REVIEW Interventional

Percutaneous ablation of small renal tumours: Current status

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ABSTRACT

The detection rate of small renal cell carcinoma (RCC) has been significantly increased in the last twenty years due to the expansion of number of diagnostic scans performed for other reasons. The management of small, asymptomatic RCC generates significant controversy. The gold standard still remains surgical excision; nevertheless nephron sparing minimal invasive ablation treatment appears to offer similar oncologic outcomes and less complication than surgery. Active surveillance is only reserved for patients that are not suitable for any treatment. Purpose of this review article is to present the current evidence on the ablation of small RCC and to delineate the role of this minimal invasive treatment in the management conundrum of such patients.

KEY WORDS
radiofrequency ablation; cryoablation; microwave ablation; renal cell carcinoma; interventional oncology

1. Introduction

Renal cell carcinoma (RCC) accounts for 2-3% of all cancers in the Westerns world [1]. The estimated number of new RCC cases per year in Europe is 115,000 (12.1 per 100,000) and of RCC related deaths 46,000 (4.7 per 100,000) [2]. There has been an increase in the incidence of RCC of approximately 1-2% per year for the last twenty years [3]. This increase is attributed to the higher number of imaging studies in comparison to the previous decades.

RCC is the most common of the solid renal masses (approximately 90% of all malignancies of the kidney). The incidence is higher in men than in women (1.5:1) and occurs most frequently between 60 and 70 years of age. RCC is related to several aetiological and genetic factors and in particular smoking, hypertension and obesity. The autosomal dominant mutation of the von-Hippel-Lindau (VHL) gene is also a predisposing factor [4-9]. The most common histological type is the clear cell RCC (>80%); other histological types include papillary RCC and cromophobe RCC.

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The majority of the cases are diagnosed with abdominal ultrasound (US). Staging is performed with contrast enhanced Computed Tomography (CT) of the chest, abdomen and pelvis [10]. Magnetic Resonance Imaging (MRI) is usually reserved for patients that cannot receive iodinated contrast or when further anatomical delineation of the lesion is required (i.e. relationship of the mass with the inferior vena cava) [11].

The treatment strategy depends on the stage of the tumour. The TNM classification and staging are presented in **Table 1** [12]. Ablation treatment may be offered for T1a and some T1b tumours (usually those smaller than 5 cm). Otherwise, Stage I tumours may be treated with either partial or radical nephrectomy; Stage II and III tumours require treatment with radical nephrectomy with a curative intent. For Stage IV tumours palliative chemotherapy may be combined with radical nephrectomy as a cytoreductive measure and further excision of metastatic deposits [12].

The aim of this manuscript is to present the current evidence on the ablation of small RCC and to delineate the role of this minimal invasive treatment in the management of such patients.

2. Management of small renal cell carcinoma

In this review are included studies of percutaneous treatment of small RCCs. The studies have been selected on the basis of the longest follow-up, the largest number of patients included and the prospective design. The parameters of each study that are assessed are the technical and clinical success, the recurrence-free survival (RFS), the overall survival (OS) and the complication rate. Special attention is given to the results of studies on single functioning kidney due to high risk of deterioration of the renal function and hemofiltration. With the term "small" we intend to define Stage I (<7 cm) RCC. Such lesions are usually not related to any symptoms and are detected incidentally during CT or ultrasound examinations performed for other reasons. As imaging cannot fully characterize solid enhancing renal masses [13], biopsy of the lesion is required in most of the cases prior to decide what will be the treatment strategy [14-17]. Biopsy can either be performed under CT or US guidance. An 18G-16G needle system is required and usually two samples are adequate to obtain histological diagnosis [18-21].

Following histological confirmation of malignancy, staging CT scan is performed to exclude any metastatic deposits. If metastases are confirmed then the lesion is considered as Stage IV and treatment is based on chemotherapy with Tyrosine Kinase Inhibitors (TKI) and in most of the cases cytoreductive surgery. According to the National Comprehensive Cancer Network (NCCN) Guidelines [12], treatment for T1a tumours consists of partial nephrectomy, radical nephrectomy (if the lesion is positioned centrally in the kidney), ablation treatment or active surveillance. The same guidelines for T1b tumours include as treatment options only partial and radical nephrectomy. However, there are a large number of operators that would treat also T1b lesions with ablation. The indications and contraindications of ablation are summarized in **Table 2**.

