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ORIGINAL ARTICLE

Current Modalities in Management of Early-stage Hepatocellular Carcinoma.

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ABSTRACT

Background & Aim: Multiple discussions have been aroused regarding which approach is the most suitable for treating early-stage HCCs as a first-line modality: surgical resection, radiofrequency ablation (RFA) or microwave ablation (MWA).

The purpose of this study was to test the null hypothesis: "The effect of liver resection (LR), RFA and MWA do not differ from each other as current first-line modalities for solitary early-stage hepatocellular carcinoma". We compared the overall survival (OS) and morbidity between LR, RFA and MWA for patients with early HCC with size up to 5cm.

Methods:This prospective study enrolled 45 patients. Those patients have been recently diagnosed to have early-stage tumors. The included patients had the criteria of: (Solitary lesions, tumor size < 5 cm, Class of Child-Pugh was A or B only). Patients were sub-divided into equally three groups: 15 patients underwent liver resection. (15) patients subjected to RFA , and lastly (15) patients treated with MWA from April 2016, to March 2019.

Results: Our results showed that three modalities(LR, RFA and MWA) did not differ significantly regarding the overall survival (OS) rates for tumors< 5cm(P= 0.3). However, significant difference was found between the three groups (LR, RFA and MWA) regarding rate of overall complications (P= 0.001). Regarding rate of minor complications, there was a significant difference between LR, RFA and MWA by (26.67%., 93.3%, 86.7%) respectively with (P= 0.001). Rate of major complications differed significantly between the three groups (P=0.01) as follows: (LR, RFA and MWA) by (26%, 0 % and 0 %) respectively.

Conclusion:RFA and MWA could be an effective alternative to liver resection (LR) amenable patients as a primary therapy for early-stage HCCs measuring as large as <5cm, with added benefits of less severe complications and minimal invasiveness. Both RFA and MWA showed near equal comparable outcomes between each other.

Keywords: Early hepatocellular carcinoma, surgical resection, radiofrequency, microwave

INTRODUCTION

Hepatocellular carcinoma is extremely prevalent disease. It is ranked the 5th among the highest frequent cancers and the 3rd universal cause of death [1]. As HCV is considered the most obvious etiological element in the development of hepatocellular carcinoma, Egypt has the highest prevalence of HCC in the world [2,3]. HCC prevalence has markedly elevated in last years as HCC was reported to account for 4.7% of CLD patients. Besides, there was an almost two fold increase in HCC incidence among chronic liver disease (CLD) patients in Egypt [2, 4].

Early small HCCs are usually silent, but proper unmasking of those quiet lesions has been recently possible by the aid of new mature screening tools. This is clearly easier in areas stamped with high predominance of the disease [5, 6].

No agreement about the ideal curative technique has been established. Results of the

main modalities (Liver transplant, ablative approaches and surgical excision) have all shown promising outcome [7-13].

Different staging systems defined early HCC. Milan criteria referred to the following criteria: tumor size < 5 cm, being solitary or multiple tumors (limited to 3 in number and 3 cm in diameter), absence of distant metastasis outside liver or vascular invasion [14]. The situation is different in Barcelona clinic liver cancer (BCLC) staging classification, as this early stage HCC is further more sorted into very early and early stages taking into account many other variables such as performance status (PS), Child-Pugh score and multiplicity of the tumor [15].

The cornerstone modality is liver resection especially in patients without cirrhosis or even with cirrhosis, but with specific selected criteria as: having small tumors and average hepatic functions [16, 17]. Being multiple and relatively larger in size are not strict factors which limit tumor resection, but it is important to take into consideration the increased possibility of extra-hepatic spread and recurrence in multiple and larger size tumors [18].

Whole removal of malignant tissue can be accomplished effectively by liver transplantation (LT). Moreover, rest of unsafe parenchyma, vulnerable to promote more malignancy progression, are extracted which hampers initiation of new malignancy cycle [19].

Donor shortage opposes involving early stage patients in transplant practice. Superiority in waiting lists shall be for those who would immensely gain benefit from transplant alone. Early stage cases have other legitimate chances in resection and ablation [20].

Vast scale of specialized centers adopts RFA as the main facility for percutaneous ablation. It is advised as the classic first mean in dealing with patients classified as early and very early in BCLC. Tumor tissues are converted into necrotic tissue by the power generated by radiofrequency. Few centimeters around the purposed area are included which additionally destroys tiny undiscovered micro metastases [21, 22].

