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Microwave ablation in the treatment of liver tumors. A better tool or simply more power?

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Abstract

It has been a long time since tumor ablation was first tested in patients with liver cancer, especially hepatocellular carcinoma. Since than it has become a first line treatment modality for hepatocellular carcinoma. Over the years, the indications of thermal ablation have expanded to colorectal cancer liver metastases and intrahepatic cholangiocarcinoma as well. Together with the new indication for ablation, new ablation devices have been developed as well. Among them microwave ablation shows potential in replacing radiofrequency ablation as the preferred method of thermal ablation in liver cancer. The debate whether radiofrequency or microwave ablation should be the preferred method of treatment in patients with liver cancer remains open. The main purpose of this review is to offer some answers to the question: Microwave ablation in liver tumors: a better tool or simply more power? Various clinical scenarios will be analyzed including small, medium, and intermediate size hepatocellular carcinoma, colorectal cancer liver metastases and intrahepatic cholangiocarcinoma. Furthermore, the advantages, limitations, and technical considerations of MWA treatment will be provided also.

Keywords: microwave ablation; hepatocellular carcinoma; intrahepatic cholangiocarcinoma; colorectal cancer liver metastases

Introduction

Tumor ablation is a minimally invasive technique that is commonly used in the treatment of many tumors including primary and secondary liver neoplasm. In secondary liver neoplasm, ablation techniques are an important option for patients who are not surgical candidates [1], while in patients with small hepatocellular carcinoma (HCC) ablation is considered a potential first-line treatment [2]. In the last two decades, percutaneous treatments for malignant liver tumors have been substantially improved. The most widely used method of those available has been monopolar radiofrequency ablation (RFA), although in the last 5 years microwave ablation (MWA) has gained acceptance as a favorable alternative and in some cases a preferred choice of ablation modality [3]. All the great improvements of the MWA generators, needles, guidance softs during the last years have allowed for the current indications of tumor ablation to expand to intrahepatic cholangiocarcinoma (iCCA) as well [4]. We already have some reports, although preliminary, for the use of MWA in the treatment of iCCA [5]. This paper reviews the evidence supporting the use of MWA in the treatment of liver cancer. The clinical application of MWA in various clinical scenarios will be discussed. Among clinical scenarios we include small, medium, and intermediate size HCC, colorectal cancer liver metasta-

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ses (CRCLM) and iCCA. Furthermore, the advantages, limitations, and technical considerations of MWA treatment will be also provided.

Mechanism of tissue heating

The goal of thermal ablation is to heat target tissues to temperatures that can induce immediate coagulative necrosis (typically over 60 °C). A complete treatment should cover the tumor plus a 5-10 mm safety margin (analogous to a surgical margin) while sparing healthy parenchyma and vulnerable non-target structures [3,6-9]. In MW ablation, the mechanism of heat generation is based on rapid frictional movement of water molecules in the high frequency (900-2500 MHz) electromagnetic field.

Unlike RFA, microwaves are capable of effectively heating and propagating through many types of tissue, even those with low electrical conductivity, high impedance, or low thermal conductivity. All MWA systems are composed of three basic elements: microwave generator, low-loss flexible coaxial cable and microwave antenna. The diameter of the antenna used commonly in clinics is 2 to 2.8 mm (14-16 G).

To prevent over-heating of the shaft, avoiding skin injury and permitting further deposition of energy into tissue with low impedance during ablation, cooled-shaft antennae have been developed [6,10]. Multiple antennae (2-4) can also be used to create larger, more conformal and confluent ablation zones [11]. Simultaneous multi-antenna MWA of liver tumors results in large (ablation volume nearly threefold larger with 3 antennas than that achieved with 2 antennas), nearly spherical ablation zones [11].