The main factors that help to decide whether a mass is *suitable* for ablation are the size and location of the tumour [22-23]. Most of the current evidence supports treatment of tumours smaller than 4 cm (T1a) [14]. An early large-scale study by the group of Massachusetts General Hospital in 2005 [14], demonstrated that radio-frequency ablation is effective treatment for tumours smaller than 3 cm. In 2004 Zagoria et al. [24], showed no residual tumour after radiofrequency ablation in lesions smaller than 3 cm. With the use of other ablation technology (cryoablation and microwave ablation) these boundaries are further expanded and larger tumours may also be successfully treated. Another crucial factor that needs to be considered is the location of the lesion within the kidney (exophytic, parenchymal, central or mixed). Ablation is more suitable for exophytic lesions because the surrounding fat pad insulates from heat dissipation and treatment is more effective. With central lesions there is risk of causing thermal damage to the pelvicalyceal system. However, with the use of adjunctive techniques this potential complication may be prevented.

3. Ablation modalities

The main ablation modalities that are used in the treatment of RCC are Radiofrequency ablation (RFA), microwave ablation (MWA) and Cryoablation (CRA) whereas some groups are also beginning to use Irreversible Electroporation (IRE). The studies that are included in this section are those with the longest follow-up, the largest number of patients included and the prospective design from each modality.

Table 1: American Joint Committee on Cancer (AJCC), TNM Staging System for Kidney Cancer (7th ed., 2010)

Primary tumour (T)			
TX	Primary tumour cannot be assessed		
T0	No evidence of primary tumour		
T1	Tumour 7 cm or less in greatest dimension, limited to the kidney		
T1a	Tumour 4 cm or less in greatest dimension, limited to the kidney		
T1b	Tumour more than 4 cm but not more than 7 cm in greatest dimension, limited to the kidney		
T2	Tumour more than 7 cm in greatest dimension, limited to the kidney		
T2a	Tumour more than 7 cm but not more than 10 cm in greatest dimension, limited to the kidney		
T2b	Tumour more than 10 cm, limited to the kidney		
T3	Tumour extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota's fascia		
T3a	Tumour grossly extends into the renal vein or its segmental (muscle containing) branches, or tumour invades perirenal and/or renal sinus fat but not beyond Gerota's fascia		
T3b	Tumour grossly extends into the vena cava below the diaphragm		
T3c	Tumour grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava		
T4	Tumour invades beyond Gerota's fascia (including contiguous extension into the ipsilateral adrenal gland)		
Regional Lymph Nodes (N)			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Metastasis in regional lymph node(s)		
Distant Metastasis (M)			
M0	No distant metastasis		
M1	Distant metastasis		
Anatomic Stage/ Prognostic Groups			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1 or T2 T3	N1 N0 or N1	M0 M0
Stage IV	T4 Any T	Any N Any N	M0 M1

Table 2. Indications and contraindications for RCC ablation
Indications for treatment with ablation
Presence of comorbidities that would increase the risk the surgical intervention (advanced COPD, heart failure)
Single functioning kidney
Impaired renal function (GFR <60 ml/min per 1.73 m^2)
Presence of more than one small renal tumour
Patient’s choice not to undergo a surgical procedure
Contraindications for treatment with ablation
Uncorrectable coagulopathy
Extensive spinal deformity that would not permit percutaneous access to the lesion (relative contraindication)

3.1 Radiofrequency ablation (RFA)

Radiofrequency ablation technology has been widely used in the treatment of RCC. Ablation is based on the use of high frequency electric current and requires a close circuit of the probe with the patient. The electrode serves as the cathode and the grounding pads as the anode. The electric current causes oscillation of water molecules and the kinetic energy is deposited in the adjacent tissue as frictional heat [25]. The energy deposition causes “coagulation necrosis” above 60°C *in vitro*. RFA electrodes may be unipolar or multipolar; they may be straight (single or clusters of three) or multi-tined and they can be internally cooled with saline (**Fig. 1 and 2**).

