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Microwave ablation of renal tumors: state of the art and development trends

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Abstract In the last decades an increased incidence of new renal tumor cases has been for clinically localized, small tumors <2.0 cm. This trend for small, low-stage tumors is the reflection of earlier diagnosis primarily as a result of the widespread and increasing use of non-invasive abdominal imaging modalities such as ultrasound, computerized tomography, and magnetic resonance imaging. Renal tumors are often diagnosed in elderly patients, with medical comorbidities whom the risk of surgical complications may pose a greater risk of death than that due to the tumor itself. In these patients, unsuitable for surgical approach, thermal ablation represents a valid alternative to traditional surgery. Thermal ablation is a less invasive, less morbid treatment option thanks to reduced blood loss, lower incidence of complications during the procedure and a less long convalescence. At present, the most widely used thermal ablative techniques are cryoablation, radiofrequency ablation and microwave ablation (MWA). MWA offers many benefits of other ablation techniques and offers several other advantages: higher intratumoral temperatures, larger tumor ablation volumes, faster ablation times, the ability to use multiple applicators simultaneously, optimal heating of cystic masses and tumors close to the vessels and less procedural pain. This review aims to provide the reader with an overview about the state of the art of microwave ablation for renal tumors and to cast a glance on the new development trends of this technique.

Keywords Microwave · Renal cell cancer · Percutaneous ablation · Nephrectomy

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Introduction

For several decades, the most pronounced increase in the incidence of new renal cell carcinoma cases has been for clinically localized, small tumors <2.0 cm. This trend for small, low-stage tumors has been proposed to be a reflection of earlier diagnosis primarily as a result of the widespread and increasing use of non-invasive abdominal imaging modalities such as ultrasound (US), computerized tomography (CT), and magnetic resonance imaging (MRI). This increased utilization of modern imaging techniques has unquestionably altered the clinical landscape of solid renal tumors. Generally, the majority of all renal tumors will be being detected incidentally and the most of them are small (<4 cm, clinically stage T1a), low grade, with a slow growth rate (0.35 cm/year), a low metastatic potential [1]. Small renal tumors are often diagnosed in elderly patients, older than 65 years, with medical comorbidities whom the risk of surgical complications may pose a greater risk of death than that due to the tumor itself, at least in short term [2, 3]. Furthermore, the high risk of end-stage renal disease after a radical nephrectomy than with a nephron-sparing surgery has encouraged the development of minimally invasive approach such as ablative modalities for selected patients [1, 4, 5]. The continuous improvements and innovations of thermal ablative modalities, as refining probe design and real-time imaging capabilities, allow to renew the great interest in these techniques, in particular for the treatment of T1 renal malignancies [1]. Thermal ablation is a less invasive, less morbid treatment option thanks to reduced blood loss, lower incidence of complications during the procedure and a less long convalescence compared with traditional surgical approach. Retrospective non-randomized studies have demonstrated good efficacy in oncologic short and intermediate term, however still be inferior than partial nephrectomy (PN) [6]. Finally, ablation has some advantages in terms of cost compared to open partial and radical nephrectomy [7]. Currently, European guidelines recommend the use of ablative techniques in patients with small renal masses, with comorbidities unfit for surgery, and in patients with impaired renal function or with only a functional kidney [8]. At present, the most widely used thermal ablative techniques are cryoablation (CA), radiofrequency ablation (RFA) and microwave ablation (MWA) [9]. CA offers the same advantages of minimally invasive surgery with a lower rate of late complications than partial nephrectomy, respectively, 2.2 versus 16.3 % [10]. Cryoablation, using tissue temperatures to between −20 and −50 °C, causes ice formation within the extracellular space leading cellular dehydration, cell membrane rupture, and finally tissue ischemia [11]. Differently, RFA utilizes alternating electrical currents to induce thermal injury to a lesion [12]. Advantages of RFA include its minimally invasiveness, reduced pain, and a shorter hospitalization, among disadvantages we found the lack of long-term clinical data, heat sink effect and charring, leading to decreased ablation zones [12]. RFA remains the most widely used ablative technique worldwide for renal tumor [13]. Otherwise, microwave ablation is based on electromagnetic waves emitted by a microwave generator [14]. Electromagnetic microwaves agitate water molecules of the tissue, causing agitation and so heat up to cellular death by coagulation necrosis [14]. MWA offers many benefits of other ablation techniques, in particular, RFA, and offers several other advantages, including higher intratumoral temperatures, larger tumor ablation volumes, faster ablation times (maximum 10 min), the ability to use multiple applicators simultaneously, optimal heating of cystic masses and tumors close to the vessels, and less procedural pain [14]. Thanks to its better convection profile, microwave energy allows a more uniform cell kill in the ablation zone tending to, thanks to new developments of antenna's design, a better roundness [14]. MWA is a relative new technique and it is starting to emerge in the literature now; however, only few studies have documented its efficacy and long-term outcomes and much about MWA still remains unknown, especially in comparison to other ablative methods [9].

