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Microwave ablation of hepatocellular carcinoma

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Abstract

Although surgical resection is still the optimal treatment option for early-stage hepatocellular carcinoma (HCC) in patients with well compensated cirrhosis,

thermal ablation techniques provide a valid non-surgical treatment alternative, thanks to their minimal invasiveness, excellent tolerability and safety profile, proven efficacy in local disease control, virtually unlimited repeatability and cost-effectiveness. Different energy sources are currently employed in clinics as physical agents for percutaneous or intra-surgical thermal ablation of HCC nodules. Among them, radio-frequency (RF) currents are the most used, while microwave ablations (MWA) are becoming increasingly popular. Starting from the 90s', RF ablation (RFA) rapidly became the standard of care in ablation, especially in the treatment of small HCC nodules; however, RFA exhibits substantial performance limitations in the treatment of large lesions and/or tumors located near major heat sinks. MWA, first introduced in the Far Eastern clinical practice in the 80s', showing promising results but also severe limitations in the controllability of the emitted field and in the high amount of power employed for the ablation of large tumors, resulting in a poor coagulative performance and a relatively high complication rate, nowadays shows better results both in terms of treatment controllability and of overall coagulative performance, thanks to the improvement of technology. In this review we provide an extensive and detailed overview of the key physical and technical aspects of MWA and of the currently available systems, and we want to discuss the most relevant published data on MWA treatments of HCC nodules in regard to clinical results and to the type and rate of complications, both in absolute terms and in comparison with RFA.

Key words: Thermal ablation; Hepatocellular carcinoma; Microwave ablation; Percutaneous microwave ablation; Laparoscopic microwave ablation; Complications

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Core tip: In clinical practice there is an increasing interest in the use of microwave radiations as ablative technique for the treatment of small and intermediate hepatocellular carcinoma nodules. No literature data are

already available about a direct comparison between radiofrequency ablation and microwave ablation; in this review we provide an extensive and detailed overview on the technical and engineering aspects of microwave devices, and we critically expose the most relevant clinical data about the experience in microwave ablation, also by making a comparison with radiofrequency ablation.

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INTRODUCTION

The purpose of thermal ablative treatments is to destroy solid tumors by raising their temperature above a lethal threshold (60 °C for instantaneous coagulative necrosis, 50 °C for prolonged exposure to heat)^[1] through direct energy deposition, which eventually turns into heat within a limited and controlled range of action. Interstitial thermal ablation is currently used for the treatment of a large variety of tumors, including liver^[2], lung^[3], kidney^[4], bone^[5], thyroid^[6] and breast malignancies^[7]. Despite the constantly increasing use of thermal ablation in extra-hepatic applications^[8], the treatment of hepatocellular carcinoma (HCC) nodules remains its most common clinical target. Resection is still the favored treatment option for early-stage HCC in patients with well compensated cirrhosis, but thermal ablation techniques provide a valid non-surgical treatment alternative, thanks to their minimal invasiveness, excellent tolerability and safety profile, proven efficacy in local disease control, virtually unlimited repeatability and cost-effectiveness^[9,10].

Different energy sources are currently employed in clinics as physical agents for percutaneous or intra-surgical thermal ablation of HCC nodules. Among them, radiofrequency (RF) currents (*i.e.*, alternating electric currents in the 400-500 kHz frequency range) are the most used^[11], while microwave (MW) radiations (*i.e.*, non ionizing electromagnetic fields in the 1 GHz frequency range) are becoming increasingly popular^[12]. Other thermal ablation agents - such as laser radiations and high intensity focused ultrasound beams^[13] - are also employed, but apparently provide less flexibility of use and a globally inferior performance in terms of maximum ablation volume attainable per probe and/or per treatment time unit compared to RF ablation (RFA) and to MW ablation (MWA)^[14].

MWA was initially introduced in the Far Eastern clinical practice in the 80s' and 90s'^[15], showing promising potential but also severe limitations in the controllability of the emitted field and in the high amount of power employed for the ablation of large

tumors, resulting in a poor coagulative performance and a relatively high complication rate^[16]. Starting from the 90s', several RFA systems were developed in the United States and in Europe, showing safe, effective and repeatable coagulative performance^[17-19]. RFA rapidly became the gold standard in ablation, especially in the treatment of small HCC nodules, at first flanking and eventually replacing percutaneous ethanol injection (PEI) treatments^[10]. However, RFA exhibits substantial performance limitations in the treatment of large lesions and/or tumors located near major heat sinks^[20,21]: Over the last 5 years, these limitations have been effectively tackled by second and third generation MWA systems, with considerably enhanced characteristics both in terms of treatment controllability and of overall coagulative performance^[22-25].

The purpose of this review is: (1) to provide a brief overview of the key physical and technical aspects of MWA and of the currently available systems; and (2) to gather and discuss the most relevant published data on MWA treatments of HCC nodules in regard to clinical results and to the type and rate of complications, both in absolute terms and in comparison with RFA.