Radiofrequency ablation is used in a variety of studies with mid and long term results and comparison to surgery. In a single-centre prospective long-term study, Krokidis et al. [26] demonstrated that the use of radiofrequency ablation for the treatment of T1a tumours, in a single functioning kidney, offers 100% technical success rate. Two minor complications (haematuria and anuria which resolved within 24 and 48 hours respectively) but no major complications occurred. eGFR at 3, 12 and 24 months post RFA was not significantly different from baseline values. There was a 17% local recurrence rate (four cases) for which repeat RFA was performed. None of the patients required renal dialysis. The authors concluded that RFA offers good long-term outcomes for the treatment of tumours measuring <3.5cm in a single functioning kidney without significant major complications. Mylona et al. [27] in a study of 18 patients with a single functioning kidney and Stage I tumours (range 1-7 cm) that were treated with CT guided RFA reported satisfactory results without major complication after a mean follow-up of 31.2 months (range: 12-72 months). There were no recurrences in patients with tumours that were smaller than 3 cm. The overall tumour recurrence rate was 11.1%.

Olweny et al. [28] identified no significant difference between RFA and open partial nephrectomy for the treatment of T1a RCC in terms of 5-year disease-free survival, metastasis-free survival and local recurrence-free survival. Similar results were also confirmed in the study of Sung et al. [29]. The authors report no statistically significant difference in the three-year cancer free survival rate between RFA and open partial nephrectomy. In addition, Stern et al. [30] also observed that the 3-year recurrence-free rate for T1a renal tumours were numerically similar, with no statistical difference between partial nephrectomy and RFA.

In the study with the longest available follow-up, Psutka et al. [31] report the results of 185 patients with Stage I renal tumour (median tumour size 3 cm) that were treated with RFA and were followed up for a median of 6.43 years (range: 5.3-7.7 years). Local recurrence occurred in 6.5% of the patients after a median time of 2.5 years however the 5-year recurrence-free survival was 96.1%.

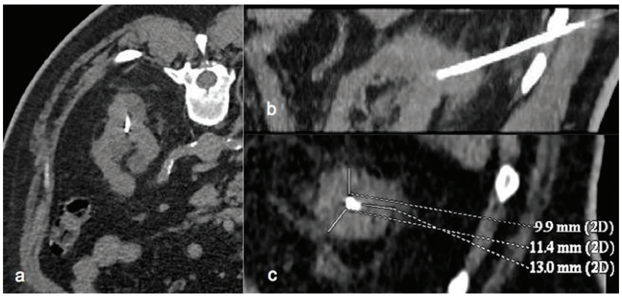

Fig. 1: *1a) Non-contrast CT scan in prone position. An RFA probe in inserted in the middle of a 3.3 cm exophytic lesion of the left kidney. 1b and 1c) Sagittal and coronal reformats are used to delineate the exact position of the lesion in comparison to the margins of the lesion prior to ablation*

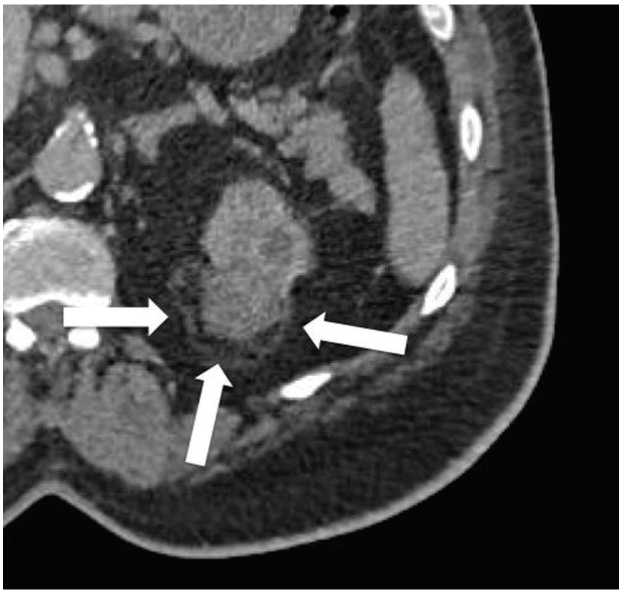

Fig. 2: *1-year follow-up of the lesion of Figure 1. There is lack of contrast enhancement and the margin between the ablated tissue and the non-ablated renal parenchyma is gradually replaced ("halo" sign) indicating successful ablation (arrows)*

3.2 Cryoablation (CRA)

Cryoablation has been the modality of choice for a number of operators, both in percutaneous but also in intraoperative setting. The physical principle of CRA is based direct cellular damage a) from osmotic cellular dehydration due to extracellular freezing and b) due to the intracellular formation of ice [32]. The temperature is which cell destruction occurs or otherwise mentioned as "lethal temperature" depends on the tissue type which for RCC is -40 °C [33].