The following sections aim to provide the reader with an overview about the state of the art of microwave ablation for renal tumors and to cast a glance on the new development trends.

Microwave energy: physic principles

Microwave radiation lies between infrared and radiowave radiation in the portion of the electromagnetic spectrum between 300 MHz and 30 GHz, and including those most commonly used for microwave ablation procedures: 915 MHz and 2.45 GHz [14, 15]. Heating of the tissue is based on agitation of water molecules inducing cellular death via coagulation necrosis; the electrical charge on the water molecule flips back and forth 2–5 billion times a second, depending on the frequency of the microwave energy [14]. Microwave energy is distinct from other energies for thermal therapy in a number of ways. The most important feature is that microwaves propagate through all types of tissues and non-metallic materials including water vapor, dehydrated, charred and desiccated tissues created during the ablative process [16]. Dielectric properties of biological tissues, as permittivity and conductivity, allow the transmission and absorption of the electromagnetic energy. However, these properties depend primarily on the type of tissue, water content, temperature and the frequency of the applied field [14]. In most tissues, the dielectric properties can be considered isotropic and can change substantially during treatment, but microwave propagation is not hindered by these changes [14]. Microwaves may also, offering more direct heating than other ablation energies, be more potent in organs with high blood perfusion or near larger vessel thanks to reduced heat sink effect [14].

Microwave ablation in kidney: experimental studies

Some preclinical studies have been published to evaluate morphology, size, and histologic features of the ablated areas in animal renal cancer. The unique physiology of the kidney has important implications in ablation planning. The kidney is a highly perfused organ with approximately four times the perfusion of the liver [17]. This difference in perfusion significantly alters the results of the bio-heat equation, which estimates the amount of energy that can be deposited in tissue, by increasing the energy lost [18]. Convection of heat due to overall perfusion and to perfusion by large central vessels can also contribute to a heat sink effect that may result in under treatment of renal tumors [18].

Experimental comparison to other thermal ablative techniques

Microwave and radiofrequency (RF) ablation are two techniques that generate heat and induce cellular death by coagulative necrosis in two different ways [18]. Heat in RF ablation is generated by converting electrical current into thermal energy by the creation of a closed-loop circuit [19]. Application of current results in marked agitation of the ions present in the tissues that immediately surround the electrode with resultant frictional heat and thermal damage to the surrounding tissues [12]. The extent of thermal damage is dependent on the tissue temperature generated and the duration of heating [19]. For adequate destruction of tumor tissue, the entire volume of an index tumor must be treated with temperatures that are above the threshold for cell death, typically 50–60 °C [19]. RFA is a reliable and safe ablation technique that has been used successfully for years in the treatment of small renal cell cancer (RCC) [1, 20]. Zagoria et al. [20], with a study with follow-up data exceeding 5 years, strongly support the durable efficacy of RFA for treatment of RCC. However, it has some drawbacks: size and sinus extension of the tumor to be treated can increase the risk of technical failure, difficulty to completely ablate irregular-shape tumors, major influence by heat sink effect by blood circulation, depends on tissue impedance [21].

