Percutaneous irreversible electroporation for the treatment of small renal masses: The first Canadian case series

Bonnie Liu, MD; Jordyn Clark, MD; Trustin Domes, MD; Chris Wall, MD; Kunal Jana, MD

Department of Surgery, Division of Urology, University of Saskatchewan, Saskatoon, SK, Canada

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Abstract

Introduction: Irreversible electroporation (IRE) is a novel technology used in the minimally invasive treatment of small solid organ tumors. Currently, there is a paucity of literature studying treatment of small renal masses (SRMs) with IRE. Our pilot study is the first case series in Canada to use IRE in the treatment of SRMs.

Methods: This retrospective cohort pilot study includes five patients (three females and two males) who presented with a SRM that was deemed not amendable to any treatment other than a radical nephrectomy or IRE. The IRE procedures were carried out by an interventional radiologist in conjunction with a urologist using the Angiodynamics NanoKnife IRE device.

Results: Mean tumor size was 28 mm (range 18–39), with a mean R.E.N.A.L. nephrometry score of 8.4±0.55. Over a mean followup of 22.8 months (range 14–31), four out of the five patients did not have a radiological recurrence. No adverse events were reported after the five IRE procedures. Renal function was stable post-IRE, with no to negligible decreases in estimated glomerular filtration rate detected (range +2 to -13 mL/min/1.73 m^2).

Conclusions: Our pilot study demonstrates that renal percutaneous IRE is safe to use in the context of challenging-to-treat SRMs. Early radiological and renal function outcomes are encouraging, but further study is required to assess oncological success. The small sample size, retrospective nature of the study, relatively short followup, and lack of routine renal biopsy to confirm malignancy are the major limitations noted.

Introduction

Since its first use in human tissue ablation in 2005, irreversible electroporation (IRE) has gained popularity in treatment of small tumors.[1] Although the mechanism of action is still not fully understood, it is hypothesized that IRE induces apoptosis in targeted cells by causing non-selective permeability of the cell membrane.[2] The procedure involves delivering high-frequency and high-voltage electrical pulses to targeted tissues via electrodes, which are carefully placed to surround the tumor. The benefits of IRE compared to cryotherapy (CRA) or radiofrequency ablation (RFA) are the lack of a heat sink effect and sparing of collagen structures. This allows for the safe treatment of tumors located near vasculature and other important structures, such as nerves, biliary ducts, and the renal collecting system.[3]

The safety of IRE in the liver has been shown in many studies, and encouraging safety results have also been observed in the prostate, pancreas, and lung tissue.[1,4,5] To improve the safety profile of IRE, muscle relaxants and general anesthesia have been used to control muscle contractions induced by electrical currents, and the synchronization of electrical pulses with the heart rhythm has greatly reduced the incidence of cardiac arrhythmia.[3] Thomson et al found the safety profile of IRE use in liver, lung, and kidney compared very favorably to currently used thermal ablation technologies, especially when used in areas near vessels or other important structures.[6]

In the kidney, efficacy data on IRE in the treatment of small renal masses (SRMs) is limited, with treatment outcomes depending largely on tumor type and location in the kidney.[3,4] Porcine models have shown complete cellular death in areas of renal IRE ablation, with preservation of the collecting system, along with evidence of future urothelial regeneration.[7,8] There are a limited number of in vivo studies looking at the use of IRE in treatment of SRMs, and results on efficacy have been mixed.[2,6,9-11] Some of these studies have shown promising results, however, the scarcity of data makes it difficult to draw definitive conclusions.[3] Our pilot study is the first case series of IRE in Canada, and we hope to add to the growing body of literature surrounding the use of IRE in SRMs. The primary outcome of this pilot study was to assess safety and feasibility of IRE.