TECHNIQUE

Physical differences between RFA and MWA

RF heating relies on the ohmic dissipation effects related with the circulation of alternating electric currents within target tissues. RF effectiveness depends on the electrical conductivity of the treated tissues, which, in turn, is strongly correlated with their water content^[26]. Dehydration and subsequent carbonisation of tissues occurring at temperatures above 100 °C is, therefore, an intrinsic barrier to further RF heating^[27]. This upper temperature threshold in the active heating zone (*i.e.*, the inner treatment region, where heating is mainly due to absorption and dissipation of the energy delivered by the ablation probe) limits and slows down also the indirect peripheral heating (*i.e.*, the passive heat transfer by mere thermal conduction from the active zone outwards), accounting for the limited coagulative performance of a single probe, the poor response of tissues with low electric conductivity and the high sensitivity to heat sinking effects typical of RFA^[28]. These limitations are overcome altogether when moving from an ohmic (*i.e.*, based on electric power dissipation within a conductive medium) to a dielectric (*i.e.*, not requiring electric currents circulation) heating modality, as in MWA^[29]. Electromagnetic radiation at industrial, scientific and medical (ISM) frequencies (*i.e.*, portions of the electromagnetic spectrum left open for applications in the Industrial, Scientific and Medical fields, in the neighbourhood of 900 MHz, 2.4 GHz and 5.8 GHz, respectively) propagating through a biologic tissue induces a fast switching rotation of the electric dipoles at the atomic or molecular level. Such microscopic charge displacement - not generating any macroscopic electric current - is countered by inter-



Figure 1 Contrast-enhanced computed tomography scan shows, in the region surrounding what was the probe active tip position during the ablation (white arrow), an inner hyper-dense core contrasting with an outer thicker and hypo-dense annulus.

dipolar interactions, producing frictional heat^[30]. The dielectric heating mechanism is particularly effective in polar (*i.e.*, featuring an intrinsic dipolar momentum) molecules, such as water. Therefore, tissues rich in water content are effectively heated by MWs, while tissues poor in water content (which would hinder RF currents circulation) absorb a smaller fraction of the applied MW field energy, allowing further propagation to the next tissue layer^[31]. Tissue carbonisation is not, therefore, an insurmountable barrier to the MW heating process, and temperatures far higher than 100 °C may be reached within the target tumor, allowing enhanced active and passive tissue heating, larger coagulation zones and more effective rejection of heat sinking effects^[32,33]. When high power MWA treatments are performed, several qualitative and quantitative differences are observed in terms of RFA: (1) the hyper-echogenic spot around the probe-active tip detectable on ultrasound-scanning during a thermal ablation procedure forms and expands at a much higher rate, providing a visual feedback of the ongoing vaporization process; (2) post-MWA follow-up scans [either computed tomography (CT) or magnetic resonance imaging (MRI)] usually show, in the region surrounding what was the probe active tip position during the ablation, an inner hyper-dense core contrasting with an outer thicker and hypo-dense annulus, the former being charred tissue (not present on RFA) and the latter being the coagulated but not carbonized zone typical of any thermal ablation modality (Figures 1 and 2); and (3) due to massive water evaporation, MWA treatments induce substantial contraction in target tissues (30%-70% in volume, according to several *ex-vivo* and *in vivo* experimental observations^[34-36]), far more than their RFA counterparts^[37]. If the appropriate shrinkage correction factor is used for accurately calculating the actual ablation volume, the coagulative performance gap between MWA and RFA widens further. Since the amount of tissue contraction relates with the initial water content of the target tissues, one may expect liver tumors of equal size and location, but featuring a different water content (*e.g.*, due to the absence or presence and degree of cirrhosis),

to give different responses to the same thermal treatment, as shrinkage phenomena would not affect the final ablation volume and aspect ratio in the same fashion. This adds to the well-known oven effect, *i.e.*, the higher energy deposition and enhanced heating observed within (pseudo-) capsuled nodules^[38,39], in accounting for different technical and clinical outcome generally observed for the thermal treatments of HCC nodules and of hepatic metastases (typically non capsuled and not on a cirrhotic background), beyond the obvious differences in histology, morphology and vascularization.

All antennas are bipolar by definition: Therefore, MWA differs from monopolar RFA treatments also for the absence of neutral electrodes applied to the patient, intrinsically ruling out the risk of skin burns at the grounding pads site^[40]. Moreover, a MW field at ISM frequencies in the 30-100 W power range propagating across a biological tissue is almost completely absorbed within just a few centimetres. Therefore, long-range non thermal effects induced by MWA probes are excluded and, unlike with RFA, patients with pacemakers or metallic prosthesis are not at risk^[41].

