TACE was followed by ablation rather than the converse [36,37]. In the present study, MWA was done 2 weeks after TACE, to facilitate targeting of the tumor by ultrasound with higher possibility for accurate placement of the ablation probes in the tumor (time allows enhanced contrast between the Lipiodol-stained tumor and surrounding liver tissue). Moreover, time allows patient to recover from any symptoms that may occur after TACE [35,38].

Based on post-treatment cross-sectional imaging findings, TACE-MWA group showed lower LTP rate (16.6%) when compared to MWA mono-therapy group (23.5%) and TACE mono-therapy group (33.3%) ( $P = 0.2$ ). These results are in agreement with **Smolock et al.**, who compared TACE mono-therapy with combined simultaneous TACE and MWA and demonstrated lower rate of LTP in the tumors treated with combined TACE and MWA (34.8%) than tumors treated with TACE alone (62.5%) ( $P = 0.1$ ) [35]. Furthermore, a retrospective study involved 258 patients with a large solitary nodule or multinodular HCCs ( $\leq 10$  nodules), and treated by TACE-MWA ( $n = 92$ ) or TACE alone ( $n = 166$ ), revealed 47.8% one year recurrence rate in the TACE-MWA group versus 74.7% in the TACE group ( $P < 0.001$ ) [39].

In the current study, no significant survival advantage was noted among the groups as the follow up period was one year. Both MWA group and combined TACE-MWA group had same OS rate (97.1%), while TACE group had 94.1% OS rate ( $P = 0.4$ ). These results are comparable with **Chen et al.**, who reported 91.7% cumulative survival rate after one year in the combined TACE-MWA group versus 87.2% in TACE mono-therapy group ( $P = 0.3$ ) [40]. In contrast, other studies demonstrated significant higher OS rates with the combined TACE-MWA therapy versus TACE mono-therapy. **Xu et al.; Zhang et al. and Zheng et al.**, reported higher OS rates at 1-year for TACE-MWA group (87.5%; 93.1% and 85.9% respectively) than that for TACE group (62.5%; 77.5% and 59% respectively) ( $P < 0.001$ ) [39,41,42].

Both TACE and MWA are minimally invasive procedures with uncommon major complications and rare mortalities [43,44]. Although performing two procedures may add more risk with each procedure, this study reported minor complications related to both MWA and TACE procedures with no statistically significant differences ( $P>0.05$ ) noted among all studied groups apart from significant increase in abdominal pain (32.4%,  $P=0.02$ ) with microwave mono-therapy that may be attributed to the site of lesion (subcapsular or peri-hilar) and the amount of tissue necrosis [45]. In addition, this study showed no procedure-related deaths or serious major events in all groups and this is consistent with Liu et al., who stated that all patients tolerated both TACE and MWA procedure well without any fatal or major complications [46]. On the other hand, Zheng and his colleagues reported major complications in 3.6% (6/166) of patients treated with TACE mono-therapy versus 2.2% (2/92) of patients treated with combined TACE-MWA therapy [39], which may be related to the higher number of patients in their study.

Furthermore, the current study showed no statistically significant differences among all studied groups regarding values of bilirubin ( $P=0.6$ ) and ALT ( $P=0.2$ ). These results are similar to Smolock et al., who reported that bilirubin values showed no difference after treatment and no change in-between the groups ( $P=0.6$ ) indicating that any of the treatment procedure has no significant hepatocyte damage [35].

Post-treatment hypoxia and tumor necrosis has been shown to lead to AFP decrease [47,48]. In the present study, non-significant improvement in the post-treatment AFP levels was noted among the different studied groups ( $P=0.9$ ). Moreover, a study done by Xu et al., showed significant reduction in AFP level after treatment with combined TACE-MWA therapy ( $P<0.001$ ) and TACE mono-therapy ( $P=0.003$ ) [41]. This decrease in AFP levels may predict advantageous therapeutic effect [49].

To the best of authors' knowledge, this is the first study to compare 3 groups (MWA mono-therapy, TACE mono-therapy and combined TACE-MWA) for treatment of HCC, while most of the studies compared only 2 groups (TACE mono-therapy versus combined TACE-MWA). Furthermore, our study is a prospective non-

randomized study unlike most of other studies that were retrospective.

The study has certain limitations. First, the follow-up period was one year with limited survival data and this may have led to biased results. Also, there was a difference in the disease burden among the studied groups with more multifocal disease in TACE mono-therapy group. In addition, all procedures were performed by the same HCC management team in our institution, with the possibility of bias from doctors' experience, patients' characteristics and equipments' quality.

## CONCLUSION

This study demonstrated that despite both combined TACE-MWA therapy and MWA-mono-therapy had the same OS rate, however, combined TACE-MWA therapy appears to be non-significantly superior to MWA mono-therapy and TACE mono-therapy in terms of complete tumor response and local tumor progression in patients with 3-5 cm HCC. Further multi-centre prospective randomized controlled trials with longer follow up periods are needed.

**Conflict of interest:** None.

**Financial disclosure:** None.

**Ethical considerations:** Approval of Institutional Review Board of the Faculty of Medicine, Zagazig University was granted. Consent was obtained from patients before the procedure after explaining risk/benefit ratio as well as the expected hazards and interventions.

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