One of the benefits of percutaneous CRA is the ablation area or otherwise mentioned, as "ice-ball" is visible with all modalities. It is important to note that the "ice-ball" does not correspond to the target lethal temperature and must cover the lesion of approximately 0.6 cm to obtain satisfactory ablation [33, 34] The treatment is divided in freezing and thawing (at 42° C) cycles. Usually two cycles of 10 minutes of freezing and 8 minutes of thawing are required.

Breen et al. [35] in a prospective study of 147 patients with T1a and T1b tumours treated with CT guided cryoablation reported single-session complete tumour treatment in 92.4% of the cases after a mean follow-up of 20.1 months. Further treatment with cryoablation was performed in nine cases and the overall technical success was 97.6%. Complication rate was 10.4% but only in 4.6% required further medical intervention.

In another study with long-term results, Georgiades et al. [36] treated 134 patients with percutaneous CRA under conscious sedation. The median tumour size was 2.8 ± 1.4 cm. The authors reported a 5-year efficacy of 97.0 %, 5-year cancer-specific survival of 100 % and 5-year overall survival of 97.8 %. Complication rate was 6 %, however no major complications occurred.

Chehab et al. [37] in a single centre retrospective study compared the cost of percutaneous CRA *vs* open and robot-assisted partial nephrectomy of T1a renal masses. The authors compared 37 percutaneous CRA cases to 128 surgery cases and concluded that even though device cost was higher for CRA vs open, but not vs robotic partial nephrectomy, the overall cost of CRA is significantly lower that both.

3.3 Microwave ablation (MWA)

The principle of MWA is the use of an electromagnetic *wave* that is emitted from an antenna and causes rotation of water molecules in the tissue. The non-equal distribution of electric charge of the water molecules causes their continuous re-orientation within the oscillating field; this movement increases their kinetic energy and is deposited in the tissue as thermal energy [38]. MWA frequencies that are in medical use vary between 915 and 2,450 MHz, the ablation effect is quicker than RFA and CRA and the ablation zone depends on the microwave power and the time of ablation [39].

MWA is a relatively novel technology for kidney ablation. However it appears to offer very satisfactory intermediate and long-term results. An intermediate-term single-centre prospective randomised study demonstrated that was no statistically significant difference in the 3-year recurrence free survival rate between microwave ablation and partial nephrectomy [40]. In a comparative study of MWA with laparoscopic nephrectomy Yu et al. [41] in 426 patients with RCC smaller than 4 cm MWA showed similar 5-year oncologic outcomes with surgery with significantly better results in terms of preservation of renal function.

Wells et al. in a retrospective review of 29 patients with 30 tumours (23 T1a and 7 T1b) that underwent treatment with MWA reported optimistic results with no local tumour progression at a median time of a year, three cases of minor and none of major complications [42].

3.4 Irreversible electroporation (IRE)

IRE is a novel non-thermal ablation modality. It is based on the use of a series of short, high voltage pulses (up to 3 kV) that when applied to human tissue increases the permeability of the cellular membrane [43, 44]. The increased membrane permeability leads to movement of molecules based on the electrochemical gradients and to cell apoptosis. In a clinical setting more than one electrode are required (usually three or four) and electrocardiographic changes may occur. However it was shown that no change in the central haemodynamic occurs [45]. There is very limited experience in RCC however some pilot studies describe promising results. Trimmer et al. [46] in the largest series reported so far on renal IRE in humans describes the results of 20 patients that underwent CT-guided IRE for exophytic T1a renal lesions (mean size of 2.2 cm ± 0.7). The authors used three electrodes for tumours up to 1.5 cm or smaller in triangular configuration, four electrodes for lesions of 1.5-2.5 cm size, and lesions >2.5 cm lesions four electrodes with sequential overlapping ablations. Technical success rate was 100% and no major complications occurred; seven patients had minor complications and residual enhancement was revealed in the 6-weeks follow-up scan that required rescue treatment with RFA.

4. Ablation Complications and Adjunctive Techniques

The most frequent complications of percutaneous ablation of renal tumours are bleeding and thermal injury of adjacent organs.