Key components of a MWA system and current implementations

A MWA system typically comprises: (1) a programmable energy source, designed to generate the power required and monitor energy delivery to the patient^[42,43]; (2) an interstitial antenna, usually a semi-rigid coaxial cable emitting MW radiations from its exposed - *i.e.*, uncovered by the outer conductor - distal end, embedded into a needle-like device; and (3) a power transmission line linking the energy source output ports to the antennas: indeed, MWA allows simultaneous multi-probe operation, either in phased-array mode (*i.e.*, exploiting synchronized field emissions in order to obtain the desired interference patterns in the individual radiation diagrams) or asynchronously - with still substantial thermal synergy - obtaining in both cases remarkably increased and more spherical ablation volumes compared to sequential, contiguous, single-probe ablations^[44,45]. On the contrary, RFA allows only switched (*i.e.*, sequential, unparallelled) multi-probe operation due to potential cross-electrode interference, with sensibly/considerably reduced synergistic performance^[46]. The MW generator consists of an oscillator working at the selected frequency of operation - either 915 MHz or 2.45 GHz in commercially available systems - and an amplifier - ranging between 40 W and 190 W output power in current systems - either magnetron-based (*i.e.*, resonating cavities built out of high-powered vacuum tubes, very much like commercial MW ovens) or in solid state (*i.e.*, transistor-based) technology. Magnetrons are less expensive but are considerably heavier (up to 3-5 times) and bulkier (up to 4-5 times in volume) than their solid state counterparts. The frequency of operation affects the antenna design and the type of interaction between the electromagnetic field with biological tissues: The higher the frequency, the shorter the corresponding radiation wavelength and

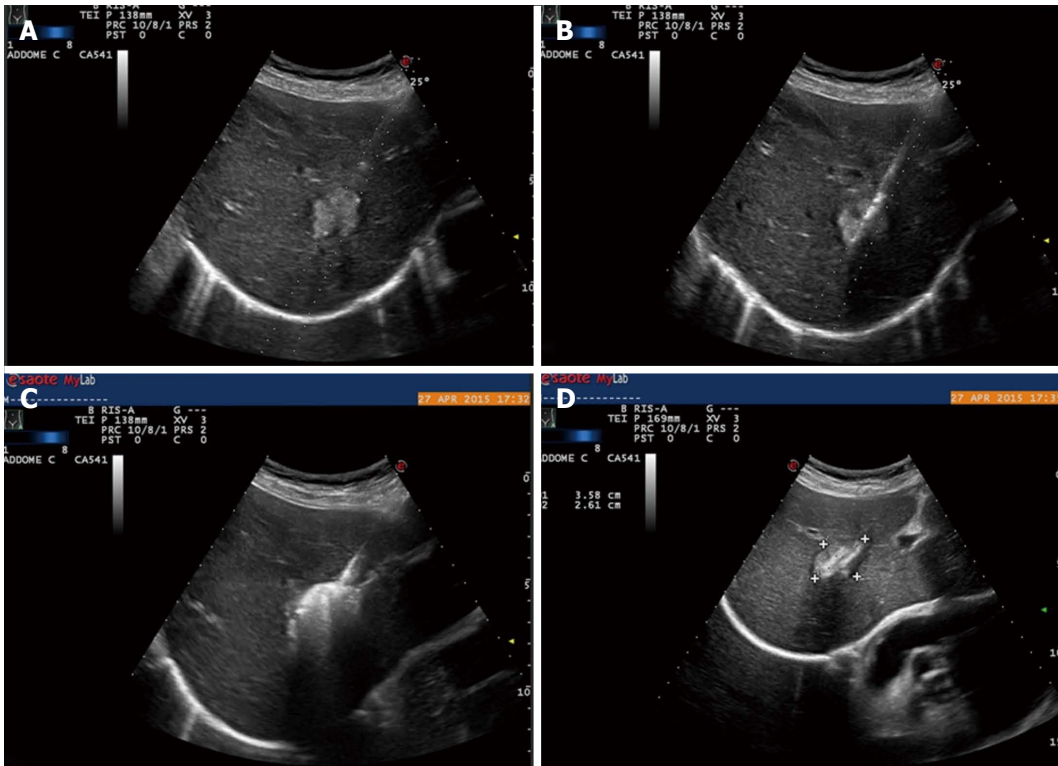


Figure 2 Time-lapse of ultrasound-guided percutaneous microwave ablation of medium-sized hepatocellular carcinoma of the right lobe. A: Ultrasound evaluation before ablation; B: Needle insertion; C: Hyperechoic boiling effect in the ablation area during the procedure; D: One month later ultrasound evaluation: The inner hyperechoic track corresponds to the position of the active probe.

the key lengths in the antenna geometry, the smaller the field penetration into the target tissues, and the higher the MW energy absorption rate by water molecules^[47]. The selection of the operating frequency is, therefore, a trade-off between conflicting requirements, which accounts for the almost identical number of commercially available MWA systems operating in the 915 MHz and in the 2.45 GHz frequency bands. Hoffmann *et al.*^[48] shows a thorough *ex-vivo* comparison of 4 different MWA systems, 2 operating at 915 MHz and 2 at 2.45 GHz, suggesting that the latest generation of internally cooled high power 2.45 GHz systems provides an overall higher performance compared to earlier low power 915 MHz systems (either in single or multi-probe configuration, cooled or not cooled) as for ablation volume, transversal diameter (*i.e.*, the coagulation size perpendicular to the antenna) and sphericity (*i.e.*, the linear or quadratic ratio between the radial and longitudinal axis of the ablation zone). However, the preliminary experience of Liu *et al.*^[49] in the treatment of large HCC nodules (> 4 cm) with both high power, internally cooled 915 MHz antennas (21 patients) and with equivalent 2.45 GHz antennas (19 patients) showed that the former were able to achieve a lower local tumor progression rate (14.3% vs 26.3%) with fewer probe insertions (3.69 ± 0.6 vs 4.71 ± 1.61).