Cryoablation has been used in the treatment of skin, breast, liver, brain, and bone tumors during the past four decades [1, 9, 19]. During cryoablation, the freezing and thawing process destroys cell membranes and organelles due to the mechanical stresses associated with phase change and ice formation [1, 9, 19]. Ice crystals denature the intracellular proteins, break up cell structures and modify cell membrane function [9, 19]. Subsequently after increasing the intracellular osmotic pressure, an inflow of water occurs during thawing resulting in tumor cells bursting [9, 19].

Cryoablation has the major advantage of real-time monitoring of the ablation zone by direct visualization of the physical changes caused by freezing, whether using CT, MRI or US [9, 19].

There is no denaturing of protein, as in hyperthermic treatment, in the architecture of supporting tissues, particularly urothelial tissue, which is therefore conserve [1, 9]. The disadvantages consist in pain or paresthesia at the probe insertion site and the potential systemic side effects associated with this use [1, 9].

During microwave ablation, tissue heating is induced by extremely fast realigning dipoles generated by an oscillating electric field [18]. Water molecules are dipoles with unequal electric charge distribution, they attempt to continuously reorient at the same rate in the microwave's oscillating electric field [14, 18]. Therefore, temperatures clearly rise due to water molecules friction beyond 60 °C, sufficient to create irreversible cell damage, as demonstrated by Sommer et al. [22] in porcine kidneys.

The benefits expected from microwave ablation compromise a more rapid and homogeneous ablation, lower sensitivity to local variation in tissue physical properties (electrical and thermal conductivity), less influenced by heat sink effects of blood circulation as demonstrated by Sommer et al. and because of the steeper temperature gradient induced in tissues resulting in a more predictable and reliable coagulative performance [14, 22]. Studies conducted in rabbits that previously had tumor implantation show that percutaneous microwave ablation can achieve results similar to those of open nephrectomy having thus the potential of being a nephron salvaging treatment for small renal tumors [23]. However, microwaves have some limitations in particular in relation to the design of the antenna that does not allow a complete control of the lesion during the ablation with an oval shape of coagulation [24, 25].

Microwave ablation in kidney: clinical studies

In the literature, it is possible to find clinical studies on MWA for the treatment of RCC in humans since the last decade. First in Japan, MW technology has been applied to partial nephrectomy to reduce intraoperative bleeding: in this study, a MW tissue coagulator is used not for tumor ablation but is applied peripherally in the healthy parenchyma surrounding the cancer with circumferential punctures producing coagulation of a conical-shaped portion of tissue [26]. Subsequently, a wedge resection was performed [26].

Phase I clinical studies

Clark et al. [27] demonstrated the first phase I study, the feasibility of MWTA in ten patients with large kidney tumors before radical nephrectomy. The intent of the study was to test the performance characteristics and safety of a microwave ablation system in the management of renal lesions, so were not placed limitations on the size of the renal lesion to treat [27]. The results of this phase 1 study

Table 1 Summary of phase I clinical study

References	No. of patients	Tumor diameter cm (mean size)	Biopsy of the surrounding parenchyma	MW energy (ablation system)	Postablation treatment	Histopathology	Type of complications
Clark et al. [27]	10	8.4 (3.9–11)	Yes	60 W for 10 min (VivaWave, Vivant Medical)	Nephrectomy	Extensive coagulative necrosis	Malfunction of one probe; no bleeding
Muto et al. [28]	10	2.75 (1.3–4.2)	Yes	45 W for 14.1 min (4–30 min) (Evident Valleylab generator, Covidien)	Enucleation	Uniform cell death in the ablation area	No bleeding
Bartoletti et al. [23]	14	4.7 (4.0–9.2)	Yes	50 W for 5 min (HS Amica, Hospital Services)	Nephrectomy	No residual vital tumor cells inside the MW-induced lesions	2/14 intraoperative bleeding, not related to the MWA tumor treatment