Methods

After obtaining ethics exemption (reference REB: BIO 494), we retrospectively collected demographic and clinical data for patients undergoing IRE. Our study involved five patients (three females and two males) who presented with SRMs

confirmed through contrast-enhanced trans-axial imaging (three found on computed tomography [CT], two patients with von Hippel Lindau [vHL] found on magnetic resonance imaging [MRI]). A change greater than 10 Hounsfield unit (HU) pre- and post-contrast on CT, or change in signal intensity of 15% pre- and post-contrast on MRI, was considered enhancement and reflective of tumor presence. The novelty of the procedure and the risks and benefits were explained to each patient, and consent obtained. Each patient had pre-procedure history, physical examination, blood work, and a chest x-ray to rule out evidence of metastatic disease. Patients were offered IRE treatment if they had a difficult-to-treat SRM that was deemed only amenable to a radical nephrectomy for tumor control, based primarily on the location of their renal mass. MRI was used to calculate the R.E.N.A.L nephrometry score[12] (radius of tumor at its maximal diameter, exophytic/endophytic characteristics of the tumor, nearness of the tumor to collecting system or sinus, anterior/posterior description in relation to polar lines, location relative to polar lines) for each patient's renal mass prior to IRE treatment. In addition, each patient's pre and post-procedure creatinine and estimated glomerular filtration rate (eGFR) (using the chronic kidney disease [CKD]-epi formula) were recorded to measure change in renal kidney function secondary to the procedure.

During the IRE procedure, all patients received a general anesthetic with muscle relaxants to protect against electrical current-induced muscle contractions. The procedure was performed with synchronization of IRE electrical pulses with the heart rhythm to prevent incidence of cardiac arrhythmias. Procedures were carried out by an interventional radiologist in conjunction with a urologist. The procedure was performed using the Angiodynamics NanoKnife IRE device, which has been approved for human use by Health Canada. NanoKnife settings varied depending on the size and location of the tumor. The 19-gauge probes were placed with ultrasound (US) and CT guidance and spaced at ranges of 1.5–2.5 cm apart. The number of probes used in each case ranged from 4–6. The IRE device was set to a maximum electrical voltage of 3000 Volts across each probe pair with at least 90 pulses per probe pair. An increase in amperage of at least 10 across each probe pair was required during treatment.

Procedure time ranged from 2–4.5 hours and all patients stayed in hospital overnight, with discharge the day following the procedure. Patients were monitored for infection and hematuria and provided with analgesia for pain control, if required. Any adverse events during the procedure were recorded and followup was planned prior to discharge. Followup included post-procedure creatinine and eGFR to monitor kidney function and MRI to monitor for residual or recurrent disease.

Results

Demographics

The mean age of the cohort was 48.2 years (range 33–72). Mean tumor size was 28 mm (range 18–39), with a mean R.E.N.A.L. nephrometry score of 8.4±0.55. Two patients had a solitary kidney and two patients had a history of vHL syndrome (Table 1).

Safety data

There were no adverse events recorded for any of the five IRE cases. Renal function was stable post-IRE, with no to negligible decreases in eGFR detected from the pre-IRE to most recent eGFR measurement (mean eGFR decrease of 5.4±6.80 mL/min/1.73m^2, range +2 to –13 mL/min/1.73m^2) (Table 2).

Tumor ablation data

With an average followup of 22.8 months (range 14–31), four out of the five patients did not have enhancement post-IRE gadolinium-enhanced MRI imaging (Fig. 1A). The patient with MRI enhancement, consistent with presumed residual tumor, was subsequently treated with RFA, and three-month post-treatment MRI suggests successful treatment of the residual enhancing renal tumor tissue (Fig. 1B).

Discussion

With the increased use of cross-sectional imaging for investigating non-specific abdominal symptoms, the incidence of SRMs has more than doubled since 1975, with 85% of patients with renal cell carcinoma (RCC) presenting asymp-

Table 1. Patient demographics

Patient no.	Age (yrs)	Gender	R.E.N.A.L. score	Tumor size (mm)	History of vHL	Solitary kidney
1	33	F	8x	25	No	Yes
2	34	F	8x	18	Yes	No
3	34	M	9p	30	Yes	No
4	68	M	8a	39	No	No
5	72	F	9x	28	No	Yes

vHL: von Hippel Lindau.