Simo *et al.*^[50] came to opposite conclusions upon a series of 48 patients with 124 hepatic tumors, out of which 72 were treated with a 915 MHz system (average nodule size: 1.7 ± 0.1 cm) and 52 with a 2.45 GHz system (average nodule size: 2.5 ± 0.2 cm): The 2.45

GHz system achieved equivalent, but more predictable and faster ablations using a single antenna.

Internally cooled MWA probes seem to provide large, more spherical and more consistent ablations over their not cooled counterparts^[51]. MW power dissipation along the coaxial cable feeding the distal antenna active tip is very high (up to 15%-30% per meter length at room temperature for operating frequencies around 1 GHz, in cables of approximately 1-mm outer diameter) and puts the probe at severe risk of shaft overheating. Either lowering the radiated power or pulsing MW energy delivery to prevent this risk has proven to excessively reduce the probe performance in terms of the maximum ablation zone achievable and/or the overall treatment duration. Newer generations of MWA probes feature either water^[51] or gas^[52] cooling within the applicator shaft, allowing very high power treatments (even up to 100 W radiated power) and large ablations (up to 5 cm perpendicular to the probe in 10 min, with a single antenna, in *ex-vivo* bovine liver), while not enlarging the probe size (still in the 13 G-17 G range).

The high power attenuation rate also affects the coaxial cables used for transferring MW energy from the generator output port to the interstitial antenna. Low attenuation cables are generally thicker and heavier^[42]: For a reasonable trade-off/compromise between ergonomics and power handling, most MWA manufacturers opt for relatively short (1.5 to 2.5 m) and fairly flexible coaxial cables, exhibiting an overall insertion loss in the 1.5-3.0 dB range (= 30%-50% loss). When setting the

working parameters for a MWA procedure, the majority of currently available systems refer to the nominal MW power at the generator output port. However, the only clinically relevant quantity is the power irradiated into the target tissues, which is significantly lower than the nominal power, and generally differs from system to system even for equal nominal power levels.

Early MWA technologies suffered from the poor predictability of the radiated field pattern and from uncontrolled back-heating effects (often referred to in literature as "comet effect"^[53,54]) due to the reflected waves (*i.e.*, MW radiations not absorbed by the target tissues and back-propagating along the probe shaft outer walls) generated by the inevitable impedance mismatches between the antenna and the tissues. On the one hand, this caused unwanted, deep cauterisation of tissues along the probe shaft, increasing the risk of complications; on the other hand, it reduced the antenna efficiency, dispersing the MW field longitudinally rather than focussing it on the probe distal end. Newer MWA probes have solved this major performance issue, finally enabling a safe delivery of large, spherical and controllable ablations, through a number of design variants, such as monopole or dipole antennas featuring a miniaturized choke (*i.e.*, an impedance transformer superimposed to the coaxial antenna, which traps reflected waves through a destructive interference pattern)^[55,56], or triaxial antennas (*i.e.*, with the main coaxial line encompassed by an outer coaxial line, serving for reflected waves absorption)^[57].

Whichever the antenna design, MWA probes are intrinsically less mechanically robust than RFA electrodes. The latter are monolithic metal tubes, either loaded with multi-tines or with a sharp metal penetration tip integral with the electrode shaft; the former necessarily exhibits a transition from a metallic to a non-metallic (typically, plastic or ceramic) material around the antenna emitting tip. Mechanic breakings of this junction have been reported, especially when targeting hard cirrhotic livers or when hitting the ribs, although recent advancements in the material selection and assembly have substantially mitigated this risk.

Unlike pronged RFA electrodes, straight RFA and MWA applicators are potentially prone to migration from their target. MWA probes exhibit an even higher risk of displacement, due to the heavier and more rigid extension cables. This problem is partly alleviated - only during the probe insertion manoeuvre, but not during the ablation treatment itself - when cryogenic cooling is used, which causes and fixes an ice-ball at the probe tip^[58].

Ultimately, it is worth noting that currently available MWA systems exhibit a great variability in key technical features (antenna design, frequency of operation, use of single or multiple probes, energy delivery algorithms, maximum deliverable power, *etc.*), offering a wider and more heterogeneous technological landscape than RFA, which further contributes to the complexity of an exhaustive and conclusive evaluation of MWA in the interventional oncology scenario, beyond the still limited

clinical experience.

