Original article

Percutaneous Microwave Ablation of Hepatocellular Carcinoma

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ABSTRACT

Background: Hepatocellular carcinoma (HCC) is the commonest primary cancer of the liver. Incidence is increasing and HCC has risen to become the 5th commonest malignancy worldwide and the third leading cause of cancer related death. According to the BCLC staging system image-guided tumor ablation is recommended in patients with early stage HCC. Microwave ablation (MWA), is a thermal ablative technique that has recently emerged as a new therapeutic option. The aim of this study was to evaluate the use of microwave ablation in hepatocellular carcinoma treatment and to assess the outcome.

Methods: This study was carried out on 52 patients proved to have HCC who presented to Radiology Department in Alexandria University Hospitals. Microwave ablation was performed percutaneously under real-time ultrasound guidance using a GE LOGIQ 5 Pro US scanner (USA) with a 3.5–5 MHz probe, to completely destroy the tumor, as well as the surrounding 0.5–1.0 cm normal appearing liver tissue (safety margins). The patients were observed two hours before discharge. Contrast-enhanced triphasic CT imaging needed to be performed at 1 month after the ablation.

Results: All patients completed the procedure safely. The outcome, as determined by dynamic CT performed 1 month after percutaneous MWA, was achieved in 66 (97%) of 68 lesions. The technical success rates for tumors smaller than 3 cm and those 3-5 cm were 97.2% (35 of 36 nodules) and 96.9% (31 of 32 nodules), respectively

Conclusion: Thermal ablation, including radiofrequency ablation (RFA) and microwave ablation (MWA), have been shown to be effective for treating HCC. Microwave ablation is a safe, effective and

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promising technique and a good replacement to surgical interference for patients who are not amenable to surgical therapy.

Keywords:Microwave ablation; Hepatocellular carcinoma; Thermal ablation; percutaneous ablation

1- Introduction:

Hepatocellular carcinoma (HCC) is the commonest primary cancer of the liver. Incidence is increasing and HCC has risen to become the 5th commonest malignancy worldwide and the third leading cause of cancer related death, exceeded only by cancers of the lung and stomach (1). The estimated incidence of new cases is about 500 000-1 000 000 per year, causing 600 000 deaths globally per year (2 & 3) Patients with cirrhosis are at the highest risk of developing HCC and should be monitored carefully to diagnose a possible tumor at an early-stage (4). Correct detection, classification and characterization of focal lesions are of paramount importance as they may significantly affect the choice of therapeutic approach in many cases (5).

According to the BCLC staging system image-guided tumor ablation is recommended in patients with early stage HCC (6). Image-guided percutaneous ablation is currently accepted as the best therapeutic choice for nonsurgical patients with early-stage disease (7).

For the treatment of HCC, minimally invasive locoregional therapies include radiofrequency ablation (RFA), ethanol injection, microwave ablation, cryoablation, irreversible electroporation (IRE), and high-intensity focused ultrasound (HIFU) ablation (8).The purpose of thermal ablative treatments is to destroy solid tumors by raising their temperature above a lethal threshold (60 ℃ for instantaneous coagulative necrosis, 50 ℃ for prolonged exposure to heat) through direct energy deposition, which eventually turns into heat within a limited and controlled range of action (9).

RFA rapidly became the gold standard in ablation, especially in the treatment of small HCC nodules, at first flanking and eventually replacing percutaneous ethanol injection (PEI) treatments. However, RFA exhibits substantial performance limitations in the treatment of large lesions and/or tumors located near major heat sinks (9).

Consequently, the shape and size of the ablation zone may be unpredictable and the efficacy of RFA may be restricted as multiple sessions are necessary for complete tumour eradication (10).

MWA uses electromagnetic energy (up to 2 cm surrounding the antenna); in the absence of current flow, the electromagnetic field creates a rapid and homogeneous heating of

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tissue and subsequently coagulation necrosis. The best heating effect is achieved in tissues with a high content of water and the worst is observed in fat (11).The aim of this study is to evaluate the use of microwave ablation in hepatocellular carcinoma treatment and to assess the outcome.

