

## Full Length Research Paper

# Microwave Ablation versus Radiofrequency Ablation for Hepatocellular Carcinoma: Effectiveness and Prognosis

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The aim of our study was to evaluate the therapeutic efficacy of percutaneous microwave (MW) ablation versus radiofrequency (RF) ablation for hepatocellular carcinoma (HCC) measuring upto 5 cm in greatest diameter. This study was performed at hepatogastroenterology unit of internal medicine department at Tanta university hospitals. Patients with conclusive diagnoses of HCC underwent percutaneous MW or RF ablation from January 2013 to December 2013. According to used type of ablation, all patients were divided into two groups. Group I: included 60 patients (with 95 tumors) had undergone MW ablation. Group II: included 70 patients (with 105 tumors) had undergone RF ablation. Complete ablation (CA), partial ablation (PA), local tumor progression (LTP), distant recurrence (DR) and complications were compared between both groups. We found that CA tumors with MW ablation were more than that in RF ablation but without significance in lesions  $\leq 3$  cm in diameter (55/60, 91.6% and 65/75, 86.6%) respectively,  $P=0.7981$ ), however, this difference was significant in lesions 3.1- $\leq 5$  cm in diameter (30/35, 85.7% and 10/30, 33.3% respectively,  $P=0.0388$ ). At same time, RF had PA tumors more than MW but without significance if lesions  $\leq 3$  cm in diameter (5/60, 8.3% and 10/75, 13.3% respectively,  $P=0.5843$ ), however this difference was statically significant in lesions 3.1- $\leq 5$  cm in diameter (5/35, 14.2% and 20/30, 66.6% respectively,  $P=0.0045$ ). During the two years follow-up period for tumors  $\leq 3$ cm in diameter of both groups, LTP was observed in eight tumors in MW group (8/60, 13%) and in sixteen tumors in RF group (16/75, 21%) with non-significant difference ( $P=0.1944$ ), while, for larger tumors 3.1- $\leq 5$  cm in diameter LTP was observed in four tumors (4/35, 11%) in MW group and in ten tumors (10/30, 33%) in RF group with a significant difference ( $P=0.0387$ ). Tumor DR was observed in 25 patients (41.6%) of MW group and in 30 patients (42.8%) of RF group with non-significant difference ( $P=1.0000$ ). Both groups had non-significant difference as regard complications. We can conclude that MW ablation is more effective than RF ablation especially in large HCC.

**Keywords:** microwave ablation, radiofrequency ablation, hepatocellular carcinoma

## INTRODUCTION

Hepatocellular carcinoma (HCC) is the 5th common type of cancer all over the world. It is often preceded by liver

cirrhosis (El-Serag, 2012; Parkin et al., 2005). In Egypt, incidence of HCC has increased over the last decade from 4% to 7.2% that may be explained by an increase in risk factors, such as the hepatitis C virus (HCV) infection (Rahman et al., 2001; El-Zayadi et al., 2005; El-Serag,

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2001; Bruix and Sherman, 2005; Arafa et al., 2005; Strickland et al., 2002).

Different treatment options for HCC are available, including both surgical modalities (resection and liver transplantation) and radiological techniques (thermal ablation, percutaneous ethanol ablation and transarterial chemoembolisation) in addition to systemic chemotherapy and molecularly targeted therapies (Magdy and Shahira, 2015).

Recently, thermal ablation therapy has been increasingly accepted due to the advantages of greater capacity to devitalize HCC with fewer treatment sessions. Among them radio-frequency (RF) ablation and microwave (MW) ablation are the most commonly used modalities (Goldberg and Ahmed, 2002; Lencioni et al., 2003).

RFA has been the most commonly evaluated option having distinctive types of electrodes including internally cooled electrodes and multi-tined expandable electrodes. The raising of temperature with subsequent cellular damage is dependent on both the degree of the temperature achieved within the tissue and the whole length of exposure to the heating process (Lencioni and Crocetti, 2007).