CLINICAL APPLICATION IN HCC

Local ablation is considered the first-line treatment option for patients with early-stage HCC, not suitable for surgical therapy^[59]. For many years, PEI has been the main technique for percutaneous treatment of HCC. However, PEI is occasionally ineffective when there is intra- or extra-capsular invasion, as fibrotic tissues hinder ethanol diffusion^[60]; moreover, the effectiveness of PEI is rapidly impaired with increasing nodule size. Thermal ablative techniques - including RFA, MWA and laser ablation - have shown higher efficacy compared to PEI in the loco-regional treatment of HCC, leading to a better disease control and a survival benefit for lesions larger than 20 mm^[61-65]. RFA is currently the most popular and widely used thermal ablation modality: It provides a reasonable compromise between a number of highly heterogeneous and often conflicting requirements, such as safety, tolerability, efficacy, ease of use and cost-effectiveness. RFA has proven to be particularly effective for HCC lesions smaller than 3 cm, with the best reported rate of complete necrosis approaching 99% of treated lesions, offering a 5-year overall survival (OS) of around 40%^[66]. However, despite the high percentage of necrosis reported by various authors, the recurrence rate is highly variable, from 2% to 39%, depending on the technique used^[67,68]. The main limitations of RFA are related to poor energy propagation into tissues with high electric and thermal impedance, to the intrinsic 100 °C upper temperature threshold that prevents tissue charring, and to the relatively slow tissue heating mechanism that leads to tissue sensitivity to convective heat sinking effects induced by blood or bile circulation in proximity of the ablation target. MWA overcomes all these limitations, due to its dielectric (*i.e.*, not related to electric currents circulation) heating mechanism rather than the ohmic (*i.e.*, based on electric power dissipation within a conductive medium) modality typical of RFA. However, higher heating velocity and efficacy are achieved through a somewhat increased technological complexity and costs compared to RFA, both for generating the required amount of energy and monitoring energy delivery to tissues, and for designing and manufacturing safe, effective and minimally invasive disposable probes suitable for percutaneous use.

Early MWA systems suffered from several technical problems, ranging from inadequate power handling to exceeding probe gauge, poor predictability of the radiated field pattern and uncontrolled back-heating effects. MWA was first used clinically in the Far East. Lu *et al.*^[69] in 2001 reported their results in 107 HCCs ranging in size from 0.8 to 6.4 cm (mean: 2.7 ± 1.5 cm), treated with MWA using a single antenna insertion in 46 nodules ≤ 2 cm, or multiple antennae insertions in 61 nodules > 2 cm. Technical success was achieved in 98% of tumors ≤ 2 cm and in 92% of nodules > 2 cm, while local recurrence was found in 2% of nodules

≤ 2 cm and in 8% of nodules > 2 cm after a follow-up of only 9 mo. Dong *et al.*^[70] reported the long-term results of 339 HCC nodules of a mean tumor size of 4.1 ± 1.9 cm treated with MWA. After a mean follow-up period of 27.9 mo, the 1-, 3- and 5-year cumulative survival rates were 92.70%, 72.85%, and 56.70%, respectively. Even if obtained using first generation, non-optimized MWA systems, these results showed similar effectiveness and survival in the treatment of small HCC nodules compared to RFA. Shibata *et al.*^[71] in 2002 published a study comparing percutaneous RFA with percutaneous MWA. Using a first generation microwave device capable of obtaining a necrotic area of 24 mm \times 16 mm for single needle insertion, the authors showed no statistically significant differences in the rate of complete ablations between patients treated with MWA and patients treated with a latest generation radiofrequency device, while the number of treatment sessions was significantly lower in the RF ablation group. Moreover the study showed no significant difference in the local recurrence rate between the 2 groups even if RF ablation group recurrence rate at 1 and 2 years was 4% and 10%, respectively, while 12% and 24% in the MWA group; the absence of statistical significance might have been due merely to the small number of patients treated.

In 2005, Lu *et al.*^[72] reported the results of a retrospective study comparing percutaneous MWA with RFA. The mean diameter of HCC nodules was 2.5 ± 1.2 cm in MWA group and 2.6 ± 1.2 cm in RFA group. They used a 2.45 GHz microwave generator connected to a 14-gauge electrode with a power output of 10-80 W. A single insertion was applied for tumors of < 2.0 cm diameter, while for > 2.0 cm tumors multiple insertions were employed. RFA was performed by using a 290 KHz-RF generator with a maximum power output of 200 Watts. Complete ablation rates were 98.6% in < 3.0 cm tumors and 83.3% in > 3.0 cm tumors in the MWA group and 98% and 81% in the RFA group: the differences between the 2 groups were not statistically significant. Moreover, they found a non-significant difference in local recurrence of 11.8% for MWA compared to 20.9% for RFA. Complications and long-term survivals were also equivalent in the 2 groups. In opposition to these data, Ohmoto *et al.*^[16] published a retrospective study comparing RFA with MWA: RFA resulted more useful for the treatment of small HCCs, obtaining a lower local recurrence rate and a higher survival rate compared with MWA.

