Microwave versus cryoablation and radiofrequency ablation for small renal mass: a multicenter comparative analysis

MICROWAVE VERSUS CRYOABLATION AND RADIOFREQUENCY ABLATION FOR SMALL RENAL MASS: A MULTICENTER COMPARATIVE ANALYSIS

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ABSTRACT

BACKGROUND: Ablative techniques emerged as effective alternative to nephron-sparing surgery for treatment of small renal masses. Radiofrequency ablation (RFA) and cryoablation (CRYO) are the two guidelines-recommended techniques. Microwave ablation (MWA) represents a newer technology, less described. Aim of the study was to compare outcomes of MWA to those of CRYO and RFA.

METHODS: Retrospective investigation of patients who underwent MWA, CRYO, or RFA from seven high-volume US and European centers was performed. The first group included patients who underwent CRYO or RFA; the second MWA. We collected baseline characteristics, clinical, intraoperative and post-operative data. Oncological data included technical success, local recurrence, and progression to metastasis. Multivariate analysis was performed to find predictors for postoperative complications. A composite outcome of "trifecta" was used to assess surgical, functional, and oncological outcomes.

RESULTS: 739 patients underwent CRYO or RFA and 50 MWA. CRYO/RFA group had significantly longer operative time ($p<.001$), but no difference in LOS, post-procedural Hb mean, intra-procedural complications ($p=0.180$), overall post-procedural complication rates ($p=0.126$), and in the 30-day re-admission rate ($p=0.853$) were detected. No predictive parameter of post-procedural complications was found. Concerning functional outcome no differences were detected in terms of eGFR at 1yr ($p=0.182$), ΔeGFR at 1-yr ($p= 0.825$) and eGFR at latest follow-up ($p=0.070$). "Technical success" was achieved in 98.6% of the cases (MWA= 100%, CRYO/RFA= 98.5%; $p=0.775$), and there was no significant difference in terms of 2-yr recurrence rate ($p= 0.114$) and metastatic progression ($p= 0.203$). Trifecta was achieved in 73.0% of CRYO/RFA vs 69.6% of MWA cases ($p = 0.719$).

CONCLUSIONS: MWA is a safe and effective treatment option for small renal masses. Compared with CRYO/RFA, it seems to offer low complication rates, shorter operation time, and equivalent surgical and functional outcomes.

1. Introduction

Ablative techniques, initially reserved for patients who were poor candidates for surgery, emerged as an effective and safe alternative to nephron-sparing surgery for treatment of small renal masses with comparable oncological outcome and favorable functional results (1–7).

Radiofrequency ablation (RFA) and cryoablation (CRYO) are the two most used and guidelines-recommended ablative techniques for the treatment of renal masses (4,8–10). Compared to these, microwave ablation (MWA) represents a newer technology and been added to the available thermal ablation technologies for treatment of solid tumors (11,12). Even if MWA application is supported by more limited evidence, early results have shown is technically feasible for renal masses (13–15). Nevertheless, direct comparisons among CRYO, RFA, and MWA are lacking, especially from institutions that routinely perform all the aforementioned nephron-sparing options.

Aim of the study was to compare outcomes of MWA to those of CRYO and RFA in a contemporary multicenter patient cohort.

2. Materials and methods

2.1 Study design and dataset

The current study is based on the analysis of a multi-institutional database. We collected data from seven high-volume US and European centers. Institutional review board approval/waiver and data-sharing agreement were gained at each institution. We performed a retrospective investigation of patients who underwent MWA, CRYO, or RFA for the treatment of a renal mass between July 2008 and December 2019. The first group included patients who underwent CRYO (16) or RFA (17); the second patients treated with MWA (18). We collected baseline characteristics, clinical, intraoperative and post-operative data. These included complications (according to the Clavien-Dindo classification (19)) and follow up data, functional and oncological. All patients had a pre-treatment computer tomography (CT) or magnetic resonance (MR) and a diagnostic percutaneous biopsy. Since about 50% of the patients in the MWA group did not have biopsy data results available, CT and MR were used to establish a presumed diagnosis of RCC.

2.2 Data collection

Baseline characteristics included age, BMI, American Society of Anesthesiologist (ASA) score, history of diabetes, hypertension, preoperative serum creatinine (sCr) value, preoperative estimated glomerular filtration rate (eGFR) value, preoperative hemoglobin level (Hb), chronic kidney disease (CKD) staging, and solitary kidney status. Clinical mass features included tumor size, localization (left, right), clinical T-stage, R.E.N.A.L. nephrometry score.