Table 2. Renal function parameters immediately before IRE and at last seen followup

Patient no.	Serum creatinine pre-IRE	Serum creatinine post-IRE	eGFR pre-IRE	eGFR post-IRE	Change in eGFR	Time (months)
1	34	36	139	133	-6	28
2	49	61	122	111	-11	32
3	118	140	69	56	-13	23
4	78	77	88	89	1	22
5	112	105	42	44	2	17

eGFR: estimated glomerular filtration rate; IRE: irreversible electroporation.

tomatically.[13] Radical or partial nephrectomy is the gold standard treatment for RCC, but with increased incidence and understanding of the natural history of SRMs, ablative techniques have gained favor. While both CRA and RFA techniques have proven to be effective for treating SRMs, higher complexity SRMs continue to be challenging to treat through local ablative techniques. Schmit et al found that SRMs with a R.E.N.A.L. nephrometry score of moderate (7–9) or high (10–12) treated with either RFA or CRA were associated with much higher complication and failure rates.[14] The mean R.E.N.A.L. nephrometry score for failed thermal ablation technique treatments was 7.2±1.9 vs. a mean score of 6.1±1.8 for successful treatments. Similarly, mean scores for tumors associated with major complications was 8.1±2.0 vs. 6.8±1.9 for tumors with no major complications. There was a 14.3% major complication rate and 11.4% local treatment failure rate for high-complexity renal masses, and the authors suggested avoiding percutaneous thermal ablation in high R.E.N.A.L. nephrometry score cases.

Unlike thermal ablation, this study demonstrates that another minimally invasive and nephron-sparing option, IRE, can be considered as a treatment option for patients with complex renal masses. All the patients in this cohort study had moderate R.E.N.A.L. nephrometry scores, with no adverse events following the procedure. In addition, there was no to negligible decreases in eGFR detected post-procedure. The findings of this study are in keeping with the current literature, where renal IRE has spared the urinary collecting system and maintained vessel patency.[3,4] Rubinsky and colleagues found that IRE can ablate tissue directly adjacent to blood vessels without damaging them, and Narayanan et al showed that IRE can safely treat tumors that are already encasing vessels.[15,16] This is one of the major benefits of IRE compared to RFA, where studies have shown that to achieve absolute tumor necrosis up to the vessel wall with RFA, severe damage to vessels is inevitable.[16] Vessel patency is important for protection of the normal surrounding parenchyma, as there is less ischemic damage and faster healing time.[7] Porcine studies looking specifically at the effect of IRE on the collecting system showed none of the acute and early complications seen in RFA or CRA, such as urine extravasation, fistula, obstruction, shrinkage, or necrotic ulceration.[8] Similar results have been demonstrated in vivo, where renal function following IRE was preserved in seven patients, with no complications (renal infarction, urinary leakage or retention) observed.[17] Similar to a study by Diehl and colleagues, our preliminary data shows that IRE is a viable and safe treatment option for patients with solitary kidneys.[18]

After an average MRI followup time of 22.80 months, there was one patient found with enhancement on MRI imaging, which is presumed to be residual tumor. This residual tumor was amenable and subsequently treated with RFA, with short-term imaging results suggesting success. Due to our small sample size, it is difficult to determine the significance of this. Based on imaging, Thomson et al observed a recurrence at three-month followup in two out of seven patients treated for SRMs, whereas Trimmer et al observed incomplete ablation in two of 20 patients at six-week followup.[6,19] Canvasser et al found an 87% two-year local recurrence-free survival rate in patients with biopsy-confirmed RCC or a history of RCC, which they considered suboptimal when compared to thermal ablation technologies.[20] Histological evidence of IRE has been quite varied, with most studies showing some cases with remnants of viable tumor cells in the region of ablation.[7,10,21] However, all histological examinations found that the ablation zones completely covered the tumor, with reliable necrosis and sharply demarcated areas between targeted tissue and healthy adjacent tissue.