More recent studies with newer microwave system have confirmed the efficacy of MWA in the treatment of HCC. Iannitti *et al.*^[73] published the data from the first clinical trial in the United States using MWA and a 915 MHz generator. The mean single antenna ablation volumes obtained were 10.0 mL (range 7.8-14.0 mL), and clustered antennae ablation volumes were 50.5 mL (range 21.1-146.5 mL). They treated 87 patients (45% ablations were performed open, 7% laparoscopically, and 48% percutaneously) with both HCC and metastatic

disease: they reported a local recurrence at the ablation site in 2.7% of tumors, and an OS rate for all tumor types of 47%, and for HCC of 74% at 19 mo. More recently Qian *et al.*^[74] compared the performance of MWA using a cooled-shaft antenna to the performance of RFA with a cooled electrode both *in vivo* porcine liver tissues and in patients with small HCCs (diameter range: 1.2-3.0 cm). They used a 2450 MHz MW generator (MTC-3) connected to a 14-gauge cooled-shaft antenna with a power output of 100 W (Qinghai Microwave Electronic Institute, Nanjing, China) and a Cool-tip™ RF ablation system (Valleylab, Boulder, CO, United States) connected to a 17-gauge internally cooled needle electrode with a maximum power output of 200 W. In an *in vivo* animal study a single MW ablation induced a significantly increased ablation volume compared to single RF ablation (33.3 ± 15.6 cm³ vs 18.9 ± 9.1 cm³, $P < 0.001$). Similarly, in clinical study the ablation volume of MW ablation, shown on contrast enhanced CT or MRI, was significantly larger than that of RF ablation (109.3 ± 58.3 cm³ vs 48.7 ± 30.5 cm³, $P < 0.001$). The most interesting finding of the study is that all 3 axes of the ablation volume obtained by MWA were greater than those of RFA, confirming that the technological evolution of MW devices obtains more spherical ablation areas. Poggi *et al.*^[23] reported their preliminary results on the feasibility and efficacy of thermal ablation of HCC using a new 2.45 MHz microwave generator delivering energy of 40-100 W through a 14- or 16-G internally cooled, coaxial antenna featuring a miniaturized quarter-wave impedance transformer (mini-choke) for reflected wave confinement (AMICA-GEM, HS Hospital Service SpA, Aprilia, Italy). Complete ablation was achieved in 183 lesions (94.3%), after a mean of 1.03 percutaneous MWA sessions. To estimate the amplitude of the ablation zone obtained with MWA, the authors calculated the difference between the volume of the ablation zone and the baseline volume of each treated lesion: This difference was called Δ volume. To assess how the ablated area was similar to a spherical shape, they calculated the greater and the smaller diameter ratio. For small HCCs they obtained a median Δ volume of 11.2 cm³, representing an increase of almost 100% of the volume of a 3 cm diameter lesion and they achieved nearly spherical ablations areas with a mean diameter ratio of 1.1. Using the same MWA device Di Vece *et al.*^[75] compared the ablation area produced by a single application of MWA with that produced by an internally cooled RFA system in 40 patients with both primary and secondary inoperable liver tumors. They found that long- and short-axis diameters of the ablation areas produced by MWA were significantly greater than those produced by RFA: 48.5 ± 6.7 mm vs 30.9 ± 1.1 mm ($P < 0.0001$) and 38.5 ± 4.6 mm vs 26.8 ± 2.9 mm ($P < 0.0001$), respectively. The results of clinical trials with new generation MW ablation devices seem to confirm the expectations of larger and faster ablation volumes with microwave compared to radiofrequency. Yet it is particularly difficult to compare the different technologies

available, due to the availability of many different MW devices, the constant and rapid technological upgrade and the lack of clinical outcome standardization. In this regard, in a recently published review North *et al*^[76] stated that currently the most powerful prognostic factor for ablation success that can be converted into improved progression-free survival remains the completeness of the initial ablation. However, standards of optimal MWA have not been defined yet. The authors selected 18 clinical studies, published between 2007 and 2013, on MWA of primary and secondary hepatic tumors with a sample size of at least 20 patients and a follow-up period of at least 6 mo. For each study they evaluated the proposed definitions for the effectiveness of the procedure, local recurrence, distant recurrence, morbidity, mortality and OS. Ablation success turned out to be the highest quality reporting standard while local recurrence remained highly variable, without a clearly defined distance from the initial target ablated lesion.

Given that nine microwave systems are currently available on the market with differences in the frequency used, the power supplied, the diameter of the probe, the availability of a probe-cooling system or a miniaturized device to decrease MW reflection^[77], standardization of clinical criteria for reporting MWA outcomes is pivotal to compare the different methods.