2- Patients and Methods

From June 2017 to February 2019, a total of 90 patients with HCC, deemed unsuitable for hepatic resection were referred to the interventional radiology department from the hepatic surgery department at Alexandria University Hospital. A total of 52 patients were recruited into this prospective study and treated with ultrasound-guided percutaneous MWA. The study was approved by the medical ethics committee of the hospital.

The 52 Patients included in our study had one of the following criteria:

- Single nodular HCC lesions of 5 cm or smaller.
- Less than five nodular HCC lesions with a maximum dimension of 5cm or less in each nodule.
- Absence of portal vein thrombosis.
- Absence of extra-hepatic metastases.
- Elevated alpha feto-protein.

Exclusion criteria were liver decomposition, end stage kidney or critical heart disease, and obstructive jaundice either related or non related to the targeted lesion.

2-2. Ablation procedure.

Microwave ablation was performed percutaneously under real-time ultrasound guidance using a GE LOGIQ 5 Pro US scanner (USA) with a 3.5–5 MHz probe. The ablation procedure was performed under general anesthesia with propofol (Diprivan). MWA was performed using as HS AMICA microwave delivery system (HS Hospital service S.P.A Roma, Italy).

The aim of the treatment was to completely destroy the tumor, as well as the surrounding 0.5–1.0 cm normal appearing liver tissue (safety margins). A pre-incision of the skin is done and a 14-gauge 15 cm guide needle with a sheath was inserted and positioned at the designated place of the tumor under sonographic guidance, then the stylet of the guide needle was pulled out.

After the microwave electrode was introduced through the sheath of the guide needle, the sheath was withdrawn approximately 4–5 cm while keeping the electrode needle at its place to ensure that a portion of at least 4 cm from the tip of the electrode was exposed. Usually the tip of the electrode has to be placed at the bottom of the lesion about 0.5 cm inside the tumor margin.

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During each application of microwave energy, an expanding hyperechogenic area was produced which roughly judges the size of the ablation zone, i.e., necrotic zone. The necrosis length overcomes the tip of the electrode ahead by few mm (2–6 mm) depending on power and time of the treatment while the biggest increase occurs backwards and radially as the time goes over.

These changes are visible on sonographic images but diminished rapidly as soon as the microwave generator was switched ‘‘off’’ and completely disappeared within 8 h. To minimize tumor seeding, the needle track was routinely ablated while withdrawing the antenna at about 2 cm/s (track ablation) The power has to be set at 40 W, After the MWA procedure, the punctured site is covered with a sterile dressing under pressure.

The patients were observed two hours before discharge. Contrast-enhanced triphasic CT imaging needed to be performed at 1 month after the ablation. If irregular peripheral enhancement occurred, which represents residual unablated tumor, this sign indicates incomplete ablation. If complete ablation is achieved, then routine triphasic CT and serum tumor marker are repeated every 3 months.

3-Data Management and Statistical analysis:

Data were collected, coded, revised and entered to the Statistical Package for Social Science (IBM SPSS) version 20 (Chicago, Ill, USA). The data were presented as number and percentages for the qualitative data, mean, standard deviations and ranges for the quantitative data with parametric distribution and median with inter quartile range (IQR) for the quantitative data with non parametric distribution.

Chi-square test was used in the comparison between two groups with qualitative data and Fisher exact test was used instead of the Chi-square test when the expected count in any cell found less than 5.

- *Independent t-test* was used in the comparison between two groups with quantitative data and parametric distribution and *Mann-Whitney test* was used in the comparison between two groups with quantitative data and non parametric distribution.
- The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as the following:
- P > 0.05: Non significant (NS)
- P < 0.05: Significant (S)
- P < 0.01: Highly significant (HS)

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4- Results:

According to the patient inclusion and exclusion criteria, a total of 52 patients were included (43 men and 9 women) with a mean age of 58.5+4.47 years (range: 48–71 years) with significant male predominance (82.7%) (Table 1).