There are 3 generations of microwave systems, the 3rd one with incorporating antenna cooling systems and high-power generators [12]. Conventional MWA systems use either 915 or 2450 MHz frequency. As with other heat-based thermal ablation devices the ablation zone size and shape is less predictable being influenced by physical parameters of the liver parenchyma such as thermal conductivity and perfusion rate [12]. The newer generation MWA systems with internal cooling attempt to overcome the limitations of conventional systems and to provide predictable ablation areas not impacted by tissue type or target location [12]. A large, precise, and spherical ablation zone is achieved using three different kinds of control: field, thermal and wavelength [12,13].

Major advantages of MWA over RFA

MW ablation has several advantages, including greater and more uniform penetration of energy into tissue (resulting in a larger area of ablation), higher intratumoral temperatures (>150 C), and faster ablation times [3,8,9,14,15].MWA is less susceptible to the heat-sink effect and thus it could be used to treat tumors in close contact to large vessels [3,6,9]. However, it should be kept in mind that by producing larger zones of necrosis, MWA increases the risk of potential complications owing to collateral injury to adjacent nontarget organs [10].

Technique

There are different ways to perform MWA (percutaneous, laparoscopic or intraoperative); however, the percutaneous approach offers several advantages [3,16-18]. It is the least invasive, relatively expensive, can be performed on an outpatient basis and can be repeated to treat recurrent tumors [16]. In clinical practice all patients should undergo ultrasound (US), contrast enhanced US (CEUS) and contrast enhanced computed tomography (CT) or gadolinium-enhanced magnetic resonance imaging (MRI) in order to delineate the target tumor(s) before MWA. MWA has been performed by using US, CT, or MRI guidance [15,19,20]. Compared to CT or MRI guidance, US has real time features and allows scanning the body from different positions and angles, and hence US is more convenient. In cases with difficulties in targeting the lesions or lesions not detectable at US, CEUS and/or fusion imaging techniques (US-CT, US MRI) may be used [21-24]. Patients should fast for at least 6 hours before ablation. Percutaneous MWA is usually performed under local anesthesia and analgosedation. After the procedure the patients should be monitored at least 6 hours. A one-night hospital stay is preferable and mostly practiced although outpatient procedures have been also reported [3,9,15]. As with RF ablation, MW ablation involves placement of a needle electrode directly into the target tumor, typically under US guidance (fig 1 a,b). During the procedure, the ablation zone appears on US as hyperechoic spots around the antenna, thus confirming that the heat was applied. The hyperechogenic area is caused by microbubbles and gas released from the heated tissue and does not correlate with adverse tissue coagulation [3].

In order to destroy possible micro-metastases or microscopic foci around the tumor so preventing local tumor progression, ablation with a margin of 5-10 mm around the tumor has been recommended [3,25]. In many cases, multiple overlapping ablations may be required to create the necessary ablation zone size. Overlapping ablations can be created in 2 ways: 1) multiple insertions of a single antenna to create overlapping ablation zones in a sequential manner or 2) multiple antennas ablating simultaneously to create a confluent ablation zone. Sequential antenna applications performed by repositioning a single antenna can be technically challenging as gas bubbles

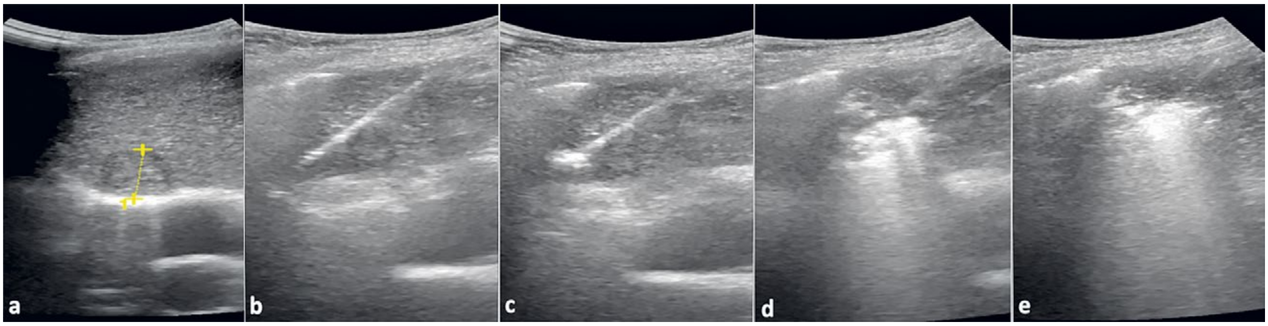

Fig 1. a) MWA of a 1,8 cm hepatocellular carcinoma nodule. b) the electrode is placed into the lesion (>).; c-e) an echogenic spot is increasing around the antenna tip, covering the lesion

