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RESEARCH

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Thermal ablation in the treatment of early renal cell carcinoma: an 11-year single-centre experience in Johannesburg, South Africa.

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1 Background

An estimated 85% of renal tumours are renal cell carcinomas (RCC) and they account for 2–3% of all adult neoplasms [1]. Worldwide, there are 170,000 deaths and 400,000 new cases annually due to RCC. A review by Atanda and Haruna in 2017 estimated the incidence of RCC in Nigeria as approximately 0.3 in 100,000 of the population [2]. Data for RCC and thus its management are still very scarce, according to Rugakingira et al. [3]. The authors found that although the National Cancer Registry (NCR) of South Africa had adequate essential demographic data on RCC, vital clinical and tumour data were almost non-existent. In this study, the predominant histological subtypes were comparable to other series: clear cell RCC: 79%; papillary RCC: 18%, and chromophobe RCC: 1.6%. This lack of data on RCC likely explains the paucity of research on thermal ablation in our setting.

Treatment options that can improve the outcomes of RCC patients need to be actively pursued due to its high morbidity and mortality. Traditionally, open and laparoscopic radical or partial nephrectomy have been the gold standard of care for localised disease, but in patients who are poor candidates for surgery due to factors such as age and/or comorbidities, percutaneous thermal ablation (PTA) has increasingly become a utilised technique. A 23-year review of 11 publications between 1996 and 2019 from four countries in Sub-Saharan Africa, by Cassell et al.[4], recommended a multidisciplinary approach for the management of renal malignancies due to the complexity of treatment options; however, these recommendations were not being followed. The study revealed that 74% of the patients were managed with open radical nephrectomies and the remaining patients were managed by either partial nephrectomies or anti-angiogenics; none of the patients were managed with ablation therapy. This was attributed to cost-effectiveness and late presentation of disease. A study by Cheiab et al., which assessed patients with small renal masses (SRM) from 2004 to 2013 using the linked Surveillance, Epidemiology, and End Results-Medicare database, found that older patients were more inclined to undergo thermal ablation and other non-surgical methods [5]. This was confirmed by Attawettayanon et al. in another study [6]. It can thus be said that with the right patient selection, PTA can be the preferred choice of treatment in RCC.

PTA has been shown to be a minimally invasive method with outcomes that are similar to surgical treatment [1]. The procedure results in sparing of functioning nephrons and preservation of the renal parenchyma, resulting in a substantially lesser decline in renal function, and the overall complication rate is far less. PTA provides the option for concomitant biopsy and is also more cost-effective than surgical management [7] . According to the American Urologic Association and the National Comprehensive Cancer Network (NCCN) guidelines for kidney cancer treatment, PTA techniques are listed as part of the primary treatment for stage 1 (T1a) RCC. PTA stands alongside partial nephrectomy, active surveillance, or radical nephrectomy as the treatment options

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for this stage [8, 9]. The American Urological Guidelines for Local Renal Mass support this and state that PTA is not only an established alternative treatment for the elderly or suboptimal surgical candidates but also for healthy patients with careful selection. However, they demonstrated that local recurrence was more common in PTA than in partial nephrectomy, but this was salvageable with a repeat ablation, whereafter the results then became comparable [6].

There are three types of PTA commonly used in the treatment of RCC, namely microwave ablation (MWA), radiofrequency ablation (RFA) (thermal) and cryoablation. MWA uses dielectric hysteresis to create heat. The destruction of tissues occurs when an electromagnetic field is applied to tissues through an interstitial antenna, and they are heated to deadly temperatures [10]. The mechanism of heating in MWA differs significantly from RFA, which applies a high-frequency, alternating current to the tissue that causes ionic agitation, generating frictional heat. This process causes cancer cell destruction when the temperatures are above 60 °C [11]. Cryoablation works with gases that obey the Joules–Thomson law that flow through a double-tubed cryoprobe and cool as they expand. Temperatures of less than −20 °C are required for the destruction of normal renal parenchyma. The resultant cell death is multifactorial—the low temperature starts the process of apoptosis, the freezing–thawing cycle causes cellular membrane disruption and cell death; lastly, vessel thrombosis causes ischaemic death [12].