All the patients (100%) had established liver cirrhosis (table 1). 51 patients (98.1%) were infected with hepatitis C virus (HCV), while the other one (1.9%) had hepatitis B virus (HBV) infection (table 1).

All patients were staged according to Child-Pugh classification as 41 (78.8%) of them as stage A while the other 11 (21.2%) patients were stage B. (table 1).

Table (1). Demographic data, cirrhosis, hepatitis and Child-Pugh class

Gender	Female	9	17.3%
	Male	43	82.7%
Age	Mean ±SD	58.54±4.47	
	Range	48-71	
Cirrhosis	Present	52	100.0%
Cirrhosis	Present	52	100.0%
Hepatitis	HBV	1	1.9%
	HCV	51	98.1%
Child-Pugh class	Class A	41	78.9%
	Class B	11	21.2%

Among all the patients, 36 (69.2%) patients had single lesion, 16 (30.8%) had two lesions (table 2).

Ultrasound findings of the patients before the procedure showed that 43 (63.2%) hepatic focal lesions were detected in the right lobe and 25 (36.8%) focal lesions were detected in the left lobe (table 2).

The mean size of the focal lesions was 3.05 + 0.47 cm, with a range of 2.2–4.5 cm. The PV was patent in all studied patients without ascites. Percutaneous US guided Microwave was utilized to ablate these 68 focal lesions (table 2).

Table (2). Lesion number, size and distribution.

		No	%
Number of lesions	Single	36	69.2%
	Two	16	30.8%
Location	LT	25	36.8%
	RT	43	63.2%
tumor size /cm	Mean ±SD	3.05 ± 0.47	
	Range	2.2 - 4.5	

The mean procedure time for MWA was 12.1+ 1.64 min ranging from 8-15 min., and the mean power used was 66.2+ 1.6 W during the MWA.

All patients completed the procedure safely. The outcome, as determined by dynamic CT performed 1 month after percutaneous MWA, was achieved in 66 (97%) of 68 lesions (table 3).

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Table (3): Study results.

		No	%
Result	Complete ablation	66	97.1%
	Incomplete ablation	2	2.9%

The technical success rates for tumors smaller than 3 cm and those 3-5 cm were 97.2% (35 of 36 nodules) and 96.9% (31 of 32 nodules), respectively (table 4).

Table (4). Complete/ incomplete ablation regarding tumor size.

		Tumor size /cm (1)				Chi square test	
		<3 cm		3-5 cm			
		No	%	No	%	X2	P value
Result	Complete ablation	35	97.2	31	96.9	0.007	0.933
	Incomplete ablation	1	2.8	1	3.1		

The two incompletely ablated tumors were subjected to a second session of MWA and technical success was achieved in both. Follow-up for all cases extended for 6 months including the first follow-up after one month, three and six months following MWA. There was no change in the Child–Pugh score before and one month after MWA. No statistically significant difference was found between the Child–Pugh score and the response to MWA. During this period, none of the patients died, no local recurrence was detected. Alpha-fetoprotein (α-FP) was measured for all patients preoperatively, mean α-FP was 342.62 ± 276.29 (Table 5).

Table (5): AFP before and after MWA.

	Min	Max	Mean	SD
AFP before (ng /ml)	82	1387	342.62	276.29
AFP after (ng /ml)	5	240	36.96	46.80

There was significant decline in the AFP level one month after ablation compared with that before the procedure (36.96 ng/mL + 46.8, P < 0.001) (Table 6).

Table (6): AFP before and after MWA.

	Mean	SD	Parried t test	
			T	P value
AFP before (ng /ml)	342.62	276.29	9.270	0.001
AFP after (ng/ml)	36.96	46.80		

Distant tumor progression in the liver (de novo lesions) developed in 3 (5.7%) patients, were recorded six months after the MWA (table7).No distant metastasis (extrahepatic) was recorded up till 6 moth follow up (Table 7).No major complication occurred related to the ablation procedure (Table 7). Minor complications including upper quadrant pain 37/52 (71.1%) and low grade fever ≤38°C 4/52 (7.6%), was relieved with the oral administration of

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analgesics (Table 7). 2 patients developed non symptomatic mild pleural effusion that needed no treatment (Table 7).No other clinically relevant complications were observed.