Successfully RF ablation is the capability to destroy all viable tumor tissues and probably a satisfactory 0.5-1 cm-thick tumor-free margin so that microscopic invasions around the margin of a tumor have been eliminated (Lencioni et al., 2010). While there is no precise tumor size beyond which RFA should not be applied, single tumor < 4 cm in diameter have the best outcome (Lu et al., 2005).

Microwave ablation is a medical term used for all electromagnetic methods that result in tumor damage by using different devices with various frequencies ( $\geq 900$  kHz). These microwaves move through the cells or other materials containing water leading to rotation of the different molecules producing a consistent and homogeneously distributed hotness, which is continued until the radiation is completely stopped. A necrosis area in the form of round or column shape, created by microwave irradiation around the needle is formed, depending on the type of needle used and the amount of power generated (Shibata et al., 2002). It has to be noted that technology of microwave ablation has improved dramatically. Newer devices seem to have overcome the limitation encountered by the small size of the coagulation area produced by a single probe insertion. Microwave ablation offers an important advantage over RF ablation in that treatment outcome is not influenced by the site of the tumor (Lencioni et al., 2010).

Several studies comparing HCCs treated by these two thermal ablative techniques have been carried out for small HCC measuring  $\leq 4$  cm with variable results (Shibata et al., 2002). However, few studies have been performed to compare these two modalities for the treatment of larger HCCs measuring upto 5 cm in greatest

diameter. The aim of this study was to compare the therapeutic efficacy of MW ablation versus RF ablation for HCC measuring upto 5 cm in greatest diameter.

## PATIENTS AND METHODS

This study was performed at hepatology unit of internal medicine department at Tanta university hospitals. Written informed consent was obtained from all patients enrolled in this study.

### Patients

This study included a total of 130 patients with conclusive diagnoses of HCC underwent percutaneous MW or RF thermal ablation from January 2013 to December 2013. According to used type of ablation, all patients were divided to two groups. Group I: included 60 patients (with 95 tumors) had undergone MW ablation. Group II: included 70 patients (with 105 tumors) had undergone RF ablation.

The patients' gender, age and tumors criteria are illustrated in table 1. The major biochemical laboratory variables including liver functions in terms of total bilirubin (TB), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and albumin (ALB) levels were tested and compared few days before and 3 days after ablation as shown in table 1.

All HCCs in our study were diagnosed according to the typical findings of either triphasic contrast-enhanced CT or dynamic magnetic resonance imaging (DMRI). The classic imaging profile associated with an HCC lesion is characterized by intense arterial enhancement or uptake followed by contrast washout in the delayed phase (Magdy and Shahira, 2015).

### Inclusion criteria

The following inclusion criteria for HCCs used for percutaneous ablation either by RF or MW: a solitary HCC lesion of  $\leq 5$  cm in greatest diameter; three or fewer HCC lesions with a greatest diameter of 3 cm or less; no radiologic evidence of vascular invasion and extrahepatic metastases; HCCs with no prior treatment; liver function classed as Child-Pugh class A or B; prothrombin time of less than 20 s and platelet count higher than 90,000 cells/dl; no history of ascites refractory to diuretics, variceal bleeding, or encephalopathy.

### Percutaneous Ablation Procedures

All ablation procedures were performed under local anesthesia with 1% lidocaine starting from the insertion site in the skin down to the peritoneum along the planned puncture track, and conscious analgesia-sedation. The skin of the insertion site was incised with a small Lancet.

Table 1. Patients and tumors criteria and laboratory data.