The main advantages of MWA over RFA are that it can generate temperatures of over 100^{o}C and it causes less pain during the procedure. MWA also produces larger ablation zones in a shorter period of time [1]. Once a blood vessel with a diameter of 3 mm or larger abuts the target lesion, this leads to a phenomenon known as heat sink, as the constant flow of blood away from the ablation zone keeps the tissue cooler than desired. This limits the effectiveness of a thermal ablation technique. Compared to RFA, MWA is less prone to the heat sink effect [1, 8]. Studies on MWA have demonstrated a similar or slightly better efficacy rate and local tumour recurrence rate than cryoablation and RFA, with a lower incidence of major complications. The most common complication reported after PTA of RCC is bleeding, which presents as small peri-nephric haematomas that typically resolve spontaneously with conservative management. Despite this, blood loss has been found to be significantly less with PTA than with laparoscopic partial nephrectomy [1]. Comparisons between RFA and cryoablation in commentaries and meta-analysis, show no difference in complication rates or efficacy, as demonstrated by Guo and Arellano [8]. Another potential complication is thermal injury to the ureter with a resultant ureteral stricture. Retrograde or antegrade irrigation of cooled saline into the ureter via a double J stent or percutaneous nephrostomy, respectively, is thus employed as a protective manoeuvre when a tumour in close proximity to the ureter is being ablated. Other protective manoeuvres involve displacing structures that are in close proximity to the tumour, such as the bowel, using fluid (hydro-dissection), carbon dioxide or balloons [12, 13].

Although there are several studies on thermal ablation in the treatment of RCC done outside the country, there are none published on the topic within South Africa. Microwave ablation is a newer ablation technique with few reports available on long-term follow-up data, including in international articles [14]. This study will seek to fill these gaps in research and add to the published literature on PTA by giving a single-centre's experience with the therapy.

2 Methods

2.1 Patient selection

This study is a retrospective observational study conducted within a tertiary private teaching hospital in Johannesburg, South Africa[redacted]. Treatment options provided at this facility included: active surveillance, surgery (total nephrectomy—open or laparoscopic assisted or partial nephron sparing nephrectomy) and PTA. Patients were selected to receive PTA based on comorbidities which made them high risk for surgery, tumours that were easily accessible to PTA, e.g. predominantly exophytic tumours, and patient preference. All patients selected to undergo PTA were deemed suitable candidates during multidisciplinary team discussions. All of these patients were referred by the treating urologist for pre-ablation cross-sectional imaging.

The inclusion criteria were patients with a tumour size smaller than 3 cm (SRMs) and histologically confirmed RCC. The exclusion criteria were patients with no proven histopathology of RCC, patients lost to clinical follow-up, and those without follow-up imaging. The choice between MWA and RFA was based primarily on availability—at the time when the procedure was first introduced at our institution, only RFA was available in the country, and once MWA was registered, it was then employed as the primary ablation technique. All the selected patients had a pre-procedural multi-phase contrast-enhanced computed tomography (CT) or a contrast-enhanced magnetic resonance imaging (MRI) scan as well as an ultrasound or CT-guided percutaneous core biopsy. The ablation zone was assessed for enhancement and recurrent or residual masses on follow-up imaging, and histological subtypes and complications were evaluated. The institute's review board and the associated university ethics committee granted permission for the study to be conducted.

2.2 Thermal ablation technique

The procedures were performed under general anaesthetic with the patient in a prone or semiprone position. Radiofrequency ablation was performed by CT and ultrasound guided placement of multipronged RITA radiofrequency ablation probes. Microwave ablation was performed with a Solero system (Angiodynamics, Inc, United States of America). Hydro-dissection using dilute contrast in dextrose water was used to displace organs away from the ablation site when necessary. Select patients with endophytic tumours had percutaneous nephrostomies inserted in a prior procedure which were then infused with cold saline during the PTA to protect the pelvicalyceal system. Nephrostomy and prograde pyeloperfusion were used instead of the commonly described retrograde method through transvesical ureteric cannulation for logistical reasons. Tract ablation was performed during withdrawal of the microwave antenna or radiofrequency ablation probe. A long-acting local anaesthetic (bupivacaine) was injected along the access tract and up to the renal capsule for post-ablation pain management. Immediate post-ablation CT scans with a low volume (50 cc) of intravenous contrast were performed to ensure technical success (defined as an adequate ablation zone of 0.5 to 1 cm around the mass as well as no discernible enhancement of the tumour). The patients were then observed overnight (or longer if required for those that developed complications) in a general ward or surgical intensive care unit (ICU), depending on the patient's clinical condition.