show that microwave thermal energy can be used to generate reproducible large ablative lesions in 10-min treatment in solid RCC [27]. Also it was demonstrated, unlike radiofrequency ablation, that microwave ablation can be performed with multiple probes simultaneously, up to three probes, allowing an easily management of large tumors [27]. In Clark's study, the mean ablative lesion size with a three-probe array was 5.7 × 4.7 × 3.8 cm [27]. In 2011, an Italian group demonstrated that with MWA provides to a extensive coagulative necrosis without skipped tumor areas, sparing the surrounding healthy parenchyma. Histochemical examinations revealed no cell death beyond the ablation area: this is particularly important in renal ablation to preserve healthy parenchyma and, above all, vascular and caliceal structures [28]. In the following year, Bartoletti et al. [23] published another phase I study with the aim to determine the tolerability of the Amica-probe in vivo in patients with solid renal masses and the effects of heating on renal tumors and normal renal parenchyma. No local bleeding after treatment was reported showing the reduced risk of bleeding of MWA [23]. The results of these studies described have been summarized in Table 1.

Percutaneous MWA of renal tumors: clinical series

After clinical phase I studies, since the last years were published some works about personal experience in vivo for the treatment of small RCC with MWA. Liang et al. [29] demonstrated, in 12 patients with small RCC, that MWA ultrasound-guided was a safe and effective technique in selected patients (Table 2). As in the previous study, Carrafiello et al. [30] enrolled 12 patients in a treatment group, in which percutaneous MWA of small RCCs was performed under contrast-enhanced ultrasound guidance. Technical success rate was 100 %, in all cases the antenna was correctly placed in the lesion; clinical effectiveness was 100 %, no patient showed a recurrence on imaging at follow-up (Table 2) [30]. Yu et al. [31] published in 2011 a retrospectively review intermediate-term clinical outcomes after microwave ablation (MWA) of renal cell carcinoma (RCC) demonstrating, according to Carrafiello et al. a very high technical effectiveness (98 %), with a cancer-specific survival rate of 100 % at 1- and 2-year and of 97.8 % at 3-year follow-up (Table 2). Therefore, the study confirms the safety and efficacy of MWA [31]. In contrast to the results shown by the authors mentioned above, Castle et al. [32] reported poor oncologic outcomes and significant complication rates in a series of ten patients with tumor diameter size ranging from 2.0 to 5.5 cm treated by laparoscopic- or CT-guided percutaneous MWA, recording in their personal series a significant recurrence rate, defined by persistent enhancement at follow-up, (38 %) with a intraoperative and postoperative

Table 2 Summary of clinical series of renal tumors percutaneous MWA

References	No. of patients (mean age, years)	Tumor diameter (cm)	MW energy (ablation system)	No. of antennae	Imaging	Type of complications	Follow-up (months)	Residual tumor	Tumor recurrence on imaging during follow-up
Liang et al. [29]	12 (57)	2.5 (1.3–3.8)	50 W for 8 min (KY2000, Kangyou Medical Instruments)	1 (lesions <2 cm) 2 (lesions >2 cm)	US	No major complications; 8/12 mild pain (grade 1) at the puncture site, requiring no analgesic medication	11 (4–20)	No	No
Carrafiello et al. [30]	12 (79)	2.0 (1.7–2.9)	45 W for 10 min (Vivant Medica, Mountain View)	1	US CBCT	No major complications; 1/12 small hematoma, requiring no specific therapy	6 (3–14)	No	No
Castle et al. [32]	10 (69.8)	3.65 (2.0–5.5)	45 W for 10 min (Valleylab Evident, Covidien)	1	CT	2 perioperative complications in 2 patients; 9 postoperative complications in 4 patients (6 Clavien grade I, 3 Clavien grade IIIb)	17.9 (14–24)	No	38 %
Yu et al. [31]	46 (63.9)	3.0 ± 1.5 (0.6–7.7)	50 W for 10 min (KY2000, Kangyou Medical Instruments)	1 (lesions <2 cm) 2 (lesions >2 cm)	US CT MRI	No major complications; 1/46 hematoma, controlled with intravenous haemostatic therapy	20.1 (6–42)	1 case of residual tumor	No

