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# Percutaneous treatment of Hepatocellular carcinoma exceeding 3 cm: combined therapy or microwave ablation? Preliminary results

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**Abstract**
*Purpose* To compare MWA and RFA combined with TACE for HCC nodules exceeding 3 cm.
*Methods* 19 lesions submitted to MWA (G1) were retrospectively compared with a combined treatment group (G2) matching by tumor characteristics (mean size 43 and 45 mm in G1 and G2, respectively). Technical success, complications, complete ablation (CA), and maintained CA (mCA) were evaluated.
*Results* Technical success was achieved in all cases. Overall mortality was zero, both in G1 and G2. No significant differences were found in complications rates (3 in G1 and 2 in G2). CA was obtained in 11 (58 %) HCC in G1 and 15 (79 %) in G2 ($p$ = n.s.). CA was obtained in 75.5 % (G1) and 89 % (G2) nodules up to 4 cm, 45 % and 70 % nodules >4 cm, respectively. At statistical analysis, size resulted as predictor for CA only in G1 (mean diameter of CA vs non-CA 39.9 vs. 47.7 mm, $p = 0.021$). During follow-up (13.1 and 14.4 months in G1 and G2), mCA occurred in 6/19 (32 %) nodules in G1, 8/19 (42 %) in G2.
*Conclusion* MWA and combined therapy are comparable as for safety. No significant differences were found in terms of technique effectiveness. Larger randomized studies should be designed to confirm MWA as a valid alternative to combined therapy.

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**Keywords** Hepatocellular carcinoma · Microwave ablation · Transarterial chemoembolization · Radiofrequency ablation · Combined therapy

## Introduction

In spite of many efforts and major advances in the treatment of HCC, this tumor is still the sixth most common cancer and the third cause of cancer-related death [1]. Imaging-guided loco-regional therapies can be considered, in selected patients, the most appropriate and potentially curative treatments [2].

Among these therapies, radiofrequency ablation (RFA) is currently offered as a first line treatment in nodules less than 2 cm (very-early stage, according to BCLC classification), and in patients unfit for surgery, it is the best treatment option even for early stage patients (single or up to 3 nodules ≤3 cm in diameter) [2, 3].

An important limitation affecting RFA is its reliability in ablating all neoplastic tissue, creating an adequate ablation zone, with sufficient safety margins. In fact, when target tumors exceed 3 cm, RFA efficacy decreases: in such cases, the combination with TACE can improve the maintained complete ablation, according to several previous retrospective studies [4, 5] and one RCT [6].

More recently, microwave ablation (MWA) has been demonstrated as a potentially more powerful technique, emerging as a possible valuable alternative to RFA in case of larger HCC nodules. In fact, MWA can reach higher temperatures and seems to be less affected by the heat sink effect due to the proximity between the tumor and the surrounding vessels [7], eventually obtaining larger ablation zones than RFA [8].

So far, no studies have been published comparing MWA with RFA + TACE in HCC nodules larger than 3 cm. The

aim of our preliminary study is to compare complications, effectiveness, and local recurrence of these two techniques in treating such tumors, in order to assess if one is better in terms of safety or efficacy.

## Materials and methods

### Ethic statement

This is a retrospective study of prospectively collected data. Written informed consent to undergo the procedure has been obtained by all the patients enrolled in the study.

All examinations and treatments were performed in the full respect of the guidelines of our institutional review board and the Helsinki declaration.

### Patient selection

Data were retrieved from a consecutive database of 787 HCC image-guided ablation procedures performed at our Department since January 2008. A retrospective analysis was conducted on 36 patients with one or two hypervascular HCC nodules exceeding 3 cm, treated up to September 2013.

Seventeen patients with 19 tumors were submitted to MWA (group 1, G1). They were compared with our last group that had undergone RFA combined with TACE selected on the basis of comparable characteristics (19 consecutive patients with 19 tumors; group 2, G2).

Nodules mean diameter was 43 mm (SD ±7.5) in G1 and 45 mm (SD ±8.4) in G2; 11 nodules in G1 and 10 in G2 were larger than 4 cm. Both in G1 and G2, 14 treated lesions were in the right lobe and 5 in the left lobe.

14 nodules in G1 and 5 in G2 were far less than 1 cm from the liver surface; 14 and 8 lesions, respectively, were far less than 5 mm from main vessels. Baseline characteristics of the two groups are shown in Table 1. All patients were selected for image-guided treatment (MWA or RFA + TACE) on the basis of a multidisciplinary tumor board assessment. Patients were considered non-surgical candidates, as a result of intermediate staging (according to BCLC classification), poor hepatic reserve, anatomic restrictions, and/or other medical comorbidities.