The upgrade of MW devices enabled the new frontier of percutaneous thermal ablation to treat medium and large HCCs. Preclinical data support this hypothesis. Brace *et al*^[57] and Strickland *et al*^[78] obtained, in an *in vivo* porcine liver model, ablation zones with mean diameters up to 6.5 cm and ranging from 3 to 6 cm respectively. Early clinical trials also reported promising results of MWA in treating hepatic tumors > 3 cm. Yin *et al*^[79] treated with percutaneous RFA or MWA 109 patients with HCCs measuring between 3.0 cm and 7.0 cm. They reported a complete ablation of 92.6%, a local recurrence in 22% of patients and a 3-year survival rate of 30.9% and they found no significant difference in the complete ablation rate between RFA and MWA. Kuang *et al*^[80] reported a complete ablation rate of 91% of tumour measuring 3-5 cm. Likewise Poggi *et al*^[23] obtained 90% of complete ablation in 49 HCC measuring 3.1-5.0 cm. More recently Sun *et al*^[81] reported retrospective data of patients with a single medium-sized HCC who underwent percutaneous MWA. The OS rates were 89%, 74%, 60% while cumulative recurrence-free survival was 51%, 36% and 27% at 1, 2, and 3 years respectively. Patient age and tumor diameter were independent factors associated with local tumor recurrence while serum albumin level and the appearance of a new lesion were independently associated with OS. Therefore, despite the high percentage of complete ablation reported, the recurrence rate for HCCs larger than 3 cm is still quite high and is often directly related with the size of the lesion. To date few studies have evaluated the role of TACE combined with MWA in the treatment of medium and large HCC. TACE can reduce blood flow, creates ischemia, increases the chemotherapeutic agent local effect on tumor cells and increases the sensitivity of neoplastic cells to

hyperthermia, resulting in synergy with the thermal ablation effect. Liu *et al*^[82] compared TACE followed by MWA and TACE alone in 34 consecutive patients with large unresectable HCC (> 5 cm). They found that the mean survival rates were significantly higher in the former than in the latter group of patients (11.6 mo vs 6.1 mo). Poggi *et al*^[83] reported their preliminary results on feasibility and effectiveness of the combination of MWA and TACE in 36 unresectable HCCs > 3 cm (size 3-11 cm, mean 4.78 cm), achieving a technique effectiveness in 83.3% of the lesions. Complete ablation was obtained in 100% of intermediate-sized HCCs. Local tumor progression was found in 3 lesions (8%) 9 mo after the procedures.

MWA is also performed through a laparoscopic approach. Hepatic lesions close to the gastrointestinal tract, gallbladder and bile ducts can be safely treated in this way. Laparoscopic MWA can also be a viable therapeutic option for patients unsuitable for hepatic resection due to impaired liver function or concurrent comorbidities. In a prospective cohort study, Cillo *et al*^[84] treated 50 HCC in 42 patient with laparoscopic MWA. They obtained a complete ablation rate of 100% in < 3.0 cm tumors and of 80% in > 3.0 cm tumors. The two-year survival rate was 81% and the two-year recurrence rate was 55% with no peri-operative mortality and a median post-operative hospital stay of three days. Cillo *et al*^[85] have recently described an innovative use of laparoscopic MWA in 2 patients affected by multiple liver metastases and a large HCC, respectively. The Authors developed a novel variation to the staged hepatectomy in which laparoscopic portal vein ligation was associated to laparoscopic MWA on the future hepatic transection plane. This modified procedure allows a complete hypertrophy of the non-occluded future liver remnant preventing the development of interlobar portoportal shunts that impair the remnant liver hypertrophy^[85,86]. Image-guided tumor ablation can also have a role in HCC "bridge" to orthotopic liver transplantation (OLT), reducing the risk of list drop-out and in HCC "down-staging" to fit patients into OLT criteria. Particularly, Zanusi *et al*^[87] reported that out of 6 cases of HCC patients which underwent laparoscopic MWA before OLT, 4 had received it as a bridge to OLT to prevent neoplastic disease diffusion, and 2 as HCC down-staging to fit into OLT criteria. In all 6 cases no peritoneal or nodal HCC macroscopic and microscopic diffusion was observed intraoperatively at the time of laparotomy for OLT. Gringeri *et al*^[88] reported 1 case of laparoscopic MWA of a single small HCC on liver graft. A complete ablation of the tumor was achieved and after 24 mo the patient was still free from local or distant recurrence, showing that MWA can be safely and effectively applied to treat HCC in liver transplant recipients.

COMPLICATIONS

According to the standardization of terminology and reporting criteria for image-guided tumor ablation by Goldberg *et al*^[77], a major complication is an event that

Table 1 Major complications of microwave ablation in literature *n* (%)

	Liang <i>et al</i> ^[91]	Bertot <i>et al</i> ^[90]	Livraghi <i>et al</i> ^[92]	Ding <i>et al</i> ^[89]	Ding <i>et al</i> ^[89]	Lahat <i>et al</i> ^[93]
Major complications	2.6%	4.6%	2.9%	3.1%	2.7%	4.6%
Intra-peritoneal bleeding	1 (0.03)	NA	2 (0.3)	2 (0.31)	NA	NA
Portal vein thrombosis	NA	NA	NA	0.15 (1/654)	NA	NA
Bile leakage	NA	NA	NA	2 (0.31)	NA	NA
Biloma	1 (3)		NA	1 (0.15)		
Bile duct injury	1 (3)		1 (0.1)	1 (0.15)		
Obstructive jaundice	NA		1 (0.1)	NA		
Liver disfunction	NA	NA	3 (0.4)	4 (0.61)	2 (2)	NA
Liver abscess	4 (13)	NA	1 (0.1)	1 (0.15)	NA	NA
Gastrointestinal perforation	2 (7)	NA	2 (0.3)	NA	NA	NA
Haemothorax	NA	NA	1 (0.1)	1 (0.15)	NA	NA
Intractable pleural effusion	NA	NA	3 (0.4)	5 (0.76)	1 (0.8)	NA
Right diaphragmatic hernia	NA	NA	NA	2 (0.31)	1 (0.8)	NA
Pneumothorax	NA	NA	1 (0.1)	NA	NA	NA
Tumor seeding	5 (16)	NA	1 (0.1)	NA	NA	NA