and tissue contraction decrease the visibility of the target area [6]. The size of the ablation zone can be roughly assessed by the expanding hyperechoic area during ablation. The ablation is considered ended when the transient hyperechoic zone around the antennae on grey-scale US merges and covers the target region (fig 1c-e) [15].

For accurate assessment of the treatment efficacy, 1-3 thermocouples can be placed percutaneously at different sites 5-10 mm outside the tumor and connected to a thermal monitoring system attached to the MW generator. The ablation is considered to be completed if the measured temperature is 60°C by the end of treatment and remain at 54°C for at least 3 min [15]. By the same system overheating can also be avoided, thus decreasing the incidence of complications [15].

The procedure should be also stopped immediately in cases of the appearance of major complications including massive bleeding, severe pain, severe pneumothorax or perforation of adjacent organs [3]. In order to ensure complete avascularity of the tumor, to delineate precisely the ablation area and its relation to the tumor or to provide guidance for retreatment of suspected non-ablated parts of the lesion, CEUS can be performed at the end of the procedure [26,27]. The resulting ablation area after 1 session tends to be much more elliptical with the conventional MWA systems and more spherical with the newer one (fig 2) [3]. With some devices 1-3 hallmarks of the antennas are seen within the lesion. If any residual tumor is found, additional ablations should be performed [26] (fig 3). Using CEUS at the end of ablation, the residual tumor rate was decreased from 16.7 to 0 % [26]. In recent years, many centers have introduced CEUS for the immediate assessment of treatment efficacy.

There are some challenges in the CEUS evaluation of the ablated zone. To avoid the hyperechoic cloud which may mask untreated areas, CEUS is usually performed 10-15 min after MWA [26,28]. Perilesional hyperemia is

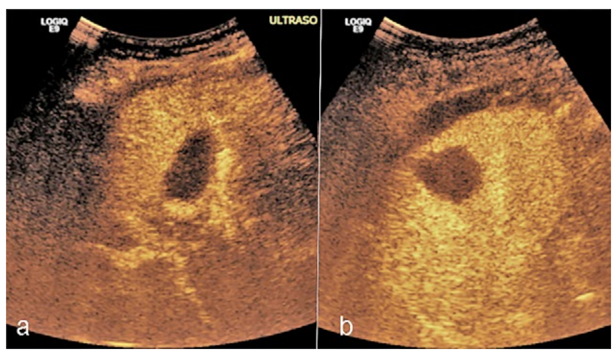

Fig 2. a) The shape of ablated zone tends to be more elliptical. CEUS image; b) an almost round ablated zone is obtained with 3rd generation systems