Microwave ablation is another unconventional avenue. It outreaches radiofrequency ablation by having the same effects with added extra improvements [23].The function of MWA is applied mainly by generating heat from polar parts “in the form of ions” of water. Water particles, then, try to adjust themselves with the waddling waves. This accelerated vibrations cause heat to be evenly allocated and eventually induce tissue coagulation and death [24]. Efficacy of RFA and MWA, when it comes in comparison with surgical resection, still renders much argument [19].

Patients and Methods

Technical Design

- **Site of study (Setting):** Our prospective study (Randomized controlled trial) took place at General Surgery Department (General Surgery Unit and Advanced center for Hepato-pancreatico-biliary Surgery) and at Radio-diagnosis department (Interventional Radiology Unit), Zagazig University Hospitals in the period from April 2016 to March 2019.
- **Sample size (population):** 45 patients with hepatocellular carcinoma (HCC) (15 patients were admitted for resection, 15 patients for radiofrequency ablation and 15 patients for microwave ablation). Owing to restricted criteria of the patients and few numbers of cases fit for our procedures, the number was limited.
- Written informed consent was obtained from all participants and the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Patients:

- **Inclusion criteria**

The patients included were with following criteria:

1. Aged 18-70 years.
2. HCC cases confirmed by computed tomography “Triple phase” with high levels of AFP.
3. Solitary tumor nodule (patients with three or fewer

tumor nodules were excluded for randomization and comparison purposes).

4. Patient with tumor size up to 5 cm..
5. Child A and B (Child-Pugh classification).
6. Stage (0) and Stage (A) (BCLC staging).
7. Patients who are consented after through explanation of procedure steps and possible complications.

➢ **Exclusion criteria**

The patients excluded were with following criteria:

1. Patients with previous history of surgical or non-surgical treatment of HCC.
2. Multiple HCCs.
3. Patients with HCC metastasis.
4. Child C stage on Child-Pugh classification.
5. Nodule size > 5 cm.
6. Current pregnancy.
7. Lesions which are not confined to the Milan criteria
8. Tumors which cannot be safely ablated like those closely related to bowel.
9. Masses with difficult access or exophytic ones.
10. Stage B, C and D (BCLC staging).

Study Design

The purpose of this study was to test the null hypothesis: "The effect of LR, RFA and MWA do not differ from each other as current first-line modalities for solitary early-stage hepatocellular carcinoma".

2- Operation design (Methods):

Surgical resection (LR Group): All resections were planned to be curative (tumor-free resection margins confirmed by pathology); the 15 cases details according to type of resection are shown in Table (1). Peri-operative preparation, intraoperative techniques and postoperative management mainlines were as follows. All patients- as preoperative preparation- were subjected to:

- Complete laboratory investigations.
- Relevant other specialties consultation whenever needed.
- Ensuring blood availability and cross matching.
- Anesthesia consultation before admission and on the day just before surgery.
- Placement of CV catheter and epidural catheter (the latter for post-operative potent analgesia), fasting for 6 hours at least.

Table (1): Various resections types used for the 15 patients in (LR) group

Surgical technique	N (15 patients)
Anatomical: Left lateral Segment VI Segment V Caudate lobe	9 patients 5 patients 2 patients 1 patient 1 patient
Non anatomical: Right lobe Left lobe	6 patients 2 patients 4 patients

Most important steps for the main surgical procedure included the following:

- ***Incision:*** J-shaped (Right subcostal with midline extension).
- ***Exploration***: Exploration of the abdomen and liver itself to assess operability and resectability.
- ***Liver Mobilization:*** Dividing all ligaments attached to the lobe intended to be resected.
- ***Minimizing hepatic bleeding:*** In some cases we needed to minimize the ongoing bleeding by performing Pringle's maneuver. It includes occlusion of inflow at porta hepatis by the traditionally used tube with its two limbs inside endotracheal tube forming an occluding ring. The process entails cycles of occlusion (20 mins) alternating with opening cycles to allow flow till full control commenced.
- ***Parenchymal Transection*:** Harmonic scalpel was the main tool to perform such transection. Vessels were ligated using proline 4/0 when needed. With appearance of bile, by naked eye or after applying gauze test, control of small bile ducts was done by the same ligatures as intrahepatic vessels. Electro-coagulation was also widely employed. Hemostatic agents, like Surgicel and surgical snow, were commonly used.