Intraoperative data and surgical outcomes included operative time, postoperative Hb level at discharge, complications (intra-operative and post-operative), length of stay (LOS), re-admission rate within 30 days. Renal function has been evaluated with eGFR at 1 year and eGFR drop has been calculated as the difference between preoperative eGFR and eGFR at 1 year (ΔeGFR). CKD upstaging for the entire cohort was assessed, evaluating the number of patients who were switched to a higher CKD class. Oncological data included technical success, defined as extension of ablation defect beyond tumor margin with absence of residual enhancing in the ablation bed on imaging obtained immediately after the procedure (20), local recurrence (assessed at 24 months of follow-up) and progression to metastasis.

2.3. Analysis

Baseline characteristics, clinical, surgical, and postoperative outcomes were compared between the two groups (MWA vs RFA/CRYO). Statistical analysis was conducted following current guidelines (21). Data normal distribution has been assessed through Kolmogorov-Sminorv test. Mean ± standard deviation (SD) has been used if normally distributed, if not medians and interquartile range (IQR) has been used in not-normal data. Frequency (%) was reported for categorical data. To compare continuous variables T-test and Kruskal-Wallis H test were used according to the distribution. For categorical ones, Fisher's exact or Pearson Chi-Squared tests were adopted to evaluate differences.

Univariate and multivariate analysis was performed to test for an association between pre- and intra-procedural variables and the risk of overall postoperative complications. Variables selected for the analysis were age (continuous), BMI (continuous), ASA score (continuous), R.E.N.A.L. nephrometry score (continuous), and type of treatment (MWA as reference).

An arbitrary composite outcome of "trifecta" was used to simultaneously assess surgical, functional, and oncological outcomes, and therefore adopted as an arbitrary parameter

representative for treatment "quality". This was defined as: no major complication (Clavien-Dindo 3-5) + no significant reduction from baseline eGFR (<25%) + technical success (defined as no residual mass/enhancement at 6 months (22)).

Two tailed hypothesis tests were used in each case, considering statistically significant a p value ≤ 0.05. All statistical tests have been performed using SPSS © 26.0 (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp).

3. Results

3.1 Baseline characteristics

We collected 789 patients including 739 who underwent CRYO or RFA and 50 who had MWA (**Table 1**). No difference was found in terms of age, BMI, ASA score, and rate of diabetes between the two groups. The MWA group presented a higher prevalence in male gender (p=.001) and a higher hypertension rate (MWA= 86% vs CRYO/RFA= 69.5%; p= 0.015).

Preoperative renal function as assessed by eGFR was similar between cohorts (CRYO/RFA= 71.7; MWA= 68.0 [SD 25.7 – 23.6, respectively]; p= 0.333). MWA group showed a higher portion of CDK>III stage (36% vs 19.9%, p=0.006). Mean clinical tumor size was not significantly different between groups (CRYO/RFA= 2.6 cm; MWA= 2.5 [SD 1.6 – 1.2 respectively]; p= 0.734) as well as cT stage (p=0.309) and RENAL score (p=0.597).

3.2 Operative outcomes

Overall operative outcomes are summarized in **Table 2**. CRYO/RFA group had significant longer operative time (CRYO/RFA= 80; MWA= 30.4 [SD 67.1 – 63.8, respectively]; p<.001), but difference in LOS was not statistically (CRYO/RFA= 2.7; MWA= 1.6 [SD 2.9 – 1.49, respectively]; p= 0.129). Also. no difference in post procedural Hb mean was found (CRYO/RFA= 12.4; MWA= 11.6 [SD 1.9 – 1.8, respectively]; p= 0.075). Also, there was no difference in intra-procedural complications (p=0.180), overall post-procedural complication rates (p=0.126), and in the 30-day re-admission rate (p=0.853). However, there was a high rate of minor postoperative complications in the MWA group (CRYO/RFA= 7.4% vs MWA= 14%; p<.001), and a higher rate of major postoperative complications in the CRYO/RFA groups (CRYO/RFA= 2% vs MWA= 0%; p<.001). No predictive parameter of post-procedural complications was found on the multivariable analysis (**Supplementary table 1**).