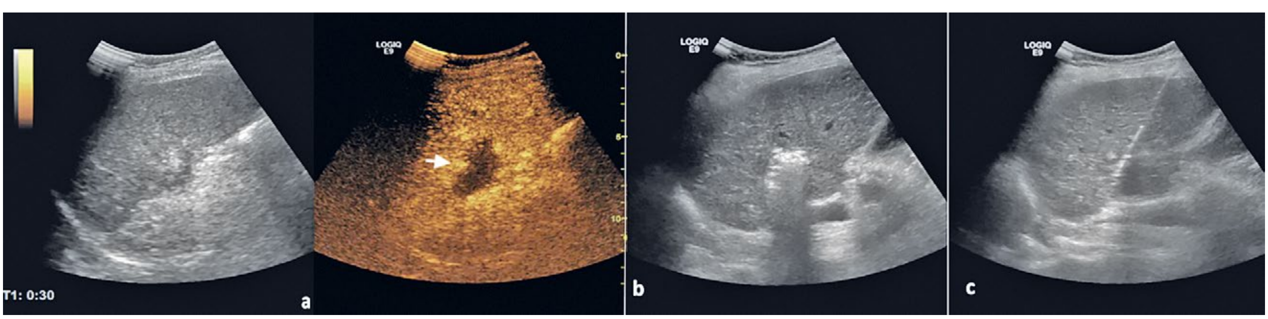

Fig 3. a) Untreated tumor zone in MWA procedure-split mode image; b) Additional insertion is performed in the enhanced area; c) ablation of that area is performed. Note the echogenic cloud covering that part of the tumor

frequently present immediately after ablation and may be mistaken as a residual tumor. Unlike a residual tumor, peri- ablation hyperemia demonstrates a uniform rim of hyperenhancement in the arterial phase which persists throughout all phases [26,28]. Pseudo-enhancement corresponds to the most echogenic region of the ablation zone on gray scale US and tends to appear during the portal venous phase, in a region which was avascular during the arterial phase [26]. Maybe the most challenging issue is to delineate correctly the ablation area and its relationship to the tumor and to detect a possible enhancing area in a 3D fashion [26]. The above issues are even more critical for metastasis ablation [26,29]. This technical limitation of CEUS may be responsible for some recurrence even in cases with postprocedural CEUS evaluation [26,28]. The evaluation may be substantially improved by using fusion techniques such as CEUS-CT or CEUS-MRI fusion imaging [24].

CEUS, CT or MRI can also be used for the evaluation of tumor response during follow-up. Currently CT remains the procedure of choice for the follow-up of patients who do not have a contraindication to iodinated intravenous contrast material [3,11,30]. CT images obtained 4-6 weeks after therapy demonstrate successful treatment as a non-enhancing area with or without a peripheral enhancing rim. In the follow-up protocol routine CEUS and contrast CT is repeated at 1 and 3 months after MWA and then at longer intervals over the course of time (4-6 months), depending on imaging findings, underlying tumor and patient risk factors [3,27].

The complications of MW ablation are similar to those reported after RF ablation. Bleeding is the most frequent complication of MWA but it rarely requires transfusion (<1 %) (fig 4) [3]. In 3 systematic reviews, minor, major complication and mortality rates for MWA were 7.3-12.9%, 2.9-4.6% and 0-0.23%, respectively [31-33]. Use of noncooled-shaft antenna and an increased number of MW ablation sessions were associated with a higher rate of major complications in a large cohort of 1136 patients treated by MWA [32]. There are no significant differences in mortality rates (0.15% vs. 0.25%) between RFA and MWA in liver tumors [31].

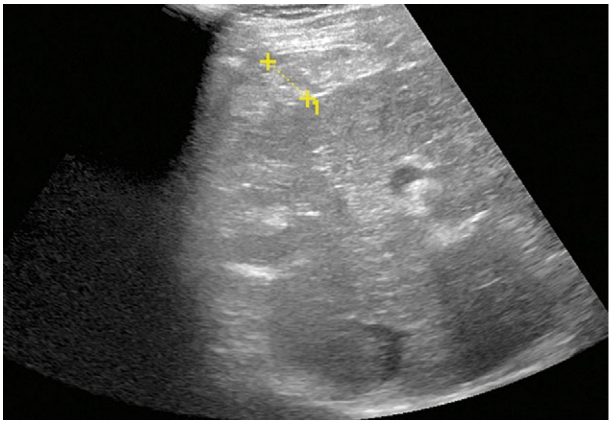

Fig 4. Perihepatic bleeding after MWA. An echogenic material is seen during ablation close to the liver capsule (<)

