

Gastrointestinal Cancer

Hypervascular Nodules and Stiffer Liver are Associated with Recurrence after Microwave Ablation in Patients with Hepatocellular Carcinoma: A Double-Center Analysis

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Abstract



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Background and Aims The aim of this study was to detect the most important risk factors for recurrence after microwave ablation (MWA) of hepatocellular carcinoma (HCC).

Materials and Methods A total of 92 patients with 110 HCC focal lesions (FLs) underwent MWA therapy. All the patients underwent triphasic CT before and after 1 and 3 months of MWA therapy. Complete ablation and recurrence rates were recorded, and the risk factors associated with recurrence were analyzed.

Results Regarding the 110 HCC FLs that were detected pre-MWA, adequate ablation was recorded post-MWA procedure in 88 FLs (80%) and incomplete ablation in 22 FLs (showed residual contrast enhancement). However, there were newly detected lesions (17 FLs). The rate of recurrence was significantly higher in patients with multiple larger (> 4 cm) sized and hypervascular nodules. Diabetics were significantly associated with a higher recurrence rate of HCC. The rate of recurrence was significantly higher in patients with baseline level of serum alfa-fetoprotein (AFP) ≥ 200 ng/mL. Stiffer liver > 25 kPa had higher incidence for recurrence after ablation.

Conclusion Meticulous follow-up is mandatory in diabetic patients, patients with AFP > 200 ng/dL starting value, hypervascular large hepatic FL, and in stiffer liver > 25 kPa, as these patients have higher incidence for recurrence after ablation.

Keywords

- ▶ hepatocellular carcinoma
- ▶ microwave ablation
- ▶ recurrence

Introduction

Hepatocellular carcinoma (HCC) is the third most common malignant tumor globally. In Egypt over the last decade, an outstanding increase in the proportion of chronic liver disease patients diagnosed with HCC was observed. The main

causes of HCC are usually secondary to either a viral hepatitis infection (hepatitis B or C) or cirrhosis. Investigations in Egypt confirmed the growing importance of hepatitis C virus (HCV) infection in the etiology of liver cancer when compared with the contribution of hepatitis B virus (HBV) and HBV/HCV coinfection.¹

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Ablative therapy presently constitutes the first-line therapy for the treatment of HCC. Furthermore, they may be powerful as bridging procedures before orthotopic liver transplantation. Among ablative therapies, microwave ablation (MWA) is an effective approach to HCC treatment.²

MWA has been broadly used as an effective approach to HCC treatment. Its minimal damage to liver function, convenient manipulation, decreased complications, and lower mortality are the main advantages of this minimally invasive maneuver.^{3,4}

Despite complete ablation of the tumor, intrahepatic recurrence limits the potential therapeutic effect on HCC.⁵ Intrahepatic recurrence is the chief obstacle in HCC treatment, and it is also a major problem in patients who undergo hepatic resection.^{6,7} MWA is a safe and powerful treatment for HCC patients with small tumors of the liver, particularly those who are not candidates for surgical resection at diagnosis.^{8,9}

The aim of this study was to detect the major risk factors for local recurrence after MWA of HCC.

Methods

This study was performed on 92 HCC patients (73 males and 19 females) who were enrolled from the tropical medicine departments of two tertiary care hospitals in the following period: November 2014 to September 2015. The Institutional Ethical Review Board approved the study. Each patient included in the study provided a written informed consent. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in *a priori* approval by the Institution's Human Research Committee.

Detailed history taking and full clinical examination were done for all the patients enrolled in the study. Routine laboratory investigations included complete blood picture, liver function tests (LFT), serum albumin level, liver enzymes, alkaline phosphatase, and serum bilirubin (direct and total). Hepatitis markers comprised hepatitis B virus surface antigen, antihepatitis B core antigen, anti-HCV. HCV and HBV diagnosis were confirmed by polymerase chain reaction. Alfa-fetoprotein (AFP), renal function tests (RFT), and random blood sugar (fasting and postprandial blood sugar if there is a history of diabetes) were additionally performed.

A total of 110 HCC focal lesions (FLs) were treated by MWA therapy. Triphasic CT and abdominal ultrasound (US) with Doppler sonography including color-coded duplex sonography and power Doppler sonography were done to all patients before and after 1 month and 3 months after ablation therapy.

Microwave Ablation (MWA)

MWA was performed under the real-time US by freehand technique. For lesions located in the right lobe, intercostal approach, with the patient in the left lateral decubitus position, was most often used. MWA was performed using an HS AMICA microwave machine (HS Hospital service S. P. A Roma, Italy), which was operating at a frequency of 2450 MHz and a power output up to 100 W or according to the guided machine protocol. A 14G (14G 150 mm) cooled shaft electrode probe

was used to deliver MW energy into liver tissue that guided to hepatic FL (HFL). With regard to the MWA technique, it was performed by using an HS AMICA microwave machine (HS Hospital service S. P. A Roma, Italy), which was operating at a frequency of 2450 MHz and a power output up to 100 W or according to machine protocol. The mean time used for MWA ranged between 3 and 10 minutes and the mean power used ranged between 40 and 100 W.