Radiofrequency ablation: (RFA Group): In this study the following RF system was used: Valleylab RF ablation system with cool tip technology (Radionics, Burlington, MA). Detection of electrode insertion approach was the preliminary step. Two types of approaches were mainly used. Right intercostal stab when the patient on the opposite side lateral position was used in case of right lobe tumors. Meanwhile, patients were instructed to be in supine position and subcostal stab was performed to reach tumors of the left lobe. Under general anaesthesia, cases were performed as an outpatient procedure with the following steps:

a- RF electrode was passed through the stab and gradually advanced till reaching target lesion.
b- US was used to prove proper positioning of RF electrode.
c- Connecting the electrode to energy source" generator".
d- The grounding pads were placed and connected then time is set to 15 min, RF on/off button is set to on, and the cooling system is deployed.

Not only the whole tumor was ablated, but also our process entailed the involvement of added neighboring areas of unaffected parenchyma encircling the lesion. This required safety margin was not less than 1 cm in all processes. Regarding the sequence, we started with the innermost before outer areas. This order was to attenuate the production of the too minute air droplets resulting from dealing with superficial parts which might have concealed the image of the inner sectors.

Microwave ablation (MWA Group): Patients were treated with a microwave generator (AMICA-GEN system, produced by the Radio Therapeutics Corporation; Frequency: 915 MHz; temperature range: 50-60 °C).

Ultrasound- guided porocess way was the preferred one to implement our MWA percutaneously. Two sizes of MW ablative electrodes were available within the apparatus (14 Gauge and 16 Gauge). Further adjustment of power output was essential to be matched with used needle. For example, smaller needles necessitated higher energy (not more than 80 Watt). While for narrower ones, lower current was efficient (about 40 Watt). Steps were followed according to main outlines done in RF technique.

Tumor diameter shaped the plan of ablation. Single cycle was enough for small tumors with diameter up to 2 cm. However, we used numerous steepy ablations from one area to another forming several cycles of ablation which were overlying each other. The ablated area totally appeared as hyperechoic zone which was the end-point of the process as it indicated full ablation. Ablation of the tract, before needle removal, was performed in all cases.

Post-procedural care (Post- thermal ablation):

Immediate prescribed drugs included strong analgesics as diclofenac 50 mg, antiemetics and IV fluids. Procedure was done as out-patient clinic with restricted access to opoids. Observation was done in the centre for 2-3 hours. We found it the suitable period to notice important complications such as internal organ injury, hemorrhage, anaeasthtics side effects or shock. On discharge, prophylactic antibiotics with analgesics were described and advised to last for 3 days.

Pain assessment was done according to Numeric pain rating scale (NRS-11). This 11-point scale uses patients' own words and description to inform and record its level from no pain at all to being severe disabling [25].

Assessment of treatment response (Follow up- all cases):

An abdominal ultrasonography and AFP were performed for all patients on 3±10 days post-procedural. Latter visits were scheduled as following: 3, 6, 9, 12, 18, and 24 months after the initial procedure. Each focal lesion detected at ultrasonography was additionally assessed with triphasic CT scan.

For surgical resection, presence of retracted parts of liver with no evidence of intrahepatic or distant recurrence was a sign of success. However, successful RFA and MWA were elicited in case of no contrast enhancement was found, being replaced with uniform hypodensity over the ablated area in CT scans. The findings were considered as a recurrent tumor if the results of the CT and AFP coincided or new lesions appeared.

Statistical Analysis

Data collected throughout history, basic clinical examination, and outcome measures coded, entered and analyzed using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences (SPSS version 20.0) **(Statistical Package for the Social Sciences)** software for analysis. According to the type of data, qualitative represented as number and percentage. Meanwhile, categorical variables were analyzed using χ2-tests or Fisher's exact test. Overall and disease-free survival rates were calculated with the Kaplan–Meier method, and the differences between the curves were assessed using the log–rank test. P-values <0.05 were considered statistically significant.

Data were collected and submitted to statistical analysis. The following statistical tests and parameters were used:

- **Mean** $\overline{x}$
- **Standard deviation (SD).**
- **The chi square** (x^2) **test:** This test was used to compare three groups regarding the distribution of different variables.
- **The *t* statistic:** to test whether the means are different
- **The log-rank test**: was used to compare the survival distributions of three groups.