Moreover, exclusion criteria for the percutaneous procedures were as follows: radiologic evidence of invasion into major portal/hepatic vein branches, extrahepatic metastases, Child-Pugh superior to B7, and history of previous treatments.

They were selected for MWA or RFA + TACE without randomization, based on the time when they visited our hospital (progressive restriction of bedrooms for longer hospital stay for combined therapy, increasing availability of MWA devices).

**Table 1** Group 1 (G1) and group 2 (G2) baseline characteristics

| | G1 | G2 |
|---|---|---|
| Patients | 17 | 19 |
| Gender (male) (%) | 14 (82.3 %) | 19 (100 %) |
| Age (year) (mean ± SD) | 48–83 (66.7 ± 10.9) | 47–84 (64 ± 9.4) |
| Nodules | 19 | 19 |
| Site (R/L lobe) | 14/5 | 14/5 |
| Diameter (mm) (mean ± SD) | 43 ± 7.5 | 45 ± 8.4 |
| Nodules >4 cm | 11 | 10 |
| Proximity to liver surface (Y/N) | 14/5 | 5/14 |
| Proximity to main vessels (Y/N) | 14/5 | 8/11 |

Pretreatment work up was made with cross-sectional imaging (multiphase CT scan and/or dynamic Gd-enhanced MR) within the month before the ablation.

### Technique

All ablative procedures were performed under local anesthesia (1 % lidocaine at the insertion site) and analgo-sedation.

#### *MWA*

The MWA device HS Amica System (Hospital Service S.p.A, Rome, ITA) was used in all the G1 series. The generator, of 2.45 GHz MW, capable of a 140 W power emission at the maximum, is connected through a flexible coaxial cable to a 14 G cooled shaft antenna coated with Teflon, in order to prevent adhesion.

Under ultrasound guidance (MyLab Twice, Esaote, Genoa, ITA), the antennas were introduced percutaneously into the tumors by two senior radiologists (C.G., A.V.) with long-time expertise in percutaneous procedures (more than 10 and 20 years, respectively); up to three overlapping ablations were performed when necessary.

The MW generator was set to 60 W for ten minutes for each delivery, according to the manufacturer protocol. To prevent possible tumor seeding or bleeding, the needle track was cauterized for few seconds ("track ablation" protocol) when withdrawing the antenna.

#### *RFA and TACE*

RFA ablation was also performed under US guidance (MyLab Twice, Esaote, Genova, ITA) by the same two senior radiologists (C.G., A.V.). Two different RF-systems were used (StarBurst XL, RITA Medical System, Mountain View, CA, USA; Med-Italia RF-system, Genoa,

ITA), with multitined electrode needles of 14 G and 16 G, respectively, following the protocols recommended by the manufacturers.

TACE was performed the day before RFA, in our angiographic suite (Allura XPer FD 20, Philips, Heindhoven, The Netherlands) by two senior radiologists (A.D.B., D.R. not author) with more than 10 and 20 years experience in transarterial procedures as well.

With transfemoral access, after demonstration of the absence of arterio-venous fistulae, the feeding arteries of the tumors were catheterized as selectively as possible using 2 or 3 F micro-catheters (Pro-great System, Terumo, Tokyo, Japan). Epirubicine manually emulsified with iodized oil (Lipiodol, Guerbet, Genova, ITA) or DC-Beads (100–500 micron, Terumo, Tokyo, Japan, each vial was preloaded with the chemotherapy agent) was injected, until the flow was static and the full saturation of the feeding arteries was obtained.

### Assessment and follow-up

Complications were counted according to the SIR classification [9]. Particularly, those that necessitated major therapies, prolongation of the hospital stay, permanent adverse sequelae, or death were considered major complications. All other complications were considered minor.

A re-staging multiphasic CT study was performed in all patients as a first control 40–60 days after the procedure (Fig. 1). Every 4 months, ablated nodules were then re-evaluated with cross-sectional imaging (multiphase CT scan or dynamic Gd-enhanced MR, preferably chosen in case of previous injection of iodized oil, unfavorable for CT evaluation). In order to compare the two techniques in terms of safety and effectiveness, versus local tumor progression (LTP), study endpoints were included:

- technical success (defined as whether the tumor was treated according to the protocols);
- major and minor complications (according to the unified standardized SIR grading system);
- complete ablation (CA) of the nodule at the first CT/MR scan;
- maintained complete ablation (mCA) at imaging follow-up; and
- LTP, as the persistence or re-grew at the original site of residual unablated tumor (partial ablation, PA, +local recurrence, LR) (Fig. 2).