2.3 Treatment results and clinical follow-up

Patients were followed up immediately post-treatment, at 3 months, 6 months, and then yearly by the referring clinician using CT or MR imaging modalities. Local tumour progression was defined as development of enhancement within the ablation zone, which was quantified as an increase of 15 HU, comparing the non-contrast and contrast-enhanced CT scans. Repeat ablation and active surveillance were employed as means of managing recurrence.

2.4 Statistical methods

The data was analysed using IBM SPSS statistics version 29. Descriptive statistics are presented as frequencies and percentages. Categorical variables are presented as means with standard deviation or median with interquartile range and for continuous data, depending on the normality of distribution of the data in question. Comparisons involving categorical data were done using the Pearson Chi-square test or the Fisher's exact test (i.e. for tables exceeding 2×2 and for 2×2 tables, respectively). Comparisons on normally distributed continuous data were done using the independent samples t-test for comparisons involving two groups or ANOVA for comparisons involving 3 or more groups. For skewed continuous data, the Mann–Whitney U test (2 groups comparisons) or the Kruskal–Wallis test (3 or more groups) was used.

3 Results

Between the years 2011 and 2022, 75 patients underwent PTA for renal masses at our centre. Thirty patients were excluded due to not having any follow-up imaging on the picture archiving and communication system (PACS). Sixteen patients were then excluded for either not having a histopathology report available or for not being diagnosed with RCC on their histopathological reports but rather a benign pathology such as an oncocytoma.

3.1 Demographics and baseline characteristics of total sample and treatment groups as presented in Tables 1 and 2

Twenty-nine patients were thus eligible for inclusion in the study. Seventeen patients were treated with MWA, and the remaining 12 were managed with RFA representing 58.6 and 41.4%, respectively, as demonstrated in Fig. 1. Twenty-one patients (72.4%) were male and eight (27.6%) were female, with a corresponding male-to-female ratio of 2.6:1. The mean age of the study population was 63 years (SD $\pm$ 11.4), with no significant difference in age between the therapeutic groups.

Ten of the patients presented with clear cell RCC, five patients presented with papillary RCC, two patients presented with chromophobe type RCC and one patient presented with clear cell papillary RCC. Eleven tumours did not have any recorded immunohistochemistry done and were therefore not categorised into an RCC subtype, as depicted in Fig. 2. Sixteen patients presented with left-sided disease while the remaining were right-sided disease. Four of the patients had a single kidney in situ with three presenting with a right kidney and one with a left kidney.

The average longest diameter of the renal masses was 2.8 cm (SD $\pm$ 0.8) with no significant differences in size between the MWA and RFA groups ($p > 0.05$). There was also no difference between these two groups in terms of sex ($p > 0.05$), histological subtype ($p > 0.05$), and the side of the body with RCC as shown in Table 2.

Two patients in the RFA therapeutic group required repeat ablation as compared to one patient in the MWA group. A total of seven patients (24.1%) developed eight complications post-procedure. These complications presented as follows: haematuria (four), pain (one), perirenal

Table 1 Demographics, baseline and clinical characteristics

Demographics, baseline and clinical characteristics		Treatment Groups		pValue
		MWA	RFA	
Gender	Sex ratio (M: F) 21:8			
Mean age at ablation (years,SD)	63 years (SD ± 11.4)			
Tumour Type				
Clear Cell	10	10	0	
Chromophobe	2	0	2	
Papillary	5	4	1	
Clear Cell Papillary	1	1	0	
Unclassified RCC	11	2	9	
Tumour Size (cm, SD)	2.8cm (SD ± 0.8)	2.8cm (SD ± 0.7)	2.8cm (SD ± 1.0)	0.865
Tumour Side				
Right	13	8	5	
Left	16	9	7	
Single Kidney	4			
Right	3			
Left	1			
Repeat PTA	3	1	2	
Complications	All complications	4	3	> 0.05
	Haematuria	4		
	Pain	1		
	Perirenal Haematoma	1		
	Urinary Retention	1		
	Thermal Liver Injury	1		