complication rate of 20 and 40 %, respectively (Table 2). Rational explanations for such similar discrepancies could be easily found by evaluating either the absence of a standardized and reproducible method for microwave administration or the adequate selection of patients.

Microwave ablation versus surgical approach for small renal tumors

Partial nephrectomy (PN) or nephron-sparing surgery has gained popularity for the management of renal lesions 4 cm or less in diameter, because local tumor resection without removing the entire kidney has proved effective [13]. However, open partial nephrectomy (OPN) and laparoscopic partial nephrectomy (LPN) are technically challenging and they may have serious complications, such as excessive blood loss and urinary fistula [13]. Guan et al. [33] in a prospective randomized study were compared PN to MWA of intermediate-term outcomes of patients with small renal. Kaplan–Meier estimates of overall local recurrence-free survival at 3 years were 91.3 % for microwave ablation and 96.0 % for PN ($p = 0.5414$); the respective numbers for renal cell carcinomas were 90.4 and 96.6 % ($p = 0.4650$) [33]. Therefore, this intermediate analysis showed that microwave ablation provides favorable results compared to PN [33]. In a recent retrospective study was also compared MWA to open radial nephrectomy (ORN) in the treatment of RCC: although the overall survival after MWA was lower than that after ORN ($p = 0.002$), RCC-related survival was comparable to ORN ($p = 0.78$) [34]. Estimated 5-year overall survival rates were 67.3 % after MWA and 97.8 % after ORN; for RCC-related survival, estimated 5-year rates were 97.1 % after MWA and 97.8 % after ORN [34]. There was one local tumor recurrence 32 months after MWA and none after ORN. Major complication rates were comparable ($p = 0.81$) between the two techniques (MWA 2.5 % vs. ORN 3.1 %) [34].

Microwave ablation beyond treatment of small renal cell carcinoma: different applications

Thermo-ablation with microwave may also be used for the treatment other renal lesions such as cystic Bosniak lesion and angiomyolipoma. Bosniak III or IV cystic lesions may carry a particular risk for malignancy even if some of these lesions (particularly Bosniak III lesions) are proven to be benign after biopsy or surgery [35]. Park et al. [36] proposed image-guided percutaneous RFA as a valuable alternative for cystic lesions unsuitable for surgery with excellent results. Carrafiello et al. [35] treated seven cystic renal lesions with a total applied energy of 45 W for an ablation time of 10 min and reported a technical success,

Table 3 Summary of published series about different applications of renal MWA

References	Tumors treated	No. of lesions/patients (mean age, years)	Tumor diameter	MW energy (ablation system)	No. of total sessions	Clinical effectiveness	Follow-up (months)	Complications
Lin (2014)	Renal cell carcinoma in patients with a solitary kidney	16/14 (51.2)	1.0–8.4 cm	50 W for 10 min (KY2000, Kangyou Medical Instruments)	22	92 % (13/14)	9.5	No major complications; minor complications: subcapsular hematoma, mild pain at the ablation site, hematuria
Carrafiello et al. [35]	Cystic renal lesions Bosniak III or IV	7/6 (74)	13.8–27 mm	45 W for 10 min (Valleylab Evident, Covidien)	7	100 % (7/7)	24	No major complications; minor complications: pain at needle insertion site, nausea, vomiting, fever
Zhi-yu et al. [37]	Sporadic renal angiomyolipoma	19/14 (49.2)	0.8–6.1 cm	45 W or 50 W for 300–1,140 s (KY2000, Kangyou Medical Instruments)	21	78 % (15/19)	10	1/14 fistula of the descending colon; 1/14 local infection around the ablation zone; minor complications: mild-to-moderate pain, fever, subcapsular bleeding