3.3 Functional and oncological outcomes

These are described in **Table 3**. The mean follow-up was statistically longer for CRYO/RFA cohort (CRYO/RFA= 53; MWA= 26 [SD 32 – 11.2, respectively]; p= 0.048). No differences between the groups were detected in terms of eGFR at 1yr (CRYO/RFA= 70.8; MWA=61.7; [SD 29.4 – 25.0, respectively]; p=0.182), ΔeGFR at 1-yr (CRYO/RFA= -2.4; MWA=1.9; p= 0.825) and eGFR at latest follow-up (CRYO/RFA= 74.9; MWA=67.5; [SD 15.7 – 23.8, respectively]; p=0.070). A not statistically significant higher rate of new on-set CDK III was recorded in the MWA cohort (13% vs 7.4%; p= 0.338).

Overall "technical success" was achieved in 98.6% of the cases (MWA= 100%, CRYO/RFA= 98.5%; p=0.775), and there was no significant difference in terms of 2-yr recurrence rate (CRYO/RFA= 8.2%; MWA= 2%; p= 0.114) and metastatic progression (CRYO/RFA= 2.16%; MWA= 0%; p= 0.203). Also, there was no difference in mortality rates (CRYO/RFA 10.4%, MWA 6%; p= 0.265). Trifecta was achieved in 73.0% of CRYO/RFA vs 69.6% of MWA cases (p = 0.719).

4. Discussion

Herein, we report a mature international multicenter experience comparing functional, surgical, and oncological outcomes of MWA versus RFA or CRYO in patients with a small renal mass. To the best of our knowledge, this study is one of the largest comparative series focusing on these ablative techniques. Overall, findings from the present analysis suggest that MWA yields equivalent outcomes compared to the more "established" CRYO or RFA.

We included the outcome of 739 patients who underwent CRYO or RFA, and 50 MWA. Overall, a high technical success was achieved (overall 98.6%, 100% for MWA, 98.5% for CRYO/RFA). Consistently with our findings, Zhou et al. reported an achievement of 95%, 96% and 85% in technical success rate in one treatment setting for RFA, MWA and CRYO, respectively; and a complete technical success (100%) considering retreatment for all groups (13). This also mirrors findings from a recent meta-analysis which showed that CRYO and RFA effectiveness ranges from 97% to 100% (23). Otherwise, Guo et al. reported 23 T1b RCCs treated by MWA (median size 5.2 cm) with a lower primary technique efficacy (87%), probably due to the greater size of the tumor (24,25). Although our oncological evaluation was limited by the lack of biopsy data in half of the MWA group, we recorded no significant differences in

recurrence (CRYO/RFA= 8.2% vs MWA= 2%, p=0.114) and metastatic progression rate (CRYO/RFA=2.16% vs MWA= 0%, p= 0.203).

We also recorded a significant reduction in operative time in the MWA cohort, as already suggested by others (26). MWA seems to produce higher and more homogeneous temperatures which allows more rapid tissue heating, thereby resulting in potentially larger ablation zones and shorter operation time (27). When looking at complications, we found only minor ones in the MWA group with a higher rate compared to CRYO/RFA (7.4% vs 14%; p<.001). On the other hand, the CRYO/RFA group presented a 2% major complication rate. These findings are in line with those reported in a single-center MWA experience by Yong at al. who found a complication rate between 10-17%, mostly Clavien Grade I (18). On the other hand, Thompson at al. in their initial experience described a 11.5% major complication rate with 2 cases of ureteropelvic junction stricture. Furthermore, we could not identify any baseline parameter as predictive factor of post-procedural complications (**Supplementary table 1**).

Beyond the initial treatment response and a reasonable complication rate, an effective therapeutic intervention would ideally achieve renal function preservation (28,29), which remains a major concern in patients undergoing nephron-sparing surgery (30,31). In our series, the technique did not affect the renal function (with regard to eGFR at 1 year; ΔeGFR at 1-yr, and eGFR at last follow up) although we observed difference in CKD>III pre-operative stage (36% vs 19.9% vs for MWA and CRYO/RFA, respectively). Similar findings were reported by Zhou and colleagues, with no significant changes in eGFR between pre-ablation and post-ablation at 2 year for all the three techniques (RFA= -0.85 ml/min; CRYO= -1.15 ml/min; MWA= -2 ml/min) (13), and De Cobelli et. al in a subset of T1a RCC patients who underwent CRYO or MWA (26). This evidence should be considered of primary importance for unfit and comorby patients and those with solitary kidney (5), in view of the mandatory need to preserve renal function and avoid kidney failure.