One major barrier to increased use of IRE treatment for SRMs is the need for general anesthetic. Whereas thermal ablation technology requires only sedation, IRE requires general anesthetic in order to achieve the necessary muscular paralysis to protect against electrically induced muscle contraction.[6] Furthermore, the time needed to treat in IRE is substantially longer, with treatments lasting on average from 2.5–4 hours at our center vs. thermal ablation technologies, where treatment time is generally less than one hour.[22] Treatment time at our center has decreased slightly due to improvement in probe placement efficiency, however, time needed to achieve cell membrane disruption is unlikely to shorten.

Although this pilot study demonstrates a 20% presumed residual tumor rate and longer treatment times, these results are still viewed with cautious optimism. Patient selection for this study was very important, with patients enrolled if they had a SRM that would only otherwise be amenable to radical nephrectomy. In two cases where patients had solitary kid-

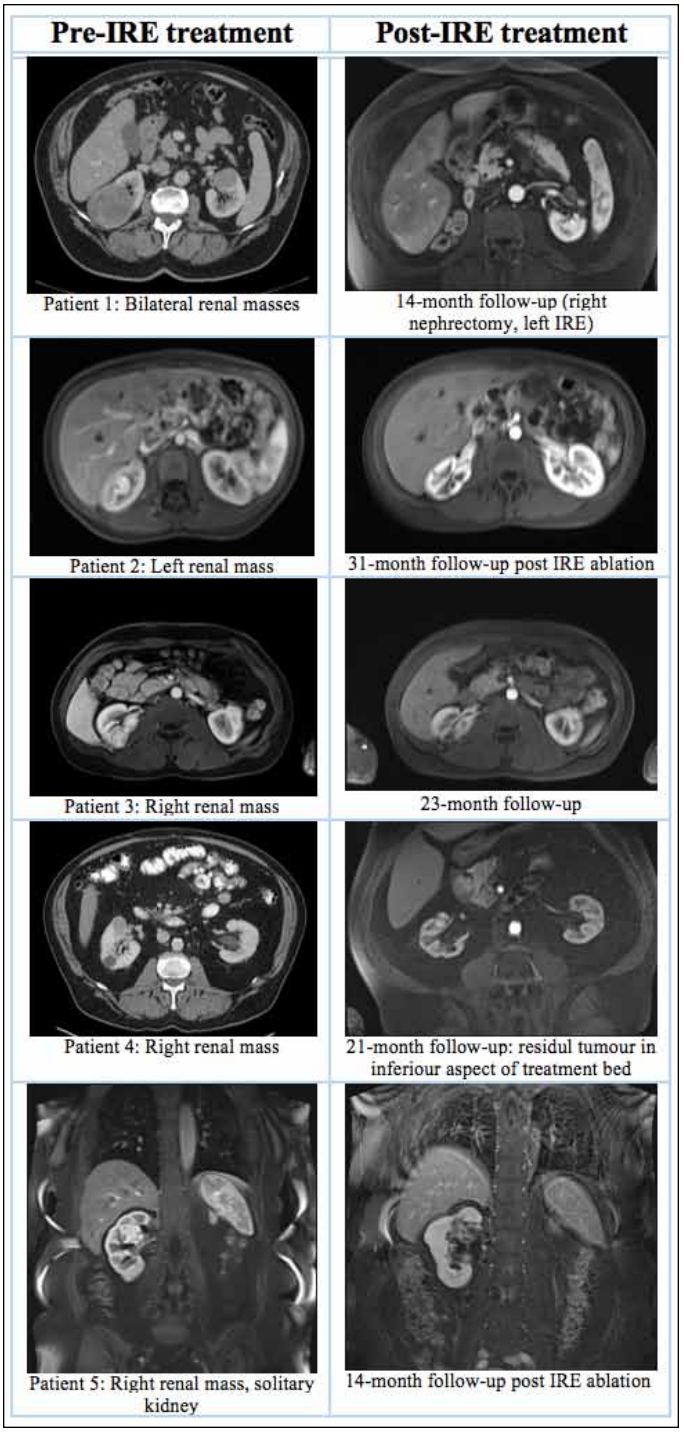

Fig. 1A. Magnetic resonance and computed tomography images of all patients pre- and post- irreversible electroporation (IRE) ablation. Only one patient had residual tumor at followup.

neys, this would have resulted in the need for lifelong dialysis. In addition, as this is a new technology to our center, there is a learning curve that may be impacting outcomes. With further practice with IRE, the impact of experience will likely play less of a role on patient outcomes.

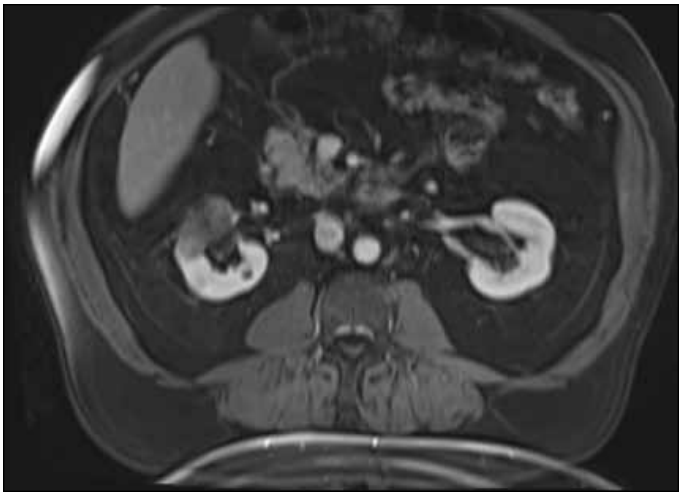

Fig. 1B. Three-month followup for patient 4 after radiofrequency ablation treatment for residual tumor showing complete ablation of tumor.