### Statistical analysis

The Mann–Whitney *U* test, Chi squared test, and Fisher exact test were used to analyze the differences in baseline

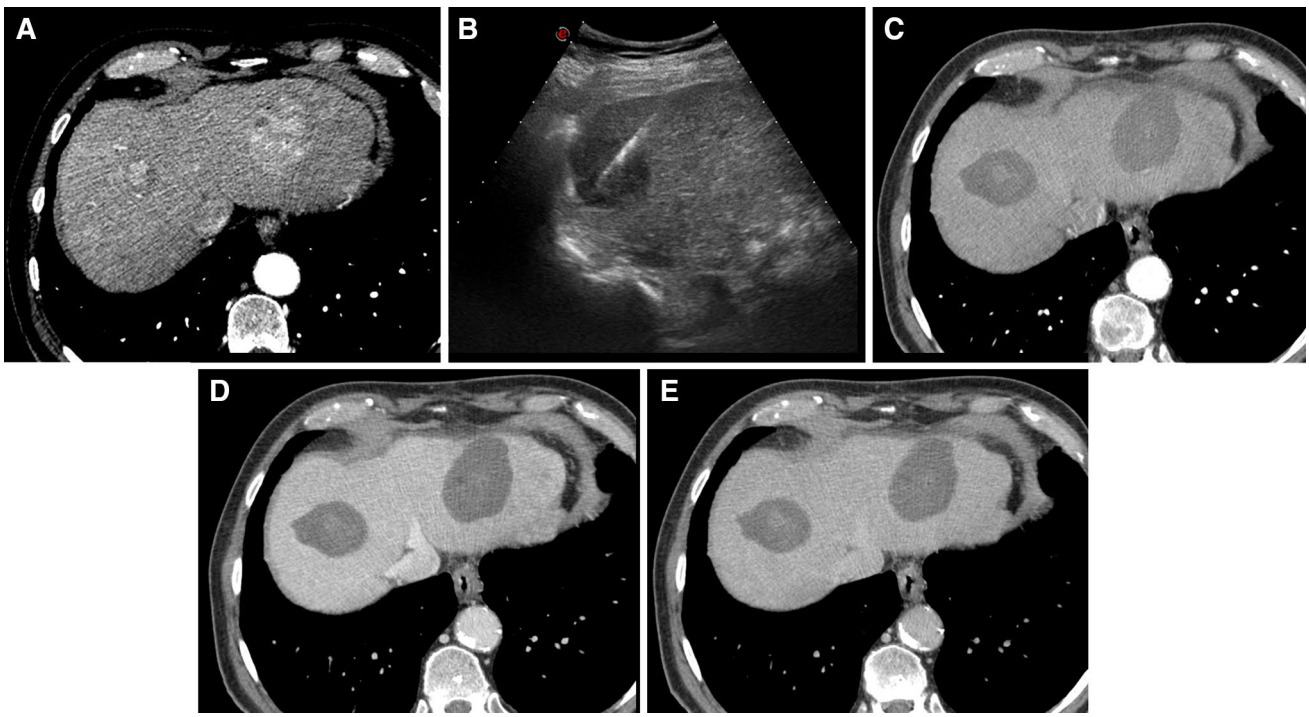


**Fig. 1** MW ablation of two HCC nodules exceeding 3 cm (41 and 35 mm maximum diameter). Pre-procedural CT study (arterial phase) (**a**). Microwave ablation of one of the nodules in the liver dome (US-guided insertion of the antenna (**b**). Complete ablation (CA) of both nodules at the first CT control: arterial (**c**), portal (**d**) and delayed phase (**e**)