| Parameter  | MWA group (n=60)       | RFA group (n=70)       | P value            |
|--|------------------------|------------------------|--------------------|
| • Gender (M/F)                                   | 40/20                  | 50/20                  | <b>0.5734 (ns)</b> |
| • Age (y): Mean±SD                               | 47.43 ± 1.28           | 47.46 ± 1.16           | <b>0.9890 (ns)</b> |
| • No. of Tumors                                  | 95                     | 105                    |                    |
| No. of pt. with one tumor                        | 35                     | 45                     | <b>0.7852 (ns)</b> |
| No. of pt. with 2 tumors                         | 15                     | 15                     |                    |
| No. of pt. with 3 tumors                         | 10                     | 10                     |                    |
| • Tumor size                                     |                        |                        |                    |
| ≤3 cm  | 60                     | 75                     | <b>0.2293 (ns)</b> |
| 3.1-5 cm   | 35                     | 30                     |                    |
| • AFP  |                        |                        |                    |
| ≥200 ng/ml                                       | 25                     | 30                     | <b>1.0000 (ns)</b> |
| <200 ng/ml                                       | 35                     | 40                     |                    |
| • Cause of underlying liver disease              |                        |                        |                    |
| CHB  | 5                      | 4                      | <b>0.1361 (ns)</b> |
| CHC  | 50                     | 65                     |                    |
| Other  | 5                      | 1                      |                    |
| • Child Pugh classification                      |                        |                        |                    |
| A  | 55                     | 62                     | <b>0.7706 (ns)</b> |
| B  | 5                      | 8                      |                    |
| • AST  |                        |                        |                    |
| Pre- ablation (Mean±SD)                          | 57.37 ± 10.54          | 57.39 ± 10.73          | <b>0.9919 (ns)</b> |
| Post-ablation (Mean±SD)                          | 73.68 ± 9.61           | 67.23 ± 11.18          | <b>0.0006 (s)</b>  |
| P value (between pre-ablation and post-ablation) | <b>&lt; 0.0001 (s)</b> | <b>&lt; 0.0001 (s)</b> |                    |
| • ALT  |                        |                        |                    |
| Pre- ablation (Mean±SD)                          | 52.55 ± 12.09          | 53.03 ± 11.86          | <b>0.8206 (ns)</b> |
| Post-ablation (Mean±SD)                          | 72.23 ± 13.94          | 63.99 ± 13.38          | <b>0.0008 (s)</b>  |
| P value (between pre-ablation and post-ablation) | <b>&lt; 0.0001 (s)</b> | <b>&lt; 0.0001 (s)</b> |                    |
| • Bilirubin                                      |                        |                        |                    |
| At time of ablation (Mean±SD)                    | 1.602 ± 0.041          | 1.607 ± 0.038          | <b>0.9229 (ns)</b> |
| Post ablation (Mean±SD)                          | 1.808 ± 0.037          | 1.814 ± 0.034          | 0.9076 (ns)        |
| • Albumin  |                        |                        |                    |
| At time of ablation (Mean±SD)                    | 3.593 ± 0.025          | 3.590 ± 0.024          | 0.9255 (ns)        |
| Post ablation (Mean±SD)                          | 3.513 ± 0.026          | 3.517 ± 0.024          | 0.9155 (ns)        |

Patient's posture was changed according to the preoperative tumor localization detection under real-time ultrasound. The aim of the treatments was to destroy the entire tumor with a safety margin of 0.5–1.0 cm. Vital signs and oxygen saturation were also monitored during the procedure.

#### Percutaneous RF ablation

It was done by using LeVeen Needle Electrode; Radiotherapeutics which was introduced starting from the site of the skin mark done before under continuous real time US guidance with a 3.5 MHz curved convex probe

using Siemens (Sonoline, Sienna) machine, until its tip reached near the center portion of the tumor, it has retractable curved electrodes and an insulated 17-gauge outer needle that houses 10 solid retractable curved electrodes that, when deployed, assume the configuration of an umbrella. The electrodes are manufactured in different lengths (2 to 5 cm umbrella diameter). The alternating electric current generator is 200 W operated at 480 kHz (RF 3000; Boston Scientific). The ablation algorithm is based on tissue impedance, and ablation is considered successful if the device impedes out. Grounding was achieved by attaching four grounding pads, two pads were attached to each thigh. For tumors  $\leq 3.0$  cm in greatest diameter, single applicator position was adopted, however, different applicator positions were needed for tumors 3.1-5 cm in greatest diameter to create overlapping coagulation zones (Peng et al., 2008). After the RF procedure was completed the hooked electrodes was withdrawn and the track was cauterized along its length up to just below the liver capsule to prevent possible tumor seeding or bleeding.