PTA = Percutaneous Thermal Ablation, MWA = Microwave Ablation, RFA = Radiofrequency Ablation, SD = Standard Deviation, RCC = Renal Cell Carcinoma

Table 2 Tumour size in type of PTA, tumour subtype, sex and side of the body groups

Type of PTA	Size (cm, SD)	pValue
MWA	2.8 (SD ± 0.7)	0.865
RF	2.8 (SD ± 1.0)	
Tumour subtype		
Chromophobe	3.6 (SD ± 0.8)	0.549
Clear cell	2.9 (SD ± 0.7)	
Clear cell papillary	2.2	
Papillary	2.7 (SD ± 0.8)	
RCC	2.7 (SD ± 0.9)	
Sex		
Male	2.8 (SD ± 0.9)	0.771
Female	2.7 (SD ± 0.7)	
Side of body		
Left	2.8 (SD ± 0.7)	0.870
Right	2.8 (SD ± 1.0)	

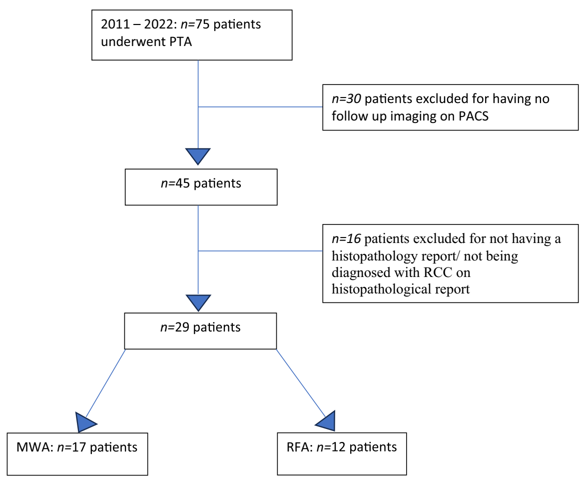

Fig. 1 Flow diagram demonstrating excluded patients

haematoma (one), urinary retention (one), and thermal liver injury (one).

3.2 Efficacy of ablation therapy as presented in Table 3

The mean percent reduction in enhancing tumour size, for the MWA and RFA treatment groups combined, increased slightly from 91.8% (SD ± 23.3) in the 1st follow-up to 94.6% (SD ± 13.5) in the 2nd follow-up. It then increased further to 100% in the 3rd follow-up, but this trend reversed in the 4th follow-up, with a mean percent reduction in enhancing tumour size of 83.9%. By the 5th follow-up, the mean percentage reduction was 100% in the study population, and this continued in the subsequent follow-up periods.

Between the treatment groups, the mean percent reduction in enhancing tumour size at the 1st follow-up for MWA was 91.3% (SD ± 22.4) and 92.6% (SD ± 25.5) for RFA with no difference in percent reduction, $p > 0.05$. During the 2nd follow-up, the study population had declined to 16 and the mean percent reduction for MWA was 89.1% (SD ± 18.0) and 100% (SD ± 0) for RFA with no statistically significant difference in percent reduction, $p > 0.05$.

3.3 Development of enhancement post-ablation

At the 1st follow-up, 17.2% of the 29 tumour sites developed enhancement. Out of the 16 patients who reported for the 2nd follow-up, 18.7% developed enhancement. In both follow-up periods, there was no significant difference ($p = 0.064$) with regard to enhancement post-ablation when the MWA and RFA groups were compared.