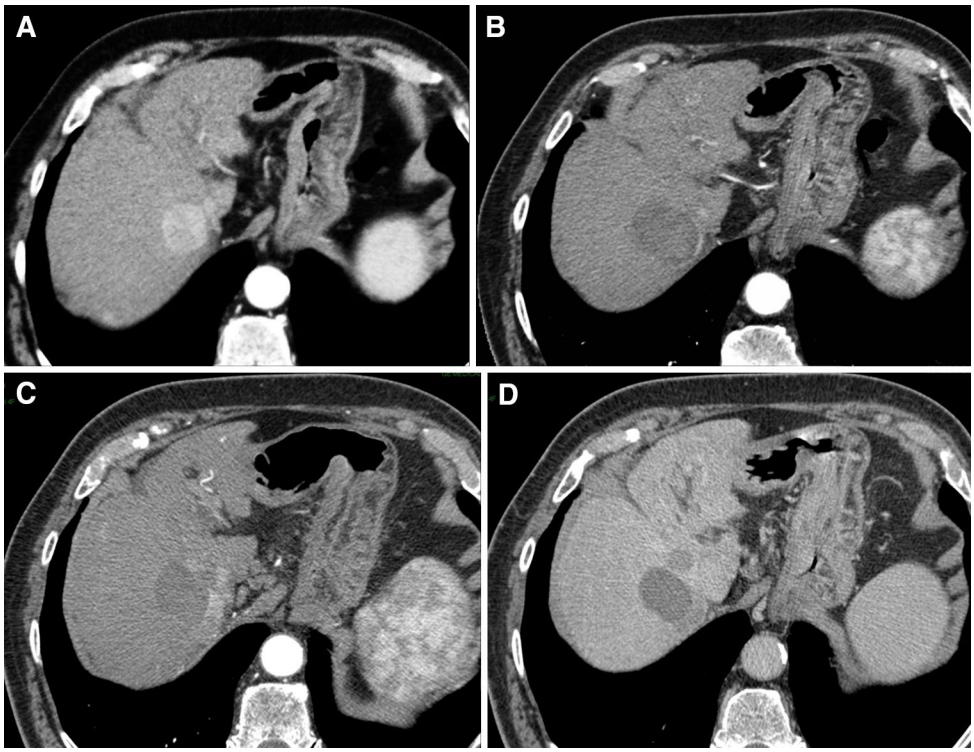


**Fig. 2** Local tumor progression (LTP) during follow-up. Pre-procedural CT (**a**). CA at the first CT Control (**b**). LTP beyond the deep margin of the ablation zone at the following CT study (arterial and delayed phase (**c** and **d**)

demographics and nodules characteristics, and in the treatment results between G1 and G2. Nodule size (mean diameter; threshold ≤ vs. >40 mm) and site (right vs. left lobe), and vicinity to liver surface (equal or less than 1 cm) or main vessels (equal or less than 5 mm to main hepatic veins or portal branches) were considered as possible prognostic factors (predictors for complications or local efficacy) at a univariate analysis. A $p$ value <0.05 was considered statistically significant.

Statistical analysis was performed using PRISM GraphPad Software (La Jolla, CA, USA).

## Results

### Baseline characteristics

Table 1 shows the characteristics of the MWA group versus those of the RFA-TACE group. No statistical differences were found between G1 and G2 ($p$ = NS).

### Technical success and adverse events

Technical success was achieved in all cases and overall periprocedural mortality was zero, both in G1 and G2.

Two perihepatic collections and one subcutaneous hematoma occurred in G1, counted as minor complications.

As for G2, one perihepatic collection (minor complication) and one femoral pseudoaneurysm (major complication, treated with US-guided compression) were observed.

No significant differences were found in major and minor complications rates between G1 and G2 ($p > 0.05$). Moreover, the correlation between adverse events and possible predictors (tumor size, hepatic lobe, liver surface, and vessels distance) was neither significant nor different in the two groups ($p$ = NS).

### Technique effectiveness and outcome

CA was obtained in 11 (58 %) HCC in G1 and in 15 (79 %) in G2 at the first CT/MR control (Fig. 3); nevertheless, the CA rate was not statistically different between the two groups ($p$ = NS).

In G1, CA in nodules up to 4 cm was 75.5 and 45 % in nodules >4 cm. In G2, CA in nodules ≤4 cm was 89 and 70 % in nodules >4 cm (Table 2).

As predictor, only nodules size showed a significance at the statistical analysis in G1; particularly, mean diameters of CA vs PA in G1 were 39.9 vs. 47.7 mm ($p = 0.021$), whereas the difference was not significant for G2 (43.3 vs. 50.7 mm, $p$ = NS) (Fig. 3a); nonetheless, based on 40 mm thresholds, the differences between CA and PA rates were not statistically significant both for G1 and G2. Also hepatic lobe and proximity to liver surface or vessels did not reach prognostic values for CA both in G1 and G2.