In nearly every case minor bleeding around the kidney occurs but this is without any clinical significance. It is of paramount importance though that the coagulation status of the patient is normal otherwise the haematoma will expand in the retroperitoneal space. Severe bleeding in patients with normal coagulation function, that would require transfusion, is reported in 1-2% of cases [47]. The acute haematoma appears as a hyperdense collection in CT that decreases in density after a few days. In case of injury of an intercostal vessel massive bleeding occurs with drop of the blood pressure within the first hour post procedure. In such cases immediate CT angiogram is required to delineate the source followed by trans-catheter embolization of the injured vessel in most of the cases.

Bleeding might also be expressed as haematuria due to the injury of small vessels that supply the pelvicalyceal system, the incidence is in 2-4% and is usually self-limiting after a couple of days [48]. In case of persistence of haematuria a new CT scan is suggested to exclude thermal damage of the pelvicalyceal system and of the proximal ureter that would appear as an area of thickening with or without a surrounding urinoma. Drainage of the urinoma and retrograde placement of a ureteric stent would be required in such cases. In order to prevent this complication, particularly in the case of ablation of central lesions, a retrograde ureteric stent may be placed prior to the procedure followed by perfusion of 5% dextrose in water solution that needs to be cold (2-6°C) in the case of RFA and MWA and warm in the case of CRA [49, 50].

Another potential complication is the thermal damage to the adjacent structures. In case of medial location close to the psoas muscle, damage to the genitofemoral nerve might occur and lead to chronic pain. A manoeuvre where the RFA electrode is used as lever to displace the kidney from the psoas muscle is described in the literature [51]. After torquing the handle of the electrode in medial direction, the kidney moves laterally, enlarging the distance from the muscle.

Furthermore, bowel thermal injury might occur due to the vicinity of the lesion with bowel loop. Accurate planning and manoeuvres of displacement of the bowel loops are required [52]. Insulation may be performed either with fluid or air. There are some experimental studies in rabbits with the use of insulating hydrogel with optimistic preliminary results however there is no commercially available product yet [53]. In the case of hydro dissection, 5% dextrose in water solution is injected. The solution may be distinguished from perirenal bleeding

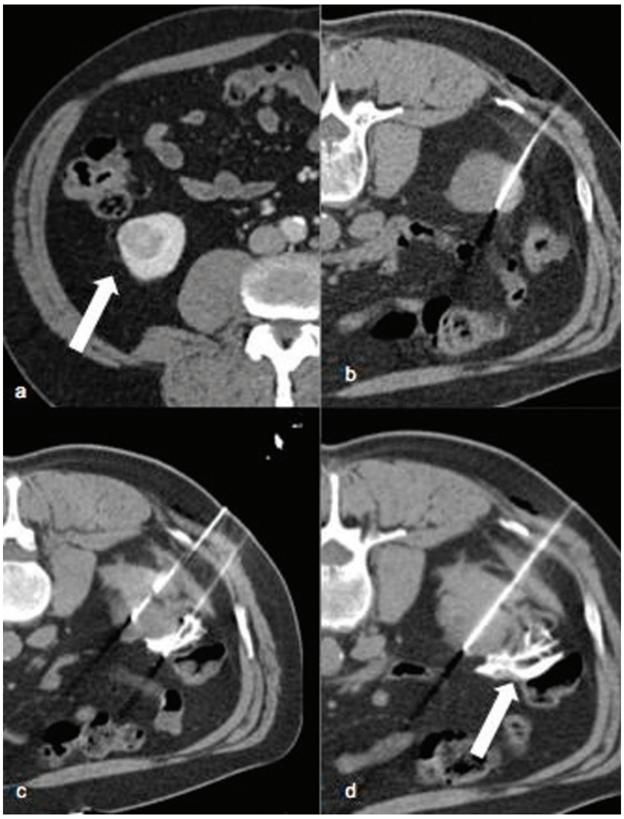

Fig. 3: *3a) Venous phase CT scan reveals a 3.2 cm exophytic lesion in the lower pole of the right kidney in a single kidney patient (arrow). 3b) An RFA probe is inserted under CT guidance in the middle of the lesion. 3c and 3d) a biopsy lesion is parallel inserted and a fine needle is inserted in the space between the lesion and the bowel loop following injection of 5% dextrose with traces of contrast (arrow)*

with a 1:100 dilution of iodinated contrast media (**Fig. 3**). In case of air dissection, CO_2 is injected that is subsequently absorbed by the vessels and eliminated by respiration. The risk of embolism is very low due to the high solubility of CO_2 [54].