defined as the correct positioning of the antenna into the lesion, of 100 %; a technical effectiveness, as the absence of thermo-ablative residues on CECT performed at 1 month after MWA treatment, of 100 %; and no major complications were recorded. This preliminary experience shows a potential role of US/CT-guided percutaneous MWA in treating Bosniak category III or IV cystic renal lesions, as a safe approach to treat selected patients unsuitable for surgery [35].

As the most common benign renal mesenchymal neoplasm, renal angiomyolipoma (AML) originates from perivascular epithelioid cells and contain a variable proportion of adipose tissue, smooth muscle, and blood vessels [37]. Large renal AML (diameter >3.5 cm) may cause symptoms such flank pain, hematuria, hemorrhage [37]. It is generally agreed that asymptomatic AMLs >4 cm and symptomatic lesions of any size should be treated [37]. For benign AMLS, renal preserving treatment such as selective angioembolization and nephron-sparing surgery are preferred [37]. Thermo-ablation as RFA has also been reported to be a promising treatment for AMLs also in patients with a solitary kidney [38, 39]. Considering the several theoretical advantages of microwave with respect to radiofrequencies, Zhi-yu et al. [37] have proposed a study to evaluate the safety and efficacy of MWA for the treatment of sporadic renal AML. In 19 lesions treated they found a technical effectiveness of 78.9 % with no AML recurrence observed during the follow-up (median, 10 months) [37]. Complications were recorded in 14.2 % of patients: a fistula of the descending colon in one patient was observed, and local infection around the ablation zone was found in another patient [37]. In conclusion, MWA can provide an effective treatment also for AML with an acceptable percentage of complications [37] (Table 3).

New development trends in MWA

To obtain an ablation as complete as possible, it is necessary to improve the ablation technique and also refining imaging guidance. Currently, the development of new technologies in the field of MWA heads in these two directions: improvements in imaging and in the technique of ablation. Imaging guidance improvement currently relies on the use of cone beam CT (CBCT) which, thanks to a flat panel detector and a C-arm gantry, allows to a pathway guidance, to a prediction of ablation area, an immediate imaging control and an evaluation of ablation area, allowing an immediate complication of problem solving. MWA has some technical limitations, which cause disadvantages such as wavelength elongation and unpredictable shape and size of ablation area. Currently, new technological developments have made it possible to overcome these