The significance level for all above mentioned statistical tests was done. The threshold of significance is fixed at 5% level (P-value)

- *P value of >0.05 indicates non-significant results.
- *P value of <0.05 indicates significant results.

Overall survival was computed from the day of intervention till end of the 24 month period after the initial procedure. Death ended the observation.

RESULTS

This study included 45 early HCC patients classified into three groups, (LR group) 1st group- was consisted of (15) patients treated with liver resection (LR), (RFA group) 2nd group –(15) patients underwent radio frequency (RFA) and lastly (MWA group)- 3rd group (15) patients subjected to microwave (MWA).

I. Patients' characteristics (Table 2):

The mean age was 47+8.6 yrs. Mean age for LR, RFA and MWA was as following (48.9, 46.8 and 46.6) respectively. The three groups did not differ significantly in age distribution with (P=0.8).

In our study most of our patients were males about 60% in each group. LR vs RFA vs MWA male percentages were (60.0% vs 53.3% vs 60.0%) respectively. No statistically significant difference found between patients involved within the 3 techniques in sex distribution (P= 0.9) (all groups were matched).

Most of our patients were HCV +ve with no statistically significant difference between the three studied groups regarding HBV and HCV prevalence. Percentages for HCV patients for LR, RFA and MWA *were* ***(***86.7%**,** 93.3% and 100%) respectively.

In our study most of our patients were Child A. Almost all of our cases had AFP more than 20. No statistically significant difference was elicited between the three studied groups in Child class or Alpha fetoprotein.

Most of our lesions in LR group were left lobe lesions. While in RF group were in the right lobe. But in MWA group almost were equal in both lobes. Most of HCC were less than 3cm in locoregional ablation groups while in LR group most of HCC lesions were with diameter from 3-5cm.

Table (2): Comparing patients characteristics between the three studied groups:-

Variable	*LR* No(15)	%	*RFA* No(15)	%	*MWA* No(15)	%	χ^2	p-value
Sex:	9	60.0%	8	53.3%	9	60.0%	0.18	0.9
Male	6	40.0%	7	46.7%	6	40.0%		(NS)
Female								
HCV	13	86.7%	14	93.3%	15	100%	2.1	0.34 (NS)
	12	80.0%	9	60%	9	60%		
Child class	3	20.0%	6	40%	6	40%	3.3	
A								
B								0.19 (NS)
Alpha fetoprotein							0.4	
Less than 20	2	13.0%	2	13.0%	1	6.0%		0.8
More than 20	13	87.0%	13	87.0%	14	93.0%		(NS)
Site of HCC	5	33.3%	10	13.0%			4.9	
Right lobe	9	60.0%	5	13.0%	7	46.7%		
Left lobe	1	6.7%	0.0	0.0%	8	53.3%		0.3
Caudate					0.0	0.0%		(NS)
Tumor size	3	20%	10	66.7%			0.5	
<3	12	80%	5	33.3%	10	66.7%		
3-5					5	33.3%		0.7 (NS)

II. Treatment Morbidity (complications) (Table 3):

All three approaches did not show difference which is statistically significant between (LR, RFA and MWA) regarding rate of overall complications by (40%, 93.3% and 86.7%) respectively. Regarding rate of minor complications, there was a significant difference between LR, RFA and MWA by (26.67%, 93.3%. 86.7%) respectively with (P= 0.001). Pain assessment was done according to Numeric rating scale (NRS-11). Only was considered positive in case of rates ≥7 on NRS. Rate of major complications differed significantly between the three groups (P=0.01) as follows: (LR, RFA and MWA) by (26%, 0 % and 0 %) respectively.

Postoperative complications after LR occurred in 6 (40%) patients. Bile leak occurred in two patients; one of them developed biloma that needed pigtail drainage. Wound infection occurred in 4 patients managed with repeated dressing and antibiotics. Two of these four patients developed incisional hernia, repaired by proline mesh after 1.5 & 2 yrs. from LR. Liver decompensation occurred in two patients. The difference between the three studied groups was statistically significant in pain occurrence with highest pain in RFA than MWA with no pain in LR (93.3% VS 86.7VS 0.00) respectively. Post-RFA complications, 14 patients experienced pain, one of them developed abscess, 2 suffered from infections and one was complicated by pneumothorax concomitantly. Post MWA complications included, 13 developed pain, one of them complicated by pneumothorax.