Table (7) study results regarding local recurrence, complications and metastasis

		No	%
Local recurrence	No local recurrence	-	-
Major complications	No	-	-
	Fever	5	9.6 %
Minor complications	Pain	17	32.7%
	Pleural effusion	2	3.8 %
Distant tumor progression in the liver (d novo lesions)	yes	3	5.7 %
Distant metastasis	No	-	-

Case no. (1)

Male patient 58 years old of child-pugh class A, presented with left lobe, segment IVb, HCC measuring about 2.9 cm in diameter. A single session of MWA was done (figures from 1-5).

Fig. (1)

Fig. (2)

Fig.1 , 2: Triphasic CT scan shows enhancing left lobe focal lesion with washout in the delayed phase.

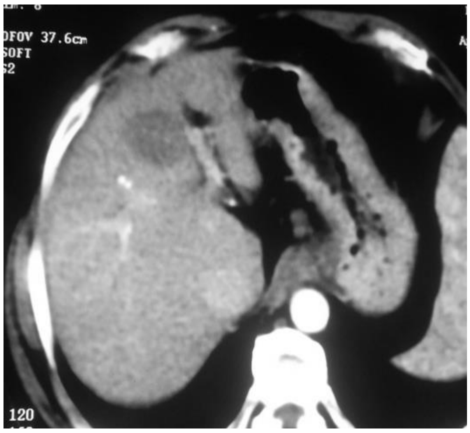

Fig. (3)

Fig. 3: Triphasic CT scan was done 1 month after ablation and the lesion was completely ablated.

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Fig. (4)

Fig. (5)

Fig. 4, 5: Follow up at 3 and 6 months with no evidence of either local or distant recurrence could be detected.

Case no. (2)

Male patient 63 years old of child–Pugh class A, presented with right lobe (V) HCC measuring about 3.0 cm in diameter. A single session of MWA was done (figures from 6-10).

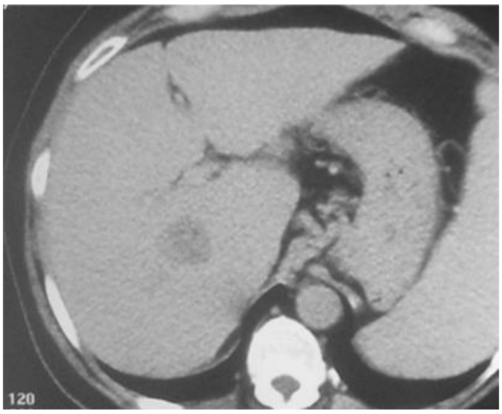

Fig. (6)

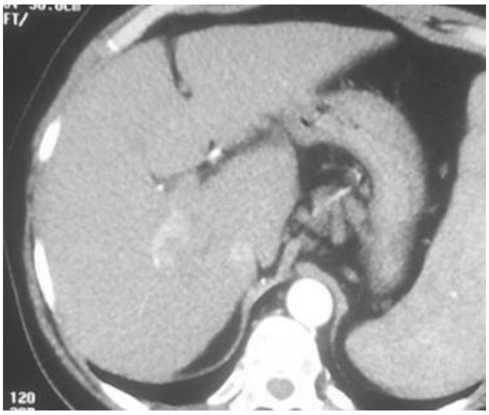

Fig. (7)

Fig. 6,7**:** Triphasic CT scan shows enhancing right lobe focal lesion with washout in the delayed phase.

Fig (8): Triphasic CT scan was done 1 month after ablation and the lesion was completely ablated.