MWA in colorectal cancer liver metastases

Colorectal cancer (CRC) is a malignancy with high incidence and 20-50% of patients have liver metastases (CRCLM), either detected at diagnosis of primary tumors (synchronous) or at a later stage (metachronous) [34]. The main method used to treat CRCLM is surgical resection. Unfortunately, only 10-20% patients are suitable for this procedure [35]. In this setting, ablation tech-

Table I. Studies comparing MWA with RFA in patients with liver metastasis

Author	Design	No of patients	Complete ablation rate	Local tumor progression	Mean ablation time	Overall survival	Complications
Sparchez [40]	Retro-spective	61	100% vs. 71.35%, p=0.008, in favor of MWA	No difference, p=0.154	10 minutes for MWA vs. 14 minutes for RFA, p=0.003	No difference p>0.05	No difference, p=0.46
Correa-Galego [38]	Retro-spective	134	Not reported	At 2 years 7% vs. 18% in favor of MWA; p=0.01	Not reported	No difference, p=0.5	No difference, p=0.8
Shady W [39]	Retro-spective	110	97% for MWA and 93% for RFA, p=0.47	No difference, p=0.84	7 minutes for MWA vs. 10 minutes for RFA, p=<0.001	Not reported	No difference, p=0.35
Martin [37]	Pro-spective	80	98% for MWA and 92% for RFA	2% for MWA vs. 17% for RFA	13 minutes for MWA vs. 40 minutes for RFA	Not reported	Not reported

MWA = microwave ablation; RFA = radiofrequency ablation; No = number; p = level of significance; vs. = versus niques are widely used. Although the available studies of MWA on colorectal liver metastasis are fewer than those of RFA, the indications, contraindications and patient selection criteria for this procedure are similar to those of RF ablation [36]. The first study comparing MWA with RFA was published back in 2010. On a prospective cohort study, Martin et al evaluated the outcomes of MWA on a variety of liver neoplasms of which the majority were CRLM. Furthermore, the matched comparison of 40 patients undergoing MWA and 40 patients undergoing RFA, MWA came advantageous in every outcome [37]. Since then, only four other studies [38-41] have compared the outcomes of these two ablation techniques (Table I). From our recently published experience we did not find any differences between MWA or RFA. However, incomplete ablation rate and the procedure time were both in favor of MWA [40].

We do have a completely different story for CRCLM with a diameter >3 cm or for those in close proximity to vessels (fig 5). For these entities MWA might be more appropriate. The study of Ierardi et al that included 25 patients with unresectable hepatic metastases in whom RFA had limited applicability (lesions either greater than 3 cm or lesions in close proximity to major vessels) reported a 100% technical success rate for MWA [42].

For the time being, it is quite difficult to state that MWA is superior to RFA in terms of OS or complication rate, since no randomized control studies have been published. However, we do know for sure that MWA is faster and we can only speculate that MWA might be more appropriate for CRCLM >3 cm. For these reasons in our center we almost always (especially for lesions between or greater than 2-3 cm, or in case of multiple or bilobar lesions) prefer MWA instead of RFA for the treatment of CRCLM not suitable for surgery. Now, there are many ablation devices on the market but we should always keep in mind that surgery is the first line treatment for these patients.

MWA in hepatocellular carcinoma

MWA is an effective local thermal ablation technique for treating HCC that exhibits many advantages over other methods [43]. Despite the theoretical advantages of MWA over RFA the majority of the studies performed between 2002-2015 have found no significant differences between these two techniques [44-46]. However, it must be emphasized that the majority of the initial studies were retrospective in nature and on small cohorts. Until now, only 5 randomized control (RCT) studies were published showing no difference between MWA and RFA for small HCC [46-50] (Table II). Consequently, two metanalysis found no major differences between the two ablation techniques [51-52]. The only difference was in terms of the local recurrence rate (MWA outperformed RFA in cases of larger nodules) [51] and in terms of local tumor progression (reduced by 30% with MWA versus RFA) [52]. After almost two decades it has now become clear that for lesions up to 3 cm there is no difference between MWA and RFA in terms of complete ablation rate, LTP, disease free survival, OS, or complications. However, in terms of costs and procedure time (9.0±4.6 minutes vs. 24.4±10.6 minutes, $p<0.001$) one RCT showed MWA to be less expensive and faster than RFA [49].