We also employed a merged outcome as “trifecta” to offer a “quality” assessment of procedural outcomes. Even if “trifecta” is usually not reported in studies on PTA, it has been widely used to evaluate in the partial nephrectomy literature (32). We applied an arbitrary composite outcome consisting of a combination of the following: no major perioperative complications, no significant eGFR reduction from baseline (<25%), and technical success (defined as no positive surgical margin for the RAPN group and as no residual

mass/enhancement at 6 months for the PTA group). In our report, a “trifecta” achievement was recorded in 73.0% and 69.6% of CRYO/RFA and MWA, respectively.

Finally, it is worth mentioning that irreversible electroporation was recently explored as novel ablative technology. Due to its non-thermal nature and connective tissue-sparing properties, it has shown utility where traditional ablative techniques face challenges such as treating tumors near vessels or critical structures (33). Therefore, it might have a growing role in the future.

Our study carries the intrinsic limitations of its retrospective design. A patient-selection bias may have influenced our findings. Also, absence of standardized pre-operative and postoperative management protocols among the different centers as well as nuances in operative techniques may have also influenced the outcomes. Moreover, the oncological analysis was biased by the incompleteness of biopsy date for the MWA group.

5. Conclusions

MWA is a safe and effective treatment option for small renal masses. When compared with CRYO or RFA, it seems to offer low complication rates, shorter operation time, and equivalent surgical and functional outcomes. Thus, MWA deserves an established role in the current landscape of kidney ablation.

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"All authors read and approved the final version of the manuscript".

Table 1. Baseline characteristics

	CRYO/RFA n= 739	**MWA n= 50**	**p-value**
Age, median (IQR)	68 (20.0-89.0)	70 (37.0-86.0)	0.057
Gender, n (%)			<.001
Male	500 (67.7)	48 (96.0)	
Female	239 (32.3)	2 (4.0)	
BMI, kg/m^2, mean (SD)	28.6 (6.3)	29.8 (6.7)	0.215
Hypertension, n (%)	514 (69.5)	43 (86.0)	0.015
Diabetes, n (%)	176 (23.8)	16 (32.0)	0.198
ASA score, n (%)			0.196
1	12 (1.6)	0 (0)	
2	216 (29.2)	9 (18.0)	
3	442 (59.8)	34 (68.0)	
4	69 (9.3)	7 (14.0)	
Pre-operative Hb, mean (SD)	14.0 (1.8)	12.8 (1.8)	<.001
Preoperative Cr, mL/, mean (SD)	1.1 (0.47)	1.3 (0.44)	0.019
Preoperative eGFR, mL/min, mean (SD)	71.7 (25.7)	68.0 (23.6)	0.333
CKD> stage III, n (%)	147 (19.9)	18 (36.0)	0.006
Solitary Kidney, n (%)	82 (11.1)	4 (8.0)	0.199
Clinical tumor size, cm, mean (SD)	2.6 (1.6)	2.5 (1.2)	0.734
cT stage, n (%)			0.309
1a	689 (93.2)	44 (88)	
1b	48 (6.5)	6 (12)	
2a	2 (0.3)	0 (0)	
RENAL score, median (IQR)	5 (2-8)	5 (4-6)	0.597

CRYO: Cryoablation; RFA: Radiofrequency ablation; MWA =: Microwave ablation; BMI: Body Mass Index, ASA score: American Society of Anesthesiology, CDK: Chronic Kidney Disease, eGFR: Estimated Glomerular Filtration Rate

Table 2. Operative Outcome

	CRYO/RFA n= 739	MWA N = 50	p-value
Operative time, min, mean (SD)	80.0 (67.1)	30.4 (63.8)	<.001
LOS, days, mean (SD)	2.7 (2.9)	1.6 (1.49)	0.129
Post-operative Hb, mean (SD)	12.4 (1.9)	11.6 (1.8)	0.075
Intra-procedural complications, n (%)	20 (2.7)	0 (0)	0.180
Post-procedural complications, n (%)			
Overall	55 (7.4)	7 (14)	0.126
Grade 1-2	40 (5.4)	7 (14)	
Grade 3-4	14 (1.7)	0	
Grade 5	1 (0.3)	0	
30 days re-admissions, n (%)	22 (2.9)	2 (4.0)	0.853