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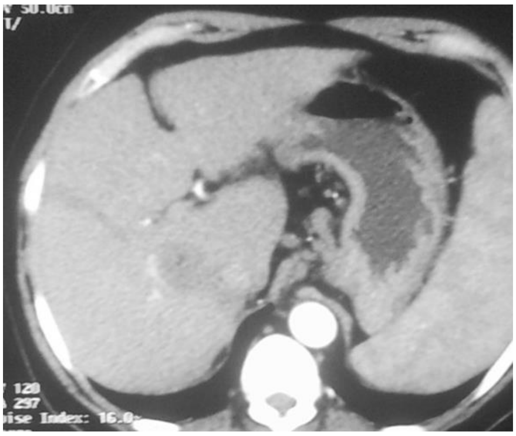

Fig.(9)

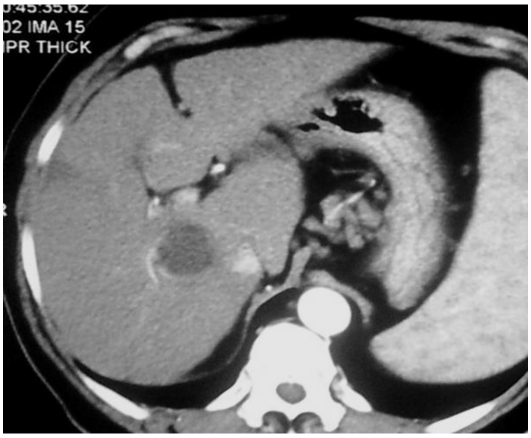

Fig.(10)

Fig.9,10**:** Follow up at 3 and 6 months with no evidence of either local or distant recurrence could be detected.

Case no. (3)

Male patient 49 years old of Child–Pugh class A, presented with left lobe, segment III, HCC measuring about 2.3 cm in diameter. Single session of MWA was done (figures from 11-15).

Fig. (11)

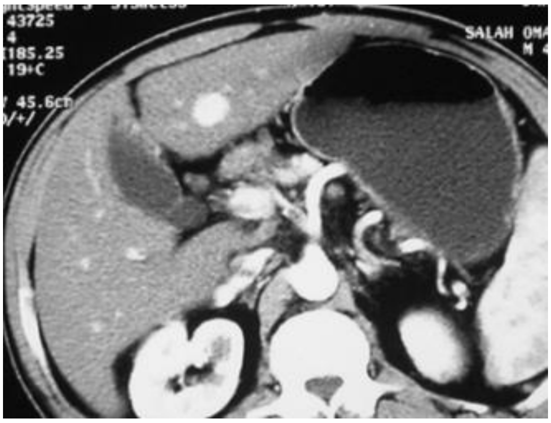

Fig.(12)

Fig. 11,12**:** Triphasic CT scan shows enhancing left lobe focal lesion with washout in the delayed phase

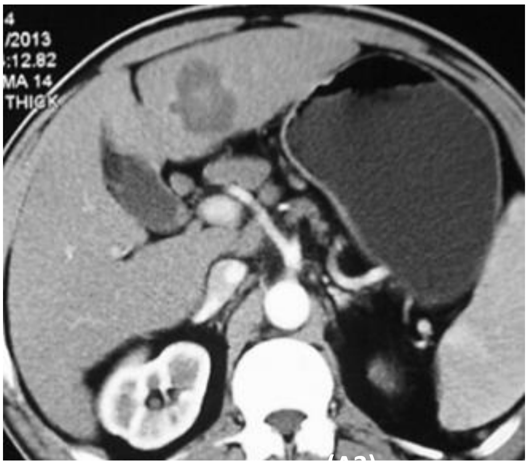

Fig. 13:Triphasic CT scan was done 1 month after ablation and the lesion was completely ablated

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Fig. (14)

Fig. (15)

Fig. 14,15**:** Follow up at 3 and 6 months with no evidence of either local or distant recurrence could be detected