Table (3): Comparing complications (morbidity) between the three studied groups:-

	Variable	LR No(15) %	RFA No(15) %	MWA No(15) %	χ^2	p-value
Minor	**Infections**	4 26.67%	2 13.33%	0 0.00%	4.6	0.8
	Pneumothorax	0 0.00%	1 6.7%	1 6.7%	1.04	0.6
	Pain	0 20.00%	14 93.3%	13 86.7%	33.8	0.001 **
	Bile leak	2 13.3%	0 0.00%	0 0.00%	4.2	0.1
	Abscess	0.0 0.00%	1 6.7%	0 0.00%	2	0.3
	TOTAL	4 26.67%	14 93.3%	13 86.7%	18.8	0.001**
Major	**Incisional hernia**	2 13.3%	0 0.00%	0 0.00%	4.2	0.1
	Liver decompensation	2 13.3%	0 0.00%	0 0.00%	4.2	0.1
	Total	4 26.67%	0 0.00%	0 0.00%	8.7	0.01 *
Overall Total		6 40%	14 93.3%	13 86.7%	12.9	0.001**

* Statistically significant difference ($P \leq 0.05$)

III. Overall survival (Table 4):

Overall survival rates exhibited no difference which is statistically significant in between the studied groups over the 24 months follow-up period with (100.0%) survival in MWA and LR after 1 year but after 2 years overall survival rates were (100.0% VS 93.3% VS 86.7%) in MWA, LR and RFA respectively(p= 0.3).

Table (4): Comparing overall survival over 24 months between the three studied groups:-

Variable	*Total number* No(15) %	*Survival after 1year* No(15) %	*Survival after 2year* No(15) %	Log rank test	p-value
Liver resection	15 100.0	15 100.0	14 93.3%	2.1	0.3 (NS)
RFA	15 100.0	14 93.3	13 86.7%		
MWA	15 100.0	15 100.0	15 100.0		

The high difference in percent is due to small sample size.

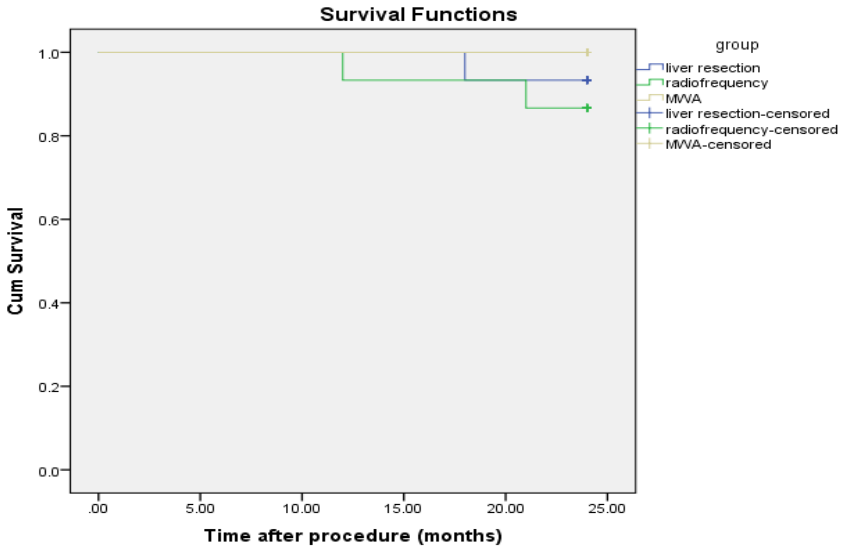

Figure (1): **Kaplan–Meier estimates of overall survival rate in the studied groups**

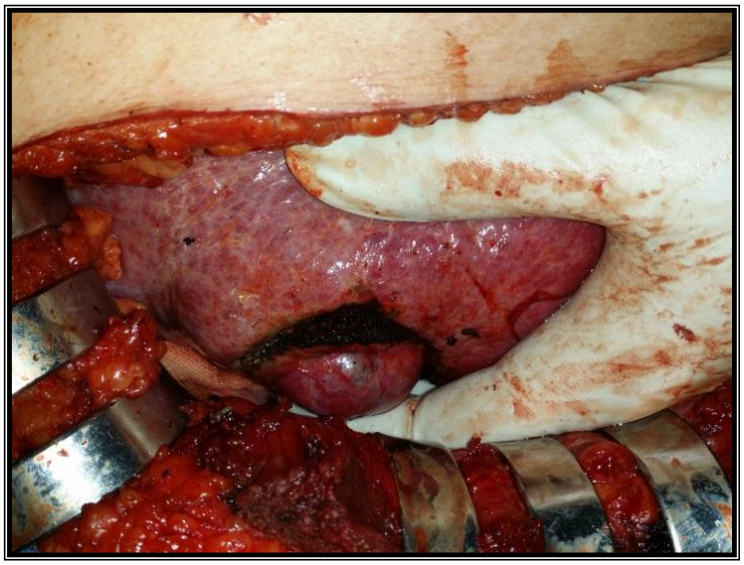

Figure (2): Liver parenchyma transection around mass in non-anatomical resection (Segment 4).