A totally different scenario is the treatment of medium size HCC, which is defined as a lesion between 3 and 5 cm (fig 6). In a recent propensity score matching analysis that included 126 patients treated with MWA and 436 patients treated with RFA, MWA resulted in a better 5-year overall survival (79.3% vs 68.4%, $p=0.021$) and a 5-year recurrence-free survival (27.9% vs 6.4%, $p<0.001$) than RFA for HCC [53]. One other treatment modality for medium size HCC is transartherial chemoembolization (TACE). For medium size HCC, MWA provided significantly better OS and PFS than TACE for both the entire cohort (OS, $p<0.001$; PFS, $p<0.001$) and the matched cohort (OS, $p=0.015$; PFS, $p<0.001$) [54].

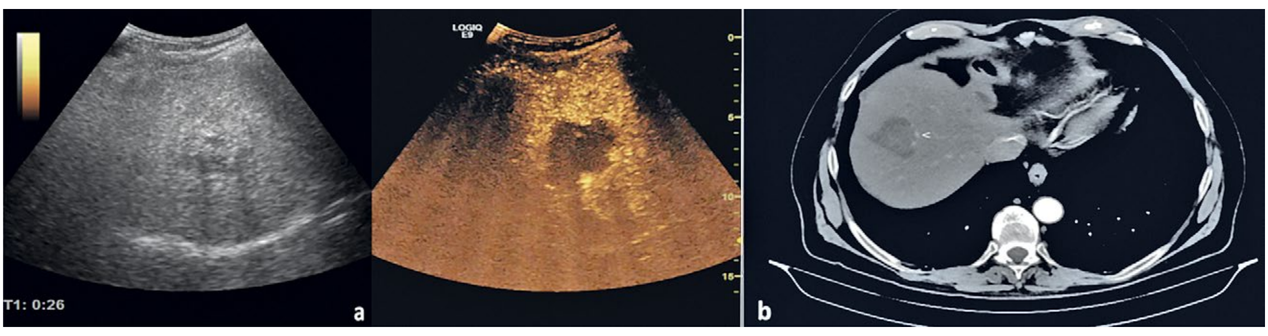

Fig 5. MWA of a 3 cm colorectal cancer metastasis: a) CEUS and b) CECT evaluation 1 month after ablation showed a necrotic area larger than the tumor (46/37mm), with no remaining enhancing areas. (>). Portal branch in the vicinity of the lesion unaffected by ablation.

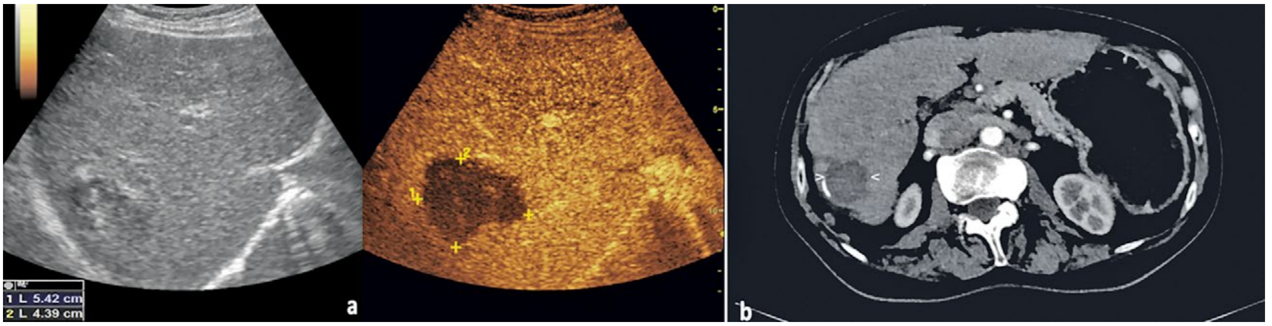

Fig 6. 4.0 cm hepatocellular carcinoma lesion in a cirrhotic liver. a) CEUS performed at the end of ablation showed a 49/46 mm necrotic area with no enhancement at the periphery; b) CT performed 3 months later confirmed that the tumor was completely ablated with no recurrence. The ablation area has shrunk to 39/36 mm.