### **Percutaneous MW ablation**

It was done by using HS AMICA microwave system composed of one AMICA generator, which can produce power output up to 100W continuous wave at 2450MH and one AMICA probe which has 11, 14 or 16-gauge. Inside the probe shaft, there are dual channels through which saline solution is circulated by a built-in AMICA pump to cool the shaft continuously.

Under real-time US guidance, the AMICA probe was percutaneously introduced into the tumor with the tip placed in the deepest part of the nodule. We adjusted the time of the ablation and the power of the generator according to the size of the lesion. To prevent possible tumor seeding or bleeding, the needle track was cauterized when withdrawing the probe.

### **Procedure effectiveness and follow-up**

The effectiveness was evaluated by comparing contrast enhanced triphasic CT or dynamic MRI images performed few days before with those obtained 1 month after the procedure. Complete ablation (CA) was defined as uniform low attenuation on CT without enhancement in the ablation zone with a diameter greater than that of treated tumor. Partial ablation (PA) was defined as any irregular contrast enhancement found inside or beside the ablation zone. Additional RF or MW ablation was performed for tumors with PA (Goldberg et al., 2005).

Any procedure-related side effect or complication was documented. The major complication is an event that leads to substantial morbidity and disability, increasing the level of care, or results in hospital admission or substantially lengthened hospital stay (Goldberg et al., 2005). All other complications are considered minor and

are expected undesired consequences of the procedure that, although occurring frequently, rarely if ever result in substantial morbidity. These include pain, the postablation syndrome, asymptomatic pleural effusions, and minimal asymptomatic perihepatic fluid or blood collections seen at imaging (Goldberg et al., 2005).

All tumors with CA were regularly followed up in the outpatient clinic of our hepatology unit every 3 months for 2 years by contrast enhanced triphasic CT or dynamic to evaluate the efficacy of thermal ablation. Local tumor progression (LTP) was defined as the reappearance of tumor enhancement inside or adjacent to the ablated tumor, and distant recurrence (DR) was defined as new presence of intra-hepatic HCC (Xu et al., 2004). For patients with LTP or DR who still met the percutaneous ablation inclusion criteria, RF or MW ablation was recommended. If patients did not meet the inclusion criteria, TACE, or conservative treatment was recommended.

### **Statistical analysis**

Continuous results were reported as the mean  $\pm$  SD. Student-t test was used for comparison of the liver function and blood count 2-4days before and 72 h after ablation. Chi-square test or Fisher exact probability was used for comparing the rates of CA, PA, LTP, DR, and complications between RF and MW ablation. A two-tailed P-value, 0.05 was considered statistically significant. Data analyses were performed using SPSS 10.0 (Statistical package for science and society).

## **RESULTS**

The results of our study showed that, there was no significant difference between the two groups as regard sex, age, tumor size, No. of tumors in each patient, alpha-fetoprotein level, underlying cause of liver cirrhosis, Child-Pugh classification and liver functions as shown in table 1.

As regard the number of tumors with CA for each procedure, we found that CA tumors with MW ablation were more than that in RF ablation but without significance in lesions  $\leq 3$  cm in diameter (55/60, 91.6% and 65/75, 86.6%) respectively,  $P=0.7981$ ), however, this difference was significant in lesions 3.1- $\leq 5$  cm in diameter (30/35, 85.7% and 10/30, 33.3% respectively,  $P=0.0388$ ). The time needed for CA in MW ablation was significantly shorter than that in RF ablation in both subgroups of tumor diameters ( $P < 0.0001$ ).