The aim of the treatment was to completely destroy the tumor and the surrounding 0.5 to 1 cm normal-appearing liver tissue as a safety margin.

Postprocedure Care

Prophylactic antibiotic, zyloric 100 mg tablets every 8 hours for 3 days, paracetamol tablets, cold fomentations whenever the patients felt more feverish, and plenty fluid intake.

Follow-up was done 1 month and 3 months after MWA. All patients were mainly subjected to abdominal ultrasound with Doppler sonography including color-coded duplex sonography and power Doppler sonography, with similar evaluation steps to that of preprocedural one, dynamic CT, AFP, LFT, and RFT. The follow-up of patients was repeated at least every 3 months in the 1st year, then every 6 months in the 2nd year after successful ablation.

Statistical Analysis

The collected data were organized, tabulated, and statistically analyzed using statistical package for social studies (SPSS). For numerical variables, the mean and standard deviation (SD) were calculated. Comparison of mean values between pre- and post-MWA groups was performed using analysis of variance (ANOVA). When the value of ANOVA (F) was found statistically significant, Tukey's test was performed to test the difference between every two groups. For categorical variables, the number and percentage were calculated, and Chi-square test was used as a test of significance.

Results

The mean age \pm SD within the HCC patients was 57 ± 7 years. Ninety patients (97.8%) were positive for HCV and two patients (2.2%) were positive to HBV. Among the HCC patients, 90 patients (97.8%) were positive for HCV and two patients (2.2%) were positive for HBV. The two HBV patients were on tenofovir, while none of the patients with HCV received antiviral treatment before, and those who were eligible for treatment, their treatment was postponed until a successful HCC ablation was confirmed.

Twenty-one patients (22.8%) had diabetes and 71 patients (77.2%) did not have diabetes. Seventy-four patients (80.4%) had one FL and 18 patients (19.6%) had two FLs. There were 74 FLs (67.3%) in the right lobe, while 36 FLs (32.7%) were in the left lobe.

Hence, before MWA, there were 110 HCC FLs with different echogenicity: 2 with hyperechoic (1.8%), 107 hypoechoic (97.3%), and 1 with halo sign (0.9%).

Size of HFL ranged from 1.2 cm to 5 cm, with mean 3.2 ± 1.13 cm; 29 HFL > 4 cm (26.4%) and 81 HFL < 4 cm (73.6%).

The severity of liver cirrhosis by modified Child–Pugh classification showed that 39 patients of this study were child A, 53 patients were child B, and none of our patients were child C (→Table 1).

Regarding the 110 HCC FLs that were detected before, good and well ablation was recorded post-MWA procedure in 88 FLs (80%) and incomplete ablation in 22 FLs (20%) that showed residual contrast enhancement. However, there were newly detected lesions (17 FLs). Hence, post-MWA, there were a total of 127 FLs (ablated, residual, or new FL). The mean time used for ablation was (7.3 ± 3.1 minute). The mean power used was 66.2 ± 11.6 W (→Table 2). Most of the new FLs were < 4 cm in the right lobe, and they were noticed

Table 1 Demographic and clinical data of all studied patients

	HCC (n = 92)	
Age: mean ± SD:	57.35 ± 7.13	%
range:	(30–76)	
	No.	
Sex		
Male:	73	79.3%
Female:	19	20.7%
DM	21	22.8%
HCV	90	97.8%
HBV	2	2.2%
Child classification		
A (5)	7	7.6%
A (6)	32	33.7%
B (7)	28	30.4%
B (8)	23	25%
B (9)	2	2.2%
Number of HFL		
1	74	80.4%
2	18	19.6%
Size of HFL		
> 4 cm	29	26.4
< 4 cm	81	73.6

Abbreviations: DM, diabetes mellitus; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV; hepatitis C virus; HFL, hepatic focal lesions; SD, standard deviation.

Table 2 Post MWA HCC focal lesions status diagnosed by triphasic CT

Focal lesions (FL) status	N	%
Well ablated FL	88 (80%)	69.3
Residual contrast enhancement	22 (20%)	13.4
New FL	17	17.3

Abbreviations: FL, focal lesion; HCC, hepatocellular carcinoma; MWA, microwave ablation.

more frequently in large hypervascular lesions, diabetic patients, or those with high liver stiffness (LS) and AFP levels.

The present work studied many factors in relation to the HCC recurrence (residual contrast enhancement and/or new FLs) as shown in →Table 3.