Further studies need to be conducted to assess long-term oncological control of IRE. Based on this pilot study, our center is currently conducting a prospective trial (n=20) to further assess the safety and efficacy of challenging-to-treat SRMs. Other studies may be warranted to determine the optimal IRE protocol to be used in SRMs. The current parameters used were originally developed based on voltage, frequency, and duration of electrical pulses needed to ablate normal tissue.[1] Tumor cells are known to be more resistant to apoptosis than normal cells and may not respond to IRE in the same way as normal tissue. Other hypothetical treatment options that merit exploration include combining chemotherapy with IRE. After IRE, there may be margins around the treatment area where reversible electroporation has occurred, making the cells more permeable to chemotherapy penetration.[3] Combining IRE with chemotherapy may be an option to eradicate any remaining viable tumor cells.

Given that this was an uncontrolled, small pilot study, the results are very preliminary and require validation. The small sample size, retrospective nature of the study, relatively short followup, and the lack of routine renal biopsy to confirm malignancy are the major limitations noted.

Conclusions

This pilot study reports the first five reported cases of IRE for SRMs in Canada. Preliminary results demonstrate that it is a safe modality that may prove useful in the context of challenging-to-treat SRMs, particularly where conventional treatment modalities would result in lifelong dialysis. Early radiological and renal function outcomes are encouraging, but further study is required to assess long-term oncological success.

Competing interests: The authors report no competing personal or financial interests related to this work.

This paper has been peer-reviewed.

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Correspondence: Dr. Kunal Jana, Department of Surgery, Division of Urology, University of Saskatchewan, Saskatoon, SK, Canada; dr.k.jana@sasktel.net