Another important clinical scenario is the intermediate size HCC, defined as a lesion greater than 5 cm. For these entities MWA is less effective with complete ablation rates of 73-85%, local recurrence rates of 19.2-40.9% and 14.3-21.4% complications rates [55-57]. Overall survival rates are significantly lower than those encountered in medium size HCC [55,56]. Probably one of the most appealing research areas in the field of locoregional treatments for intermediate size HCC is the study of combined treatments. In respect to this, one meta-analysis included 9 studies that evaluated the efficacy of TACE combined with MWA versus TACE alone [58]. The pooled odds ratios for the 1-, 2-, and 3-year survival rates were in favor of TACE+MWA (OR=3.29, 95% CI 2.26–4.79; OR=2.82, 95% CI 2.01–3.95; OR=4.50, 95% CI 2.96–6.86; respectively) [58]. With all this in mind, future randomized control studies to confirm the superiority of combined MWA and TACE in comparison to TACE monotherapy are required.

Altogether, the treatment of small, medium and intermediate size HCC is not always straightforward. One should always keep in mind the facilities and local expe-

Table II. Randomized control clinical trials comparing MWA with RFA in patients with small HCC

Author	No of patients	Complete ablation rate	Local tumor progression	Disease free survival	Overall survival	Complications
Shibata [6]	72	96% for RFA and 89% for MWA, p=0.26	4% vs. 10% at 1 year 12% vs. 24% at 2 years for RFA vs. MWA, p=0.20	Not reported	Not reported	No difference, p=0.67
Chong [47]	93	95.7% for MWA and 97.8% for RFA, p=0.99	Not reported	51.1% vs. 57.7% at 1 year 24.1% vs. 22.7% at 3 years for MWA vs. RFA, p=0.91	42.8% vs. 56.7% at 1 year for MWA vs. RFA, p=0.89	No difference, p=0.99
Kamal [48]	56	Not reported	9.1% vs. 9.1% at 1 year for MWA vs. RFA p=0.93	Not reported	78.6% vs. 82.1% at 1 year for MWA vs. RFA p=1.0	No difference, p=1.0
Yu [49]	203	99.6% for MWA and 98.8% for RFA, p=0.95	11.4% vs. 19.7% at 5 years for MWA vs. RFA, p=0.11	36.7% vs. 24.1% at 5 years for MWA vs. RFA, p=0.07	67.3% vs. 72.7% at 5 years for MWA vs. RFA p=0.91	No difference, p=0.59
Vietti Violi [50]	152	5% for MWA and 4% for RFA, p=0.94	6% vs. 12% at 2 years for MWA vs. RFA, p=0.27	Nor reported	52% vs. 44% at 2 years for MWA vs. RFA, p=0.18	No difference

MWA = microwave ablation; RFA = radiofrequency ablation; No = number; p = level of significance; HCC = hepatocellular carcinoma; vs. = versus

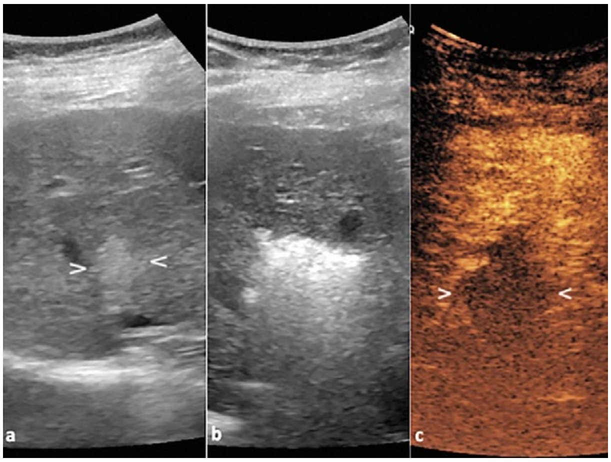

Fig 7. a) 1.8 cm hepatocellular carcinoma nodule close to a hepatic vein (><). b) image during MWA; c) postprocedural CEUS confirmed the complete ablation of the lesion (><)