4 Discussion

The objective of this study was to evaluate the outcomes of PTA for stage 1a RCC within a single centre in South Africa. We evaluated changes in size of the enhancing tumour, development of enhancement within the ablation zone or complete radiological response of disease. It was demonstrated that PTA is a feasible and efficient method of treating RCC in resource limited settings. We also demonstrated that the demographics within the RCC population in South Africa are similar to those seen internationally. RCC is approximately two times as

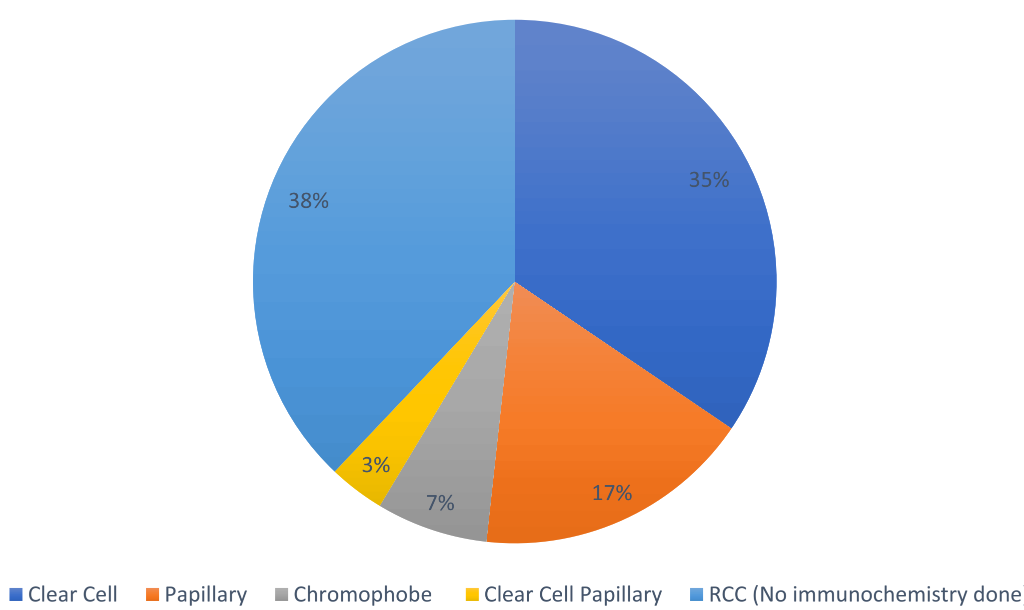

Fig. 2 Histology and immunochemistry of the study population

Table 3 Details of outcomes and morbidities

Details of outcomes and morbidities			Treatment Groups		pValue
			MWA	RFA	
	N	Mean percent enhancing tumor size reduction, %(±SD)			
Follow-up 1	29	91.8(±23.3)	91.3(±22.4)	92.6(±25.5)	0.064
Follow-up 2	16	94.6(±13.5)	89.1(±18.0)	100.0(±0.0)	0.064
Follow-up 3	9	100.0(±0.0)			
Follow-up 4	8	83.9(±45.5)			
Follow-up 5	6	100.0(±0.0)			
		Post Therapy Enhancement, %			
Follow-up 1	29	17.2%	23.5	8.3	0.370
Follow-up 2	16	18.7%	37.5	0	0.200
Follow-up 3	9	0.0%			
Follow-up 4	8	12.5%			
Follow-up 5	6	0.0%			

MWA = Microwave Ablation, RFA = Radiofrequency Ablation, SD = Standard Deviation

common in males than in females, in keeping with the data analysed that demonstrated a male-to-female ratio of 2.6:1. Out of the 18 patients that had immunochemistry performed on their biopsy specimens, the clear cell subtype was the most prevalent and seen in 10 patients (55.6%). The papillary subtype was the second most prevalent with five patients (27.8%), followed by chromophobe with two patients (11.1%). These results follow a similar pattern seen in literature with subtype prevalence as follows: clear cell—75–85% of tumours; papillary—10–15% and chromophobe—5–10% [15].