With regard to the size of HFLs, among 92 patients with 110 HFLs, recurrence was significantly higher in patients with large HFLs ≥4 cm (37.9%) than HFLs < 4 cm (13.6%). Regarding the number of HFLs, among the 92 HCC patients, 18 patients had 2 HFLs, and recurrence was detected in 10 patients of them (55.6%) which was significantly higher than in patients who had only one single HFL (20/74 patients; 27%).

With respect to the hypervascularity of HFL, Doppler US detected the vascularity of HFL and measured the peak systolic (PS) and minimum diastolic frequencies of the detected intralésion vasculature; by putting a cutoff value 40 cm/s, for (PS) oddly, we compared the recurrence of HCC in hypervascular HFL (high vasculature with peak systole ≥40 cm/s) to hypovascular FL (low vasculature + PS <40 cm/s) or the HFL with no detected signals, as detected pre-MWA, and we found that there was a significantly higher recurrence rate in hypervascular FL (38.2%) compared to hypovascular FL (15.4%) and HFL with nondetected signals (4.2%) (→Table 4).

It is important noting that all the HCC FLs that showed post-MWA residual contrast enhancement were of resistive index volume ≤0.4.

With regard to diabetes mellitus, from among 92 HCC patients, there were 21 diabetic patients and 71 nondiabetic. HCC recurrence was detected in 14/21 diabetic patients (66.6%) which was significantly higher than in nondiabetic (16/71 patients; 33.4%).

Value of AFP also affected the recurrence rates, as from among 92 HCC patients, the recurrence was significantly higher in patients with AFP > 200 (36.8%) compared to patients with AFP < 200 (29.5%). This is shown in →Table 5 and →Fig. 1.

Finally, with regard to the degree of LS, Fibroscan was performed, as available, in 50 patients among 92 patients. HCC FLs and those with LS value ≥25 kPa (n = 32) showed significant higher recurrence rate (28/32; 87.5%) than those with LS value < 25 kPa (n = 18) that had recurrence rate only in one patient (1/18; 0.6%). This is demonstrated in →Table 6 and →Fig. 2.

Discussion

MWA is safe and effective curative treatment for HCC with less complications and recurrence. In our study, the total recurrence was 30.7% (13.4% in the same FL and 17.3% of new lesions). Tumor recurrence was also defined as newly developed lesions on CT, which showed hyperattenuation in the arterial phase with washout in the late phase.¹⁰

In our study, recurrence was significantly higher in patients with large HFL ≥ 4 cm (37.9%) than HFL < 4 cm (13.6%). This is in agreement with Moneir et al,¹¹ who performed their study on 40 cirrhotic patients (Child–Pugh class A or B) with solitary HCC ≤8.0 cm in diameter, or multiple HCC ≤3 lesions, each ≤3.0 cm in diameter. They found

Table 3 Factors associated with local intrahepatic recurrence

Recurrence	Size		Number		Vascularity			DM		LS		AFP	
	> 4 cm	< 4 cm	1	2	Hyper	Hypo	No	Yes	No	> 25 kPa	< 25	> 200	< 200
Yes	11	11	20	10	13	8	1	14	16	28	1	24	6
	37.9%	13.6%	27%	55.6%	38.2%	15.4%	4.2%	66.6%	22.5%	87.5%	0.6%	63.2%	11.1%
No	18	70	54	8	21	44	23	7	55	4	17	14	48
	62.1%	86.4%	73%	44.4%	61.8%	84.6%	95.8%	33.3%	77.5%	12.5%	96.4%	36.8%	88.9%
Total (100%)	29	81	74	18	34	52	24	21	71	32	18	38	54
Chi-square	6.465		4.143		11.519			12.425		28.480		25.177	
p value	0.011		0.042		0.003			< 0.001*		< 0.001*		< 0.001*	

Abbreviations: AFP, alfa-fetoprotein; DM, diabetes mellitus; LS, liver stiffness.

Table 4 Doppler indices AFP and Fibroscan statistical analysis

							Paired differences		Paired samples Test	
		Range	Mean	±	SD	Mean	SD	t	P-value	
PS	Pre MWA	5 – 40	21.458	±	6.132	-0.417	6.830	-0.293	0.772	
	Post MWA	10 – 35	23.138	±	6.753					
MD	Pre MWA	3.5 – 25	12.744	±	4.624	-0.370	6.473	-0.274	0.787	
	Post MWA	7 – 20	14.646	±	4.082					
RI	Pre MWA	0.14 – 0.7	0.361	±	0.102	0.029	0.127	1.046	0.308	
	Post MWA	0.18 – 0.4	0.307	±	0.083					
AFP	Pre MWA	5.9 – 6067	250.027	±	746.055	176.742	698.304	2.414	0.018*	
	Post MWA	3.7 – 2039	75.835	±	214.880					
LS	Pre MWA	18.5 – 38	26.816	±	4.984	-0.070	0.311	-1.594	0.117	
	Post MWA	19.5 – 37	26.886	±	4.841					

Abbreviations: AFP, alfa-fetoprotein; LS, liver stiffness; MD, minimum diastolic velocities frequencies; MWA, microwave ablation; PS, peak systolic velocities frequencies; RI, resistive index.