rience from each center. Our experience with percutaneous thermal ablation in HCC has been published a couple of years ago [59]. However, since then, we have changed our daily practice. For small HCC, if the nodule is less than 2 cm and solitary, we usually perform RFA. If the nodule is between 2-3 cm or in case of multiple nodules, we always prefer MWA, mainly because it is faster and in an overcrowded center, time is important. For medium size HCC we usually do MWA while TACE is reserved for those patients in whom percutaneous approach or ultrasound guidance is not possible. For intermediate size HCC patients, we first do TACE and then MWA if necessary.

MWA in intrahepatic cholangiocarcinoma

For a long time considered a rare clinical entity, the thermal ablation of iCCA has just recently been investigated by scientists. Therefore, the amount of evidence is rather limited at least when compared to HCC or CRCLM. The first study included 15 patients with iCCA. The ablation success rate, the technique effectiveness rate, and the local tumor progression rate were 91.7% (22/24), 87.5% (21/24), and 25% (6/24) respectively. The cumulative overall 6, 12, 24-month survival rates were 78.8%, 60.0%, and 60.0%, respectively [60]. Later on, another study that included 107 patients found out that Child–Pugh class A and less tumor number predict prolonged OS in patients with ICC treated by MWA [61], results which are similar to HCC patients. Nevertheless, MWA can also be used in patients with recurrent iCCA. In one retrospective study, the estimated 5-year OS rates were 23.7% after MWA and 21.8% after surgical resection (SR), while major complication rates in the SR group were higher than that in MWA ($p<0.001$) (SR, 13.8% vs. MWA, 5.3%) [62]. For the time being it is quite difficult to say which category of patients would benefit the most from MWA. It is certainly that surgery remains the first choice of therapy. Therefore, until further evidence and clinical practice guidelines, our best option is to use the criteria from HCC in iCCA as well.

MWA in particularly located lesions

Percutaneous ablation (RFA in particular) was shown to be less effective or associated with more complications in so-called “risky locations”. More power (in case of MWA) equals less heat-sink effect but at the same time, more power might be more dangerous to the surrounding structure. Lesions located near large hepatic vessels (higher risk of partial necrosis or recurrences with RFA) can be treated effectively by MWA (fig 7) [63].

Lesions close to the diaphragm treated with MWA had a higher rate of recurrence and a higher complication rate compared to lesions away from the diaphragm (5.5% vs.0%) but without statistical significance [64]. Lesions located near the gallbladder, hepatic hilum or adjacent to the gastrointestinal tract may be effectively and safely treated with MWA alone and/or in combination with ethanol injection. However, special precautions should be taken (less power setting) and additional techniques (e.g. strict temperature monitoring, artificially ascites or intrabiliary injection of cold saline) should be implemented to avoid damage of those structure [65-67].

Conclusions

MWA in liver cancer: is it a better tool or simply more power? In theory it is a better tool. However, in clinical practice more power is not always better. An evidence based answer for this intriguing question is quite challenging nowadays. However, some educated answers are warranted. For small HCC, MWA is simply more power and not a better tool since several RCT trials found no superiority over other ablative techniques. For CRCLM, there is, for sure, more power, but it is also possible to have a better tool at least when keeping in mind the existing literature, albeit retrospective. Medium and intermediate size nodules (HCC and metastasis) instead, is the place where more power becomes a better tool. Indeed, multi-centered, prospective and randomized controlled trials are still required in order to obtain evidence based answers for these challenging questions.

Conflict of interest: none

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