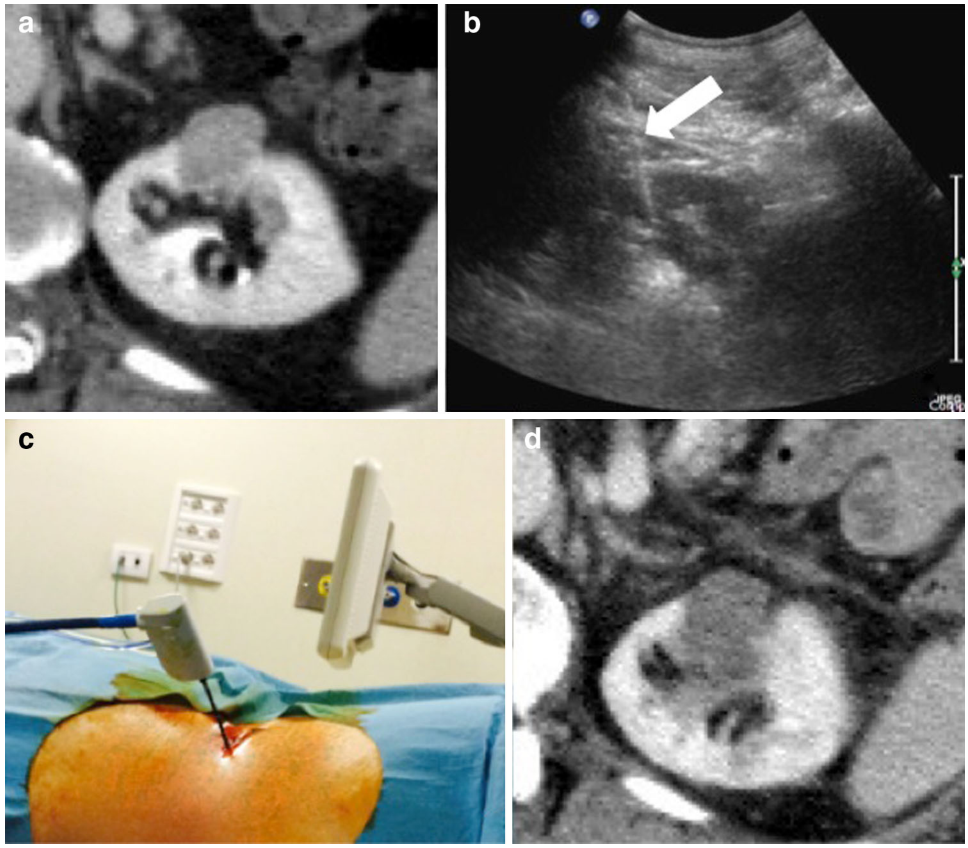

Fig. 1 82-year-old man with left kidney RCC; **a** enhanced CT image of renal lesion; **b** US image shows the antenna inside the renal lesion (*white arrow*); **c** photo of percutaneous MW antenna placement in left flank; **d** follow-up enhanced CT image shows a complete ablation of the left renal lesion with no contrast enhanced of ablated area

limitations. Thermosphere™ Technology (Covidien) with its new probes, provides three kinds of spatial energy control—thermal, field and wavelength, holding a predictable spherical ablation zones throughout procedures. By employing this system could overcome the uncertain clinical outcomes of other ablative technologies, giving an increased freedom and confidence to plan and execute with predictable outcomes in every procedure. In our personal experience, two renal lesions have been treated using such system (Fig. 1).

The importance to obtain an ablation area that is more spherical as possible arises from the fact that renal tumors are generally spherical and that the prediction area, outlined by the software with CBCT, is round. From this derives the idea that the ablation MW area will be all the more spherical it will be possible to completely ablate the renal lesion.

Conclusion

Ablative techniques have been introduced with the aim to control the spreading of a local tumor and to preserve the surrounding parenchyma's function, with curative or local control as the primary objectives, when surgery is not feasible [7–9, 11, 13]. Different ablation techniques such as radiofrequency ablation, cryoablation, or microwave ablation have been available for some time, resulting in few complications, most of which are self-limited or readily treated, with great advantages if compared with surgical management [1, 9]. Use of microwave ablation has been studied extensively in the liver, but remains limited for the kidney. Actually, the literature supports the use of MWA for the treatment of small renal tumors with rare objections [7, 29–31]. This technology can be applied in selected patients who are not candidates for surgery, as an alternative to other ablative techniques [11, 29–31]. Though MWA achieved comparable results to those obtained with RF ablation or cryoablation, MWA needs a relatively short ablation time and may be more suitable for patients with a variety of comorbidities who cannot tolerate long-time anesthesia [31]. MWA is a technology that can reliably and reproducibly produce a large ablative lesion of solid renal neoplasms with a uniform tissue necrosis without skip areas [27]. MWA is also an optimal method for hemostasis making laparoscopic tumor enucleation easier and possible without renal pedicle clamping and hemostatic sutures subsequent to tumor removal [28]. Additional randomized controlled studies are needed to whether MWA is a safer and more effective therapy for small renal carcinoma in particular compared to other methods.

Conflict of interest The authors declare no conflict of interest.

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