5- **Discussion:**

Treatment of HCC is a challenge that requires multi-disciplinary team to individualize therapy for each patient. Although orthotopic liver transplantation and primary resection are effective; underlying liver disease and shortage of liver donors are barriers against these modalities. Subsequently advances in loco regional therapies and targeted systemic therapy provide hope for patients in whom liver function and HCC morphology are obstacles against surgery. This is because loco regional therapies are minimally invasive and relatively safe, therefore can be repeated several times for HCC recurrence which exceeds 70% in 5 years *(12).*

Microwave ablation can be performed percutaneously, laparoscopically, thoracoscopically, or at laparotomy. Percutaneous treatment offers several advantages over other approaches *(13).*

The percutaneous approach is the least invasive, relatively expensive, can be performed on outpatient basis, and can be repeated to treat recurrent tumor, laparoscopic and thoraco-scopic approaches may be employed to ablate tumors at locations inaccessible by the percutaneous approach *(13).*

Our study was conducted on 52 patients by ultrasound guided percutaneous approach which was well tolerated by all patients and post procedural hospital admission was not required.This is in agreement with *Abdel Aziz et al.* who recorded a small rate of minor complications and there were no major complications or death occurred *(14).*

A large multicentric Italian study that included 14 centers that performed microwave ablations for 736 patients with 1,037 lesions finally confirmed the safety of

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microwave procedures with low rate of major complications (*15*)

The mean age of the patients in our study was 58.54±4.47 years. Similar mean age group was studied by *Soliman et al. (16)*. Older mean of age was documented to cases studied by *Pusceddu et al.* being 69 ± 10.4 (46–85) *(17).*

In nearly all populations, there was a higher rate of liver cancer in men than women, with usual male to female ratios of 2:1 to 4:1 on average *(18).* Similarly, in our study a significant male predominance was 82.7%, as was also reported by *Liu et al.* with a male predominance of 92.5% *(19).*

Majority of our patients were infected with HCV (98.1%) while the rest were HBV-positive (1.9%). The same finding was observed by *Poggi et al. (20).*

This was in contrast to *Liu et al.* who found that their patients were mainly infected with HBV (98.75%), this can be explained by the different groups of the studied patients *(19).* Additionally, most patients were classified as Child–Pugh A (78.9%), while the Child-Pagh B was represented in (21.1%) and this is similar to that of *Medhat et al. (21).*

Regarding the preprocedural ultrasound findings of our patients, all had liver cirrhosis with no PV thrombosis or ascites as this were part of our inclusion criteria for appropriate selection of the cases. This is in agreement with other studies *Liu et al. & Bruix et al. (19 & 22).*

The majority of focal lesions in this study were detected in the right lobe, which is agreed by *Abdel Aziz et al. & Medhat et al. (14 & 21)* and disagreed by *Hetta et al.* which stated that the focal lesions were evenly distributed within the right and left lobes *(24)*. This was explained by the fact that the right lobe is much larger than the left *(25).*, however in many of our cases the left lobe was larger which is expected in cirrhotic liver.

Most patients had solitary (69.2%) lesions while the rest of patients 30.8% had two focal lesions which is confirmed by *Liu et al. & Yin et al.(19 & 26).*

The mean procedural time of MWA was 12.3 + 3.1 min and the mean power was 57.8 + 18.2 W; however, these were different from those from other studies done by *Liu et al. & Poggi et al.* which may be attributed to the use of different microwave machines *(19 & 20).*

In our study we achieved a good overall success rate of 97 % of ablation of initial complete ablation of 66 out of the 68 focal lesions ablated. The complete ablation rates for tumors < 3 cm and those 3-5 cm were 97.2% (35 of 36 nodules) and 96.9% (31 of

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32 nodules), respectively this was statistically non-significant (P value=0.93).

This is disagreed with *Hetta et al* who stated that MW ablation success was higher in lesions less than 3 cm (57/58 lesion 98.3%) in comparison to lesions more than 3 cm (37/40, 92.5%) *(24).*

The two lesions with suspected residual activity were treated with additional MW ablation sessions and complete ablation rates was achieved in both. These results were comparable to those reported by *Martin et al.* who treated 100 patients with 270 hepatic tumors. Of these patients, all 17 patients with HCC lesions measuring 2-5.9 cm achieved complete ablation, with a complete ablation rate of 100% (27). Similar results were obtained in the study done by *Liu et al.* with respect to tumors measuring 3-5 cm (19).