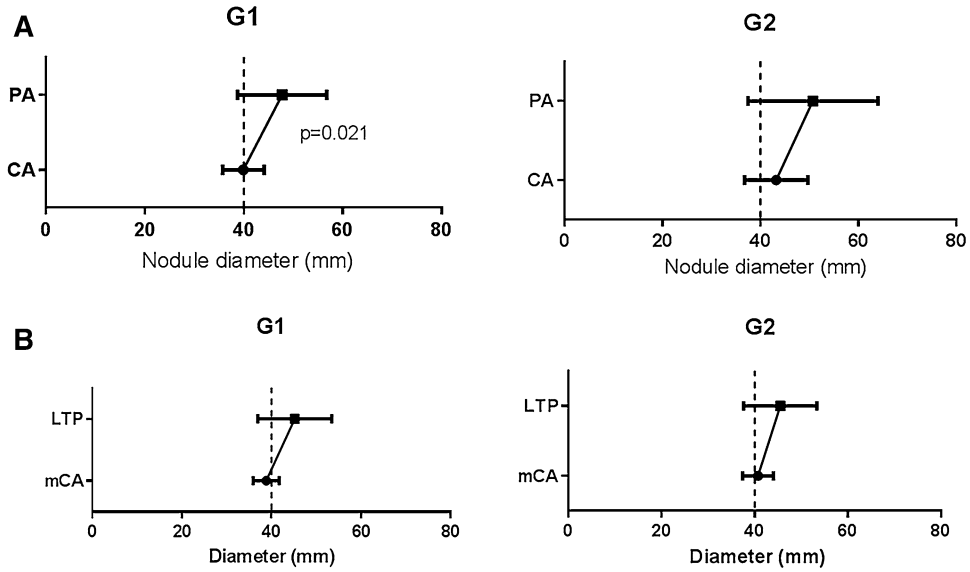


**Fig. 3** Comparison between the diameters (mean ± SD) of the treated nodules in the two groups stratified by the results of the ablation at the first imaging control (**a** PA vs. CA) and during follow-up (**b** LTP vs. mCA)

**Table 2** Group 1 (G1) and Group 2 (G2) results at the first CT control (CA: Complete Ablation)

| | G1 | G2 |
|---|---|---|
| CA (%) | 11/19 (58 %) | 15/19 (79 %) |
| CA in nodules ≤40 mm (%) | 6/8 (75.5 %) | 8/9 (89 %) |
| CA in nodules ≥40 mm (%) | 5/11 (45 %) | 7/10 (70 %) |

**Table 3** Group 1 (G1) and Group 2 (G2) at the follow-up (CA: Complete Ablation)

| | G1 | G2 |
|---|---|---|
| Maintained CA (%) | 6/19 (32 %) | 8/19 (42 %) |
| mCA in nodules ≤40 mm (%) | 3/8 (37.5 %) | 6/9 (67 %) |
| mCA in nodules >40 mm (%) | 3/11 (27 %) | 2/10 (20 %) |

The mean follow-up period after treatment was 13.1 months in G1 and 14.4 months in G2. During follow-up, 3 patients in G1 and 5 patients in G2 died.

Local recurrence was observed in 5 out of the 11 initially CA (46 %) in G1 (Fig. 2) and in 7/15 (47 %) in G2; consequently, mCA occurred in 6/19 (32 %) nodules in G1, and 8/19 (42 %) in G2. From another point of view, LTP was found in 13/19 nodules in G1 (68 %) and 11/19 nodules in G2 (57 %) at follow-up imaging ($p$ = NS).

In G1, mCA in nodules ≤4 cm was 37.5 and 27 % in nodules >4 cm. In G2, mCA in nodules up to 4 cm was 67 and 20 % in nodules >4 cm (see Table 3).

Even though mean diameter of mCA was lower both in G1 (38.8 vs. 45.2 mm) and G2 (40.7 vs. 45.5 mm), no statistical differences were found (Fig. 3b), as for 40 mm threshold.

Hepatic lobe, liver surface distance, and vessels proximity also did not reach prognostic values for mCA both in G1 and G2.

## Discussion

### Rationale

After being accepted as a standard of care in HCC nodules smaller than 2 cm and even in nodules up to 3 cm when surgery is not feasible [2, 3], one of the major challenges of imaging-guided therapies is their capability to treat safely and effectively bigger lesions.

So far, combination of different therapies (TACE + RFA) has been considered the treatment of choice for unresectable tumors larger than 3 cm [5, 6].