There was no statistically significant difference between the efficacy rates seen in the MWA and RFA groups. This is in line with current literature for the treatment of T1a RCC. Aarts et al. discovered in their study of 164 patients treated with RFA or MWA that there was no significant difference between the two groups in terms of changes in estimated glomerular filtration rate (eGFR), complications, and efficacy [14]. Overall, the mean percent reduction in enhancing tumour size went from 91.8% at the 1st follow-up (at an average of 5.8 months) to 100% at the 3rd follow-up (at an average of 18.8 months). The decrease at the 4th follow-up, at an average of 29.8 months, to 83.9% was due to an outlier single patient out of the eight patients that had followed up to this point. The other seven patients had complete radiological response by this follow-up, but the 8th patient developed a 5.4-cm recurrent mass. This patient had missed earlier follow-up imaging resulting in the recurrence presenting late. There was no statistical difference with regard to percent reduction in enhancing tumour size between the MWA and RFA groups. Enhancement occurred in 17.2% of tumour sites at the 1st follow-up and 18.7% at the 2nd follow-up with no statistical difference between the treatment groups.

A study by Carbonara et al. compared the use of cryoablation and RFA in the treatment of patients with a single cT1 solid renal mass [16]. Their findings suggested that not only were both techniques valid minimally invasive options for treating SRMs, but they were appropriately suited for patients who are poor surgical candidates with high peri-operative morbidity and mortality risk. Furthering the discussion on the efficacy of PTAs, a study by Aveta and colleagues conducted a comprehensive review paper which looked at different ablative techniques in managing SRMs; there were variable recurrence rates among the various techniques, however RFA and cryoablation had comparable outcomes. They also went a step further to look at the management of recurrence post PTA and supported salvage surgery as an option in situations where ablative techniques fail [17]. A number of patients were lost to follow-up in our current study, and this made it challenging to incorporate vital information such as rate of recurrence and the management options employed. This is certainly a weakness of our study; however it sets a basis for more research to be done with cohorts more adherent to follow-up, within our setting.

Four patients within the MWA group developed complications and three within the RFA group—24.1% of the 29 patients. The complications were all Clavien–Dindo grade I–II, the majority of which (four patients) developed haematuria that cleared on day 1 post-procedure. The complications are presented in Table 1, and the Clavien Dindo classification is detailed in Table 4.

Table 4 Clavien–Dindo scale of surgical complications [21]

Clavien Dindo Scale of Surgical Complications	
Grade I	Any deviation from the expected postoperative course without the need for radiological, surgical and endoscopic interventions or pharmacological treatment.
Grade II	Requiring pharmacological treatment with drugs other than those allowed for Grade I complications. Blood transfusions and total parenteral nutrition (TPN) are included.
Grade III	Requiring radiological, surgical or endoscopic intervention.
Grade IIIa	Intervention not under general anesthesia.
Grade IIIb	Intervention under general anesthesia.
Grade IV	Life-threatening complication requiring intensive care management.
Grade IVa	Single organ dysfunction.
Grade IVb	Multi organ dysfunction.
Grade V	Death of a patient

Tomida et al. demonstrated more severe complications, Clavien–Dindo grade III, when robot-assisted partial nephrectomy (RAPN) was used in treating RCC [18]. An additional study found that peri-operative mortality following radical nephrectomy (Clavien–Dindo grade V) in the management of RCC was 5.1% in three West African countries and 2.8% in Europe and North America [4]. These findings are corroborated by a study done this year that looked at cryoablation as non-operative management of SRMs as compared to RAPN [19]. This study showed a significantly lower rate of postoperative complications of any grade in the cryoablation group as compared to patients in the RAPN group (7.8 vs. 16.9%, respectively). In a study by Chlorogiannis et al., they compared MWA to robot-assisted partial nephrectomy in the treatment of stage 1 RCC and found that 7% of the patients that underwent MWA experienced complications as opposed to 11.4% within the RAPN group. A systematic review of 8 studies demonstrated that partial nephrectomy has a higher complication rate as compared to ablation therapies [20]. Even though our study was unable to compare surgical groups to RFA and MWA, our results with regard to severity of complications are consistent with the available evidence.

This study has limitations, including its single institution and retrospective design with a small study group and irregular follow-ups. Oncological outcomes will be better assessed with a larger cohort, more consistent follow-ups by patients, and record keeping of survival data for these patients. Strengths of the study include it being the first of its kind in South Africa, a low-income setting. Larger series studies can be performed in Sub-Saharan Africa to minimise the described limitations. Patient care will also be improved with more adherent follow-up, and once more centres provide PTA as an alternative, it will give patients an efficient method for the treatment of early RCC (Figs. 3, 4).