As regard the PA tumors for each procedure we found that RF had PA tumors more than MW but without significance if lesions  $\leq 3$  cm in diameter (5/60, 8.3% and 10/75, 13.3% respectively,  $P=0.5843$ ), however this difference was statically significant in lesions 3.1- $\leq 5$  cm in diameter (5/35, 14.2% and 20/30, 66.6% respectively,

Table 2. Results for both procedures and follow up observations.

| Parameter                                 | MWA group (n=60)   | RFA group (n=70)  | P value      |
|---|--------------------|-------------------|--------------|
| • Time needed for CA:                     |                    |                   |              |
| If tumor size $\leq 3$ cm (Mean $\pm$ SD) | 5.900 $\pm$ 1.100  | 7.653 $\pm$ 1.133 | < 0.0001 (s) |
| If tumor size 3.1-5 cm (Mean $\pm$ SD)    | 8.086 $\pm$ 0.8531 | 15.60 $\pm$ 2.387 | < 0.0001 (s) |
| • No. of tumors with CA:                  |                    |                   |              |
| If tumor size $\leq 3$ cm                 | 55/60 (91.6%)      | 65/75 (86.6%)     | 0.7981 (ns)  |
| If tumor size 3.1-5 cm                    | 30/35 (85.7%)      | 10/30 (33.3)      | 0.0388 (s)   |
| • No. of tumors with PA:                  |                    |                   |              |
| If tumor size $\leq 3$ cm                 | 5/60 (8.3%)        | 10/75 (13.3%)     | 0.5843 (ns)  |
| If tumor size 3.1-5 cm                    | 5/35 (14.2%)       | 20/30 (66.6%)     | 0.0045 (s)   |
| • No. of tumors with LTP:                 |                    |                   |              |
| If tumor size $\leq 3$ cm                 | 8/60 (13%)         | 16/75 (21%)       | 0.1944 (ns)  |
| If tumor size 3.1-5 cm                    | 4/35 (11%)         | 10/30 (33%)       | 0.0387 (s)   |
| • No patients with DR:                    | 25/60 (41.6%)      | 30/70 (42.8%)     | 1.0000 (ns)  |
| • Complications:                          |                    |                   |              |
| Minor: Post-procedural pain               | 40/60 (66.6%)      | 42/70 (60%)       | 0.7779 (ns)  |
| Asymptomatic pleural effusion             | 4/60 (6.66%)       | 5/70 (7.1%)       | 1.0000 (ns)  |
| Fever                                     | 15/60 (25%)        | 18/70 (25.7%)     | 1.0000 (ns)  |
| Major:                                    | 5/60 (8%)          | 5/70 (7%)         | 1.0000 (ns)  |

P=0.0045).

From the previous results we can say that MW ablation was more effective than RF ablation especially large tumors 3.1- $\leq$ 5 cm in diameter with shorter time needed for CA.

As regard the effects of ablation of both procedures on patients' laboratory variables we found that AST and ALT levels were significantly elevated at 72h after both RF ablation and MW ablation compared with the baseline levels (P $\leq$ 0.0001). The increase in the AST and ALT levels was significantly larger in MW ablation group than in RF ablation group (P=0.0006, 0.0008 respectively).

Post-procedural pain, fever, and asymptomatic pleural effusion were the most commonly minor complications after the procedure in our study with no significant differences between both MW and RF procedures (P value=0.7779, 1.0000 and 1.0000 respectively). Major complications were observed in 5 of the 60 patients (8%) in the MW ablation group and 5 of the 70 (7%) in the RF ablation group with no significant difference between both groups (P=1.0000). In the MW ablation group, major complications included biliary fistula requiring drainage (n=2), Peritoneal hemorrhage requiring blood transfusion (n=2) and hemothorax requiring drainage (n=1). In the MW ablation group, major complications included hemothorax (n=2) and peritoneal hemorrhage (n=3). No procedure-related death was observed in this study.

During the two years follow-up period for tumors  $\leq$ 3cm in diameter of both groups, LTP was observed in eight tumors in MW group (8/60,13%) and in sixteen tumors in RF group (16/75,21%) with non-significant difference (P=0.1944), while, for larger tumors 3.1- $\leq$ 5 cm in

diameter LTP was observed in four tumors (4/35,11%) in MW group and in ten tumors (10/30, 33%) in RF group with a significant difference (P=0.0387). Tumor DR was observed in 25 patients (41.6%) of MW group and in 30 patients (42.8%) of RF group with non-significant difference (P=1.0000) as shown in table 2.