Figure (3): U/S guided microwave ablation with the needle inside the lesion.

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DISCUSSION

Patients with early stage HCC are candidates for surgical resection, orthotopic LT, and ablative techniques such as thermal ablation (MWA and RFA) [26]. This prospective study aimed to compare the survival and morbidity outcomes of LR, RFA and MWA in treating patients with early HCC.

In our study, patients of the three groups treated by different methods did differ significantly regarding 1-year & 2-year overall survival rates (OS). These results are similar to previous studies like those, carried out by ***Lei et al.*** , ***Xu & Zhao*** and ***Vietti et al***., which found no significant difference regarding overall survival in groups treated by the different modalities [27, 28,29].

Hepatectomy has been constantly adopted to be superior to thermal ablative approaches mainly in domains of recurrence and overall survival. Sticking to Milan criteria usually aids in such surpass for LR decreasing possibility of intrahepatic recurrence and rendering better local control. Proper justification is present; it is the variation in nature of malignancy removal between surgery and ablative modalities. Resection offers more complete removal of the primary malignant focal lesion and any masked minute microscopic extensions by excision of the whole Couinaud's segment. In contrast, energy-mediated ablation can be considered accomplished with only further 1 cm circumferentially which increases chances of "missing" vital undesired areas as obscure venous metastases and other grossly unrevealed affected areas[30].

Ways of dealing with relapse after RFA and MWA are more effective and radical than after LR resection. We find this a proper explanation for the close rates of overall survival between the three groups.

Owing to recent advancement in surgical tools and technology, surgical resection tends to show better short-term outcome. There is no established agreement within many studies regarding the actual negative effect of resection on morbidity outcomes or definite interpretation of severity of post-operative complications. Post-resection complications are attributed to the higher invasive character of surgical intervention and to the functional aspect of the liver genuinely [31].

Three centimeters (3cm) safety margin is the least approved width with liver resection [35]. Moreover, formal hepatectomies are advised to submit better results than restricted non-anatomical resections leading to excess liver removal[36]. Lastly, notable congestion is usually encountered, caused by the unavoidable vascular destruction in remnant surrounding tissue. Therefore, enormous amount of healthy liver is destructed resulting in more severe complications. On the other hand, narrower area of normal tissue is injured to be out of function during thermal ablation by RF or MW[27] .

In our study, RFA and MWA showed "less severe pattern" of post-procedural complications. LR showed higher incidence than RFA and MWA regarding major complications: liver decompensation and incisional hernia. This rate was significantly higher in LR (P=0.01). Most of minor complications as pain, pneumothorax and abscess formation were more frequent in RFA and MWA groups.

Limited expectation of the resultant destruction range with MWA, has implicated the belief of many authors that MW had not offered the same level of safety as RFA[32].

However, Livraghi et al., have shown in 2012 that the performance of new advanced devices of MW apparatus-with cooled tip- has turned this status with improved safety standards[33] . The percentage of complications after MWA ,in their study, did not exceed 2.9%

We also found and matched them that both ablative techniques provided comparable results in terms of morbidity and complications, with only few minor complications. These results are partially consistent with findings of *Lei et al.,* who used the same classification system for comparison[27] and with Shibata[34]. However, these were not the same findings reached by *Xu et al.,* who found that the complications incidence were significantly lower in MWA group than LR. The explanation might be that they ignored most of minor complications incidence rates as pain occurrence [28].

In conclusion, RFA and MWA could equally be an effective alternative to liver resection (LR) amenable patients as a primary therapy for early-stage HCCs measuring as large as <5cm, with added benefits of less severe complications and minimal invasiveness. Both RFA and MWA showed near equal comparable outcomes between each other.

Conflict of Interest: There is no conflict of interest.

Financial Disclosures: Nil

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