In fact, TACE combined with RFA is beneficial because it enables greater ablation zone than that achieved with RFA alone, according to previous experiences in the literature [4, 5], including a recent RCT [6]: causing ischemia and reducing heat sink effect, embolization of the tumor feeding arteries can increase the RF-induced necrosis (6 % LTP with combination of the two techniques versus 39 % with RFA alone [6]).

The order of interventions in the combined therapy is still debated. In our study, transcatheter arterial chemoembolization was performed the day before the percutaneous ablation. In fact, according to several studies [4–6], TACE prior to RFA reduces the cooling effect of hepatic blood flow on thermal coagulation by decreasing hepatic arterial flow, enhancing the nodule ablation.

More recently, microwave ablation has emerged as a treatment with the potential to address the limitations of

RFA. MWA creates an electromagnetic field in the tissue surrounding the antenna, without the flow of electric current through a closed circuit. This allows for a direct and potentially more homogeneous energy deployment, without the detrimental effects of tissue impedance, and can yield a more rapid and larger ablation [10].

At our knowledge, there are no studies in the literature comparing combined RFA and TACE versus MWA for HCC nodules larger than 30 mm.

Thus, this pilot study has been designed to compare the two methods in terms of safety and efficacy in a mid-term perspective (one-year follow-up).

### Safety

As for safety, no major complications were counted (0/19 treated nodules) and only 3 minor complications were observed in MWA group. This is consistent with the data reported in a joint study published by 14 institutions in which no deaths and an incidence of serious complications of 2.9 % were reported [11]. Another study by Ding et Al. [12] reported a similar incidence of serious complications (3.4 %).

In G2, two complications (one minor and one major, 5.3 %) were counted. Also these data are consistent with previous experience in the literature (6.5 % of major complications reported by Veltri et al. [6]). Therefore, we can affirm that the incidences of complications caused by RFA-TACE and MWA are very low and comparable, so that the two therapies can be considered equally safe in treating HCC nodules larger than 3 cm.

### Efficacy

As for CA at the first imaging control, statistical analysis showed no differences between G1 and G2.

However, combined RF + TACE seemed to show a trend toward better results in terms of early CA, mostly based on multiphase CT studies; looking also at the following more balanced mCA rates between the two groups, this could be probably due to residual-iodized oil uptake inside the ablation zone causing an underestimation of the persistence of viable tissue in G2, a well-known phenomenon already described in the literature [5, 13].

As shown in Tables 2 and 3, treatment of nodules ≤4 cm yields better local results than that of nodules >4 cm for both G1 and G2.

Considering MWA, mean diameter of nodules with CA at the first CT/MR control resulted significantly smaller than the PA group ($p < 0.05$).

However, in the ≤4 cm subgroup, MWA CA rate (75.5 %) has been similar but worse in comparison to the combined therapy (G2, 89 %), and also to the MWA data reported by Liu et Al (87.5 %) [14]. Maintained CA was 32 % in G1 and 42 % in G2 in our series. Even though no significant statistical differences were found between G1 and G2 for mCA, MWA rate resulted still inferior than combined therapy and did not reach the percentages (67.5 %) recently reported by Liu et Al.

G1 results in nodules bigger than 4 cm still seem below expectations.

G2 results in nodules up to 4 cm (67 %) have been consistent with others already reported (70 %) [6]. Moreover, despite a lower overall mCA rate, also MWA mean diameter of mCA subgroup resulted smaller than that of nodules with LTP, confirming the size of the tumor as the leading factor that affects local recurrence [15]. Studies with larger population groups, possibly randomized, will be eventually able to find out a statistically significant difference.

In conclusion, according to our data, MWA seems to be so safe and effective to carve out a role in the treatment of HCC nodules between 3 and 4 cm. Its standardization as a care for these tumors would be desirable, considering the longer hospital stay and the higher costs of the combined therapy. Even though no statistically significant differences were found between the two treatments, due to the apparently noticeable difference in terms of local efficacy, a larger preferably randomized study should be designed to confirm MWA as a valid alternative to the combined therapy in case of HCC larger than 3 cm.

**Conflict of interest** All the authors declare no conflict of interest.

**Ethical standards** This is a retrospective study of prospectively collected data. Written informed consent to undergo the procedure has been obtained by all the patients enrolled in the study. All examinations and treatments were performed in the full respect of the guidelines of our institutional review board and the Helsinki declaration.

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