NA: Data not available.

leads to substantial morbidity and disability, increasing the level of care, or results in hospital admission or substantially lengthened hospital stay. All other events are considered minor complications.

As stated by literature data, no statistically significant difference in mortality rates, neither major nor minor complications between the RFA and MWA is detected^[89]; in particular, microwave ablation-associated mortality ranges from 0% to 0.36%, showing that it can be considered a safe technique for the treatment of liver tumors^[90-93]. With respect to major complications, data from meta-analysis of comparative studies between RFA and MWA shows that there are not significant differences between the 2 ablative techniques. However, it should be pointed out that there are still few studies focused on a large number of patients, and data are collected both from randomized and observational studies: These bias are still too strong to making a solid conclusion^[77].

Major complications can be divided in vascular, biliary, mechanical, infectious and functional.

Vascular complication includes bleeding and thrombosis; bleeding complications (intra-peritoneal bleeding, intra-hepatic haematomas) are mainly due to injury of blood vessels during ablation caused by mechanical trauma with the needle or by of an indirect thermal damage by tissue coagulation and necrosis. To avoid these complications, patients with severe coagulation dysfunctions should not be treated. Moreover, the complete cauterization of the needle track can reduce the risk of major bleeding.

Portal thrombosis that can lead to portal hypertension and liver failure, can occur when the ablated area is close to the portal vein, where blood flow is often already slow due to cirrhotic disease: this condition reduces the "heat-sink" effect that normally protects the vessel wall, through the cooling property of the blood flow.

Bile duct injuries, as bile leakage, biloma formation and obstructive jaundice, mostly occur while treating lesions adjacent to the bile ducts. While bile leakage

is often transient, biloma has a high risk of secondary infection, and it should be promptly treated with catheter drainage and antibiotics. Obstructive jaundice can be caused by biliary injury at the porta hepatis and should be treated with stent placement.

Perforation of the gastrointestinal wall related to thermal injury can occur while treating lesions adjacent to a gastrointestinal lumen (*i.e.*, subcapsular lesions or nodules of the left lobe), more frequently with a percutaneous approach in patients with a history of abdominal surgery, intestinal adhesions and anatomical variations.

MWA of lesions adjacent to diaphragm can cause thermal damage, resulting in pleural effusion or, rarely, in diaphragmatic hernia. Moreover, through a percutaneous intercostal approach, the damage to the intercostal or diaphragmatic vessels during needle insertion could cause haemothorax.

Liver abscess is uncommon, but it can occur in high-risk patients, such as patients with diabetes, post-biliary-enteric anastomosis, duodenal sphincterotomy and biliary stent placement. In these categories of patients, a prophylactic antibiotic therapy should be considered to prevent infections.

Tumor seeding can occur when the lesion is near the liver surface, more often when a diagnostic biopsy is performed before the ablation. A complete needle track ablation with cauterization when the antenna is withdrawn may prevent tumor implantation.

Liver failure is more common after the ablation treatment of patients with Child-Pugh Score of B or above, and with multiple lesions.

Table 1 summarizes data of these complications found in literature.

Minor complications include asymptomatic pleural effusion not requiring drainage, liver decompensation requiring only home therapy, subcapsular hematoma, skin burns, slight thickening of the gallbladder wall, asymptomatic portal thrombosis, hemobilia, arterial-portal shunt. Periprocedural pain and fever are con-

sidered symptoms of post-ablation syndrome, and are related to the side of lesion (subcapsular or peri-hilar) and the amount of tissue necrosis.

To reduce the percentage of major complications, the selection of patients and the choice of either percutaneous or surgical approach are fundamental; high-risk patients for infections, coagulation disorders, previous abdominal surgery should be evaluated to establish the right cost-benefit rate of the procedure. Gastrointestinal perforation or thermal biliary injury should be avoided with the use of thermocouples to check the temperature, as to timely interrupt the procedure. Finally, the learning curve of the physicians and the improvement of MW antenna technology have considerably reduced complications due to thermal damage.

CONCLUSION

In conclusion, the recent improvement in ablation microwave technology has significantly improved clinical efficacy of this treatment. The devices of the latest generation allow to obtain faster and larger ablation areas than RFA. However, large-scale randomized prospective clinical trials comparing MWA and RFA are needed to determine the future clinical role of MWA.

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