5 Conclusion

Within a private tertiary academic institution in Johannesburg, South Africa, it has been demonstrated that in the treatment of Stage 1a RCC, PTA is a feasible and effective method with fewer and less severe complication rates as compared to surgical methods. Secondarily, it was also found that MWA is equally as effective as RFA within our setting. This study should serve as a basis for further studies on PTA with larger cohorts and more adherent patient follow-up within Sub-Saharan Africa.

Fig. 3 A RCC treated by RFA with the RFA needle in situ: oblique maximum intensity projection (**A**) and axial (**B**) planes

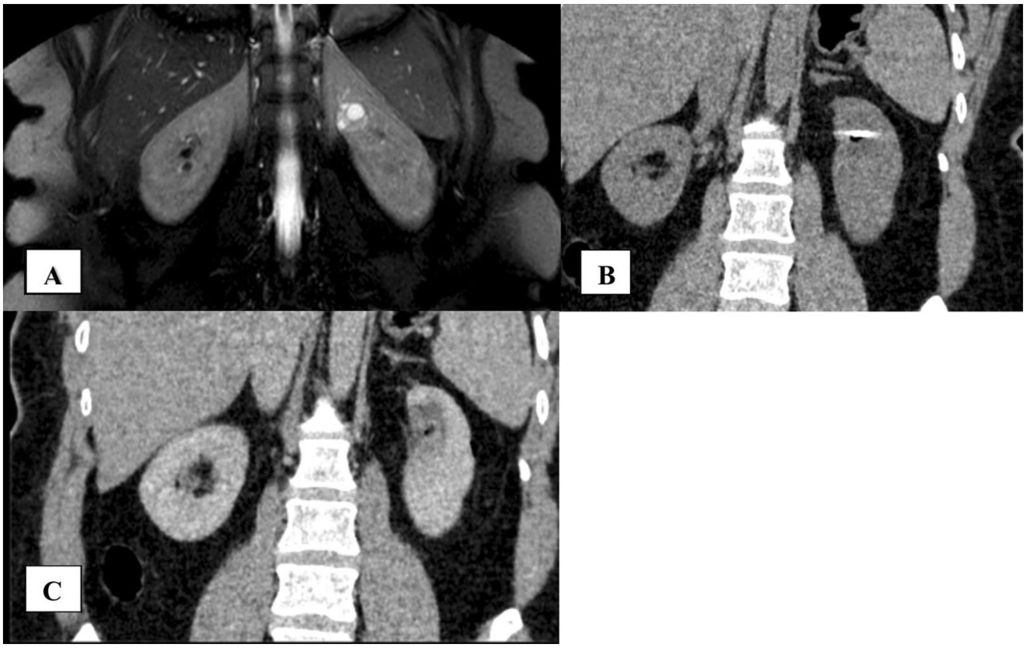

Fig. 4 Left kidney upper pole RCC treated with MWA. **A** Pre-treatment MRI demonstrating the T2 hyperintense RCC. **B** MWA probe in situ within the mass on CT. **C** Post-contrast CT demonstrating technical success with no enhancement within the ablation zone and an air locule

Abbreviations

eGFR	Estimated glomerular filtration rate
MWA	Microwave ablation
PTA	Percutaneous thermal ablation
PACS	Picture archiving and communication system
RAPN	Robot-assisted partial nephrectomy
RCC	Renal cell carcinoma
RITA	Radiofrequency interstitial tissue ablation
RFA	Radiofrequency ablation

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Author contributions
A.A.T.A. was involved in conceptualising and designing the study, conducting the literature review, preparing clinical studies, and drafting the original manuscript. D.N.P. assisted with the study design, supervised the study, read the scans and participated in reviewing and editing the writing. C.S. was involved in conceptualising the study and reviewed and edited the study. All authors reviewed and approved the final manuscript.

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Data availability
The datasets generated during this study are not publicly available due to patient confidentiality but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Approval by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, Johannesburgwas granted with Clearance Certificate Number M230928 MED23-08-017. Additionally, the Wits University Donald Gordon Medical Centre gave approval for the study to be conducted. This study was therefore performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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