CRYO: Cryoablation; RFA: Radiofrequency ablation; MWA =: Microwave ablation

Table 3. Tumor pathology and follow-up

	CRYO/RFA n= 739	MWA n=50	P-value
***Technical succes, n (%)**	728 (98.5)	50 (100)	0.775
Follow-up, month, mean (SD)	53 (32)	26 (11.2)	0.016
eGFR at 1 year, ml/min, mean (SD)	70.8 (29.4)	61.7 (25.0)	0.182
Latest eGFR, ml/min, mean (SD)	74.9 (15.7)	67.5 (23.8)	0.070
ΔeGFR at 1-yr, mean	- 2.4	-1.9	0.825
New-Onset CKD III, n (%)	(7.4)	(13.0)	0.338
Recurrence, n (%)	60 (8.2)	1 (2)	0.114
Metastasis, n (%)	16 (2.16)	0 (0)	0.203
Death, n (%)	77 (10.4)	3 (6.0)	0.265
Trifecta achievement, (%)	(73.0)	(69.6)	0.719

CRYO: Cryoablation; RFA: Radiofrequency ablation; MWA =: Microwave ablation; eGFR: Estimated Glomerular Filtration Rate, ΔeGFR: differences in Estimated Glomerular Filtration Rate; *Residual mass/enhancement at 6 months; CDK: Chronic Kidney Disease;

Table 1. Baseline characteristics

	Cryo/RFA n= 739	MWA n= 50	p-value
Age, median (IQR)	68 (20.0-89.0)	70 (37.0-86.0)	0.057
Gender, n (%)			<.001
Male	500 (67.7)	48 (96.0)	
Female	239 (32.3)	2 (4.0)	
BMI, kg/m^2, mean (SD)	28.6 (6.3)	29.8 (6.7)	0.215
Hypertension, n (%)	514 (69.5)	43 (86.0)	0.015
Diabetes, n (%)	176 (23.8)	16 (32.0)	0.198
ASA score, n (%)			0.196
1	12 (1.6)	0 (0)	
2	216 (29.2)	9 (18.0)	
3	442 (59.8)	34 (68.0)	
4	69 (9.3)	7 (14.0)	
Pre-operative Hb, mean (SD)	14.0 (1.8)	12.8 (1.8)	<.001
Preoperative Cr, mL/, mean (SD)	1.1 (0.47)	1.3 (0.44)	0.019
Preoperative eGFR, mL/min, mean (SD)	71.7 (25.7)	68.0 (23.6)	0.333
CKD> stage III, n (%)	147 (19.9)	18 (36.0)	0.006
Solitary Kidney, n (%)	82 (11.1)	4 (8.0)	0.199
Clinical tumor size, cm, mean (SD)	2.6 (1.6)	2.5 (1.2)	0.734
cT stage, n (%)			0.309
1a	689 (93.2)	44 (88)	
1b	48 (6.5)	6 (12)	
2a	2 (0.3)	0 (0)	
RENAL score, median (IQR)	5 (2-8)	5 (4-6)	0.597

Cryo: Cryoablation; RFA: Radiofrequency ablation; MWA =: Microwave ablation; BMI: Body Mass Index, ASA score: American Society of Anesthesiology, CDK: Chronic Kidney Disease, eGFR: Estimated Glomerular Filtration Rate

Table 2. Operative Outcome

	Cryo/RFA N = 739	MWA N = 50	p-value
Operative time, min, mean (SD)	80.0 (67.1)	10.4 (63.8)	<.001
LOS, days, mean (SD)	2.7 (2.9)	1.6 (1.49)	0.129
Post-operative Hb, mean (SD)	12.4 (1.9)	11.6 (1.8)	0.075
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Table 3. Tumor pathology and follow-up

	Cryo/RFA n=739	MWA n=50	P-value
***Technical failure, n (%)**	20 (2.7)	0 (0)	0.048
Follow-up, month, mean (SD)	43 (32)	26 (11.2)	0.016
eGFR at 1 year, ml/min, mean (SD)	70.8 (29.4)	61.7 (25.0)	0.182
Latest eGFR, ml/min, mean (SD)	74.9 (15.7)	67.5 (23.8)	0.070
ΔeGFR at 1-yr, mean			
ΔeGFR at latest F/Up, mean (SD)			
New-Onset CKD III, n (%)	(7.4)	(13.0)	0.338
Recurrence, n (%)	80 (10.8)	1 (2)	0.048
Metastasis, n (%)	16 (2.16)	0 (0)	0.203
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