Table 5 Results of ROC curve at AFP cutoff value 200 ng/mL post MWA

α-FP post MWA					
Cutoff	Sensitivity	Specificity	PPV	NPV	Accuracy
~200	46.6%	91.3%	64%	88.9%	69%

Abbreviations: AFP, alfa-fetoprotein; MWA, microwave ablation; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operator characterizing.

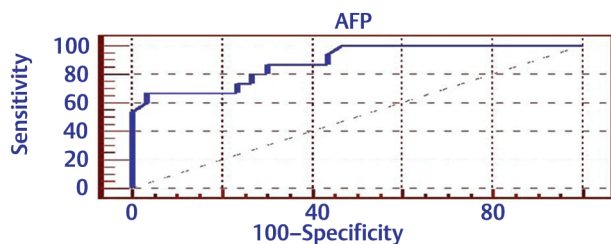


Fig. 1 Receiver operating characteristic (ROC) curve at alfa-fetoprotein (AFP) cutoff value 200 ng/mL postmicrowave ablation.

in this study that tumor size > 7 cm was associated with higher relapse rate “66.7%” than tumor size ≤ 7 cm “39.3%,”

with highly significant relation between tumor size and relapse rate.¹²

The recurrence rate was significantly higher in patients with multiple and hypervascular nodules. This is in agreement with Toshimori et al¹³ who reported a significantly increased recurrence in HFL > 2 cm, hypervascular lesions, and multiple nodules.

As available in 50 cases in our study, Fibroscan was used to measure LS in HCC patients with HCV before and after MWA, and it was of F4, with mean 26.816 ± 4.984 kPa (18.5–38 kPa) and 26.886 ± 4.841 kPa (19.5–37 kPa), respectively. Among the studied patients, it was found that HCV patients with HCC FL and LS value ≥ 25 kPa (n = 32) had significant higher recurrence rate (28/32; 87%) than those with LS value < 25 kPa (n = 18) who had recurrence rate in (1/18; 0.6%). However,

Table 6 Results of ROC curve at liver stiffness cutoff value 25 kPa post MWA

Fibroscan postoperative ROC curve between patients with HCC presence and absence					
Cutoff	Sensitivity	Specificity	PPV	NPV	Accuracy
> 25	89.66	85.71	89.7	85.7	91.5%

Abbreviations: HCC, hepatocellular carcinoma; MWA, microwave ablation; NPV, negative predictive value; PPV, positive predictive value.

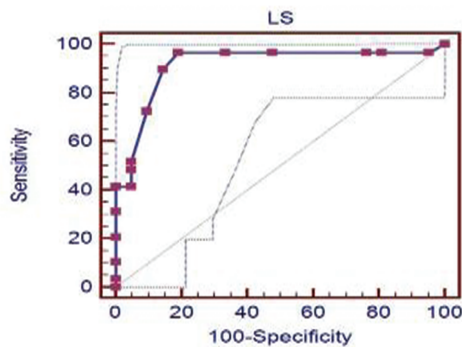


Fig. 2 Receiver operating characteristic (ROC) curve at liver stiffness (LS) cutoff value 25 kPa by Fibroscan postmicrowave ablation.

Fibroscan mean value in our study showed no statistically significant difference between pre and after 1 month of MWA.

Lee et al¹⁴ used Fibroscan for follow-up after radiofrequency thermal ablation (RFA) and transcatheter arterial chemoembolization (TACE) and reported no significant changes in LS values after ablation therapy 1 and 3 months. Moreover, they reported that patients with a previous history of intervention and higher LS values, > 13 kilopascals, were at a significantly greater risk of de novo recurrence after RFA.

Furthermore, this goes with Jung et al¹⁵ who reported that LS value could be used for predicting late HCC recurrence.

The limitations of the study were performing Fibroscan, which was only performed on 50 of the patients. This was mainly due to financial issues. Also, the relatively short follow-up of patients in the study.

Hence, in conclusion, MWA has several theoretical advantages with increased effectiveness in HCC therapy and low recurrence and complications. In hypervascular FLs that can be detected by Doppler US, recurrence rate is high after ablation therapy. Hence, TACE can be considered in this category of patients.

Meticulous HCC therapy follow-up is mandatory in diabetic patients, patients with AFP > 200 ng/dl starting value, hypervascular large HFL, and in stiffer liver > 25 kPa, as these patients have higher incidence for recurrence after ablation.

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Nil.

Conflicts of Interest

None declared.

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