## DISCUSSION

In the past two decades, thermal ablation therapy by using energy sources has been increasingly accepted due to the advantages of greater capacity to devitalize HCC with fewer treatment sessions. Among them radio-frequency (RF) ablation and microwave (MW) ablation are the most commonly used modalities (Goldberg and Ahmed, 2002; Lencioni et al., 2003). The two methods differ in their mechanism of action (RFA uses current as opposed to MWA that uses electromagnetic energy), with MWA having a more advantageous profile in terms of ablation volume, procedural time and simultaneous treatment of multiple lesions. However, with respect to clinical end-points, there is no solid proof as yet to support the advantage of one over the other. The evolution of devices and instruments coupled with the progress of multidisciplinary patient management may allow a better stratification that would maximize treatment benefit (Loukia et al., 2015).

We tried in this study to compare the therapeutic effect of MW ablation versus RF ablation for HCCs upto 5 cm in its greatest diameter.

Our results showed that the number of completely ablated (CA) tumors with MW was significantly more than that in RF group if tumors 3.1-≤5cm in diameter, however this difference did not reach a significant level in smaller tumors ≤3cm. At the same time the number of partially ablated tumors (PA) by MW was significantly less than that in RF group if tumors 3.1-≤5cm in diameter, however this difference did not reach a significant level in smaller tumors ≤3cm. In this respect, the time needed for CA by MW was significantly shorter than that in RF group.

During the two years follow up period, our study revealed that the number of tumors showing LTP in MW group was significantly less than that in RF group in tumors 3.1-≤5cm in diameter, however this difference did not reach a significant level in smaller tumors ≤3cm. On the other hand there was no significant difference as regard DR tumors and complications in both groups.

From these results we can say that MW ablation was more effective than RF ablation especially in large tumors 3.1 up to 5cm in diameter.

Our results are similar to that revealed by Xu HX et al. (Xu et al., 2004) who concluded that thermal ablation therapy by means of microwave and RF energy application is an effective and safe therapeutic technique for HCC. Large tumors can be completely ablated, but have a significantly higher risk of local recurrence at follow-up.

On the other hand Lei Zhang et al. (Zhang et al., 2013), Shibata T et al (Shibata et al., 2002) and Qian GJ et al. (Qian et al., 2012) studies -that compare the therapeutic efficacy of MW versus RF in HCC- revealed that there were no significant differences in CA, LTP, DR and complications between the two groups.

Our results are similar to Lei Zhang et al. (Zhang et al., 2013) and Qian GJ et al. (Qian et al., 2012) As regard laboratory variables after treatment, as we found that AST and ALT levels were significantly elevated at 72 h in patients after both RF ablation and MW ablation compared with the baseline levels ( $P \leq 0.0001$ ). The increase in the AST and ALT levels was significantly larger in MW ablation group than in RF ablation group ( $P = 0.0006, 0.0008$  respectively). This increase may be attributed to the advantages of MW ablation over RF ablation, such as higher treatment temperatures, larger ablation zones (Wright et al., 2005).

The limitations of MW and RF thermal ablation in the past years were related to long procedure duration and small ablation size. Recently, different technologies for these thermal ablations have been conceived, trying to obtain better results such as local effectiveness, feasibility, and safety (Sun et al., 2012). Moreover, these results come from only the comparison of one type of RF ablation generator and one ablation electrode with one type of MW ablation generator and one ablation antenna, which cannot be presumed to provide equivalent results. A prospective multi-institution trial with variable clinical validation models would be advantageous.

## CONCLUSION

From these results we can conclude that MW ablation is more effective than RF ablation especially in large tumors 3.1 up to 5cm in diameter, at the same time this study suggest that MW ablation and RF ablation are both relatively safe procedures with significant differences in complication rates.

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