It is also comparable to the results of *Poggi et al.* who noted a complete ablation was achieved in 100%, 90% and 69% of small (<3 cm in diameter), intermediate and large lesions, respectively (20). Our results also agreed by *Xu et al.* who reported initial complete ablation rates of 98.3% (28).

Our results were different from the results of *Shibata et al.* whose technical success rates for ablating 46 focal lesions less than 4 cm in 36 patients was 89% (29).

Additionally our present results were also different from those of *Soliman et al.* whose reported 84.7 % and 92% success rate for HCC in difficult sites and in the control group respectively (16).

We found that there was a significant decrease in the serum AFP level (P = 0.001), after one month of the MW treatment which may be explained by the successful ablation in most of the treated lesions, which agreed by *Mulier et al. & Liu et al. (10 & 19).*

We found no local recurrence at a median of 6 month after MW treatment which is agreed by *Soliman et al. (16). Poggi et al.* recorded recurrence in 10.5% of patients with large lesions (20), and *Liu et al.* recorded a local recurrence rate of 40.9% in large-sized (5–8 cm) lesions (19).

Also we noticed that there were denovo lesions in 3 patients (5.7%) while *Liu et al. & Poggi et al.* found de novo lesions in 27.7% and 50% respectively at a median of 6 months after MWA treatment, this higher rates may be a result of larger HCC size (5–8 cm) in their studies (19 & 20).

In this study no MW ablation related major complications were recorded, this may be attributed to the proper selection of the cases (Child A predominance) and lesions by excluding the focal lesions at risky locations (e.g. exophytic abutting a bowel loop or near common bile duct), this was in agreement

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with *Medhat et al & DE-Chao et al. (21 & 30).*

While *Xu et al.* reported that two patients (0.7%) experienced major complications included intestinal perforation (n=1), which was treated with intestinal surgery, and persistent jaundice (n=1) (28).

However, using MW ablation in risky sites, major complications reported were also low, as reported by *Zhou et al.*, (tumor seedling 1/53 (1.9%) (31), *Li et al.* (moderate to massive pleural effusion 3/96 (3.1%) sub capsular lesions) (32) and *Huang et al.* reported one case of portal vein thrombosis (0.7%) and two cases of tumor seedling (1.4%) out of 139 perivascular lesions (33).

Peri-procedural pain and fever are considered symptoms of post-ablation syndrome, which may be the result of an inflammatory response to the necrotic tissue with cytokines production *(34).*

In the present study 22 (42.3%) patients experienced mild degree of fever and or pain with none of them reported pain that impaired their daily life.

These results were lower than reported by *Xu et al.* where they reported that pain and fever were observed in 65.5% (197/301) of patients (28). Pain was experienced in 17 out of the 52 patients (32.6%) while low grade fever was noticed in 5 patients (7.6%). This results was disagreed by *Hetta et al.* who reported three patients (3.1%) whose tumors were located in the liver dome had severe right upper quadrant pain & 48 out of 72 (66.6%) patients had a mild fever (24).

Two patients developed non symptomatic mild pleural effusion (3.8%) which compares favorably with what reported by *Soliman et al.* who reported 3 cases with subcapsular lesions that developed pleural effusion out of 44 patients (6.8%) (16).

The occurrence of post thermal ablation pleural effusion was said to be due to transient pleurisy related to thermal effect. The direct thermal damage of pleural membranes might cause increased pleural capillary filtration and interferes with parietal pleural fluid removal leading to pleural effusion formation *(35).*

Although survival rates are beyond objectives of this study, yet in our limited study period (6 months), the survival rate was 100%. This compares favorably with study of *Lu et al.* where the 1 year survival rate for 36 patients was 96%, (36) and that of *Ding et al.* 1 year survival rate for 85 patients was 98.7% (37).

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