5. Results from Comparative Studies and Meta Analyses

In a retrospective review of 385 patients Atwell et al. [55] compared the results of RFA (220 patients) *vs* CRA (163 patients). There was no statistically significant difference between the RFA recurrence-free survival (RFS) rates of RFA (100%, 98.1% and 98.1% at 1, 3 and 5 years respectively) and CRA (97.3%, 90.6% and 90.6% at 1, 3 and 5 years respectively). Mean follow-up for the tumours treated with RFA that did not recur was 3.2 years (median, 2.8 years range, 0.3-8.6 years) and for the tumours treated with CRA that did not recur was 1.8 years (median, 1.4 years; range, 0.3-6.5 years). The authors conclude that both treatments are equally effective for lesions smaller than 3cm and that major complications with either modality are infrequent.

Furthermore, Thompson et al. [56] recently published a retrospective single centre comparison of ablation with partial nephrectomy for Stage I RCC. The study included 1,424 patients with T1a lesions, 1,057 of which underwent partial nephrectomy, 180 underwent percutaneous RFA, and 187 underwent percutaneous CRA. There was no difference among the three treatments on RFS. The study also included 379 patients with T1b lesions, 326 of which were treated with partial nephrectomy and 53 with CRA. There was no difference in the RFS rates between those two treatments either. Metastases free survival was superior for partial nephrectomy and CRA patients however metastases occurred in only four patients that were treated with RFA at 0.3, 0.5, 1.4, and 2.1 years post treatment. Overall survival was superior for partial nephrectomy but the patients treated were significantly younger.

In the vast majority of studies, ablation appears to show comparable results to surgery for patients that are older and not fit for surgery (patients with American Society of Anaesthesiologists (ASA) score >3). Ma et al. [57] in a single centre retrospective analysis of 11 years of experience reviewed the results of 52 healthy adults with T1a RCC who underwent treatment with percutaneous RFA even though they would have been suitable for surgery (ASA score of 1 or 2). Mean tumour size was 2.2 cm and follow-up for a mean time of 60 months (range 48-90 months) was performed. The authors reported RFS of 94.2% at both 5 and 10 years and overall 5- and 10-year survival rates of 95.7% and 91.1% respectively and concluded that RFA treatment provides durable oncological and functional outcomes for T1a tumour in healthy patients.

Katsanos et al. [58] in recent review and meta-analysis identified no significant difference in disease-free survival (DFS) between thermal ablation and surgical nephrectomy. There were fewer major complications reported with thermal ablation but this was not deemed statistically significant. The authors report a significantly higher repeat treatment rate with thermal ablation versus surgical nephrectomy. However, the overall rate of complications was significantly lower in thermal ablation cases versus surgical nephrectomies. There was a similar local recurrence rate of RCC in the two groups but a significantly higher eGFR reduction was reported in the surgical nephrectomy group.

Yang et al. [59] conducted a meta-analysis of six studies, to compare RFA with PN for small renal masses. The parameters that were placed into comparison were: Local recurrence rate, the 5-year-disease-free-survival, complications and impact of treatment on renal function. Studies where laparoscopic and intraoperative RFA was performed where also included. No statistical difference was revealed in the oncologic parameters and the complication rate however the treatment with RFA appears to preserve more of the renal function.

Yin et al. [60] in another meta-analysis included twelve retrospective comparative studies between RFA and partial nephrectomy for small renal tumours. The results of the data extrapolation were that the two methods offered similar outcomes regarding the oncologic outcomes (local recurrence rate and distant metastasis) and complication rate; RFA appeared to be associated with shorter hospitalization and with preservation of renal function.

6. Conclusion

Percutaneous ablation of small renal tumours is an established, minimally invasive treatment with excellent long-term oncologic results, particularly for T1a tumours. It offers similar cancer control with partial nephrectomy with lower morbidity and mortality and should be an available option for patients that are either not suitable or not willing to undergo surgical resection. R

Conflict of interest:
The authors declared no conflicts of interest.

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