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Original Article

Feasibility and safety of irreversible electroporation (IRE) in patients with small renal masses: Results of a prospective study

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Abstract

Background: Irreversible electroporation (IRE) has the potential to overcome limitations of thermal ablation, enabling small renal mass (SRM) ablation near vital structures.

Purpose: To assess feasibility and safety of percutaneous IRE for the treatment of SRMs.

Materials and methods: This prospective study is a phase 2 trial (NCT02828709) of IRE for patients with SRMs. Primary endpoints are feasibility and safety. Device- and procedural-adverse events were assessed by Clavien-Dindo and Common Terminology Criteria for Adverse Events version 4.0 grading systems. Technical feasibility was assessed by recording the technical success of the procedures. Technical success was evaluated by performing a CT immediately after ablation where complete tumor coverage and nonenhancement were evaluated. Tumor charcateristics and patient characteristics, procedural and anesthesia details, postprocedural events, and perioperative complications were recorded.

Results: Ten SRMs were included with a mean tumor size of 2.2 cm (range 1.1−3.9 cm) were treated with IRE. Renal mass biopsies revealed 7 clear cell and 1 papillary renal cell carcinoma. Two renal mass biopsies were nondiagnostic. The median follow-up was 6 months (range 3−12 months). Technical success was achieved in 9 out of 10 cases. One patient had a grade 3 Clavien-Dindo complication (1/10, 95% Confidence interval (CI) 0.0179−0.4041). Mean anesthesia time was 3.7 hours (range 3−5 hours), mean procedural time was 2.1 hours (range 1 hour 45 minutes−2 hours 30 minutes) and mean ablation time was 50 minutes (range 20 minutes−1 hour 45 minutes). The creatinine preoperative and postoperative (1 week, 3 months, 6 months, and 12 months) did not significantly differ. In total, 8 out of 10 cases did not experience postoperative pain.

Conclusion: IRE in SRMs is safe and feasible. Renal function is not affected by IRE and postoperative pain is rare. Anesthesia time and procedural time are a potential concern.

Keywords: Irreversible electroporation; Small renal mass; Ablation; Safety; Feasibility; Creatinine; Postoperative pain

1. Introduction

Renal cell carcinoma (RCC) is one of the most lethal malignancies among urological cancers, and its incidence is increasing mainly due to the rise of the small renal masses (SRMs; <4cm) [1]. Thermal ablation is a nephron-sparing, minimal-invasive approach with the aim to obtain local tumor control while maintaining low toxicity profile. Guidelines generally recommend thermal ablation in elderly, comorbid patients, or in patients with a high risk of

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complete loss of renal function following surgery [2,3]. Although results are good, thermal ablation still has its limitations including the so-called heat sink effect, in which perfused blood vessels nearby the tumor cause inconsistent ablation effect [4]. Additionally, centrally located tumors are unsuitable for thermal ablation due to damage to the collecting system and the increased risk of bleeding and strictures [5,6].

Irreversible electroporation (IRE) is an electricity-based ablation modality, creating small nanopores in the cell membrane of tumor tissue while sparing connective tissue of the collecting system and vital structures [7]. Few retrospective studies regarding IRE in SRMs in humans have been published on safety and feasibility [8−11]. Translating IRE into clinical practice requires prospective assessment of its feasibility and safety following the idea, development, exploration, assessment, long-term study (IDEAL) criteria. Hence, phase 2 studies are needed before implementation of a new technology. The primary objective of this report is to assess feasibility and safety of IRE for the treatment of SRMs in a prospective IDEAL phase 2 study. Secondary objective is to assess the functional outcome by measuring the renal function and postoperative pain.

2. Materials and methods

2.1. Study design and patients

This prospective, IDEAL phase 2, human, in vivo study on feasibility and safety of IRE in SRMs study was approved by the local Institutional Review Board (2016_55/NCT02828709). The study was implemented according to the study protocol as previously reported [12]. Trial registration has been completed at the Dutch Central Committee on Research Involving Human Subjects (NL56935.018.16, www.ccmo.nl) and in the clinicaltrials.gov database (NCT02828709). This study conforms to the recommendations of the IDEAL collaboration and can be categorized as a phase 2 trial [13]. Primary endpoints were feasibility and safety. All patients gave written informed consent. Inclusion criteria were age ≥18 years, a SRM with contrast enhancement on cross-sectional imaging, signed informed consent, and candidate for ablative therapy. As a part of shared decision making, different treatment options for cT1a tumors were discussed with the patients including surgery, active surveillance, and ablation. The patient indications as well as the postablation scans were evaluated by a multidisciplinary kidney tumor panel including medical oncologists, interventional radiologists, and urologists. Single kidneys were also included as this is an indication for ablative therapy. All patients were admitted the day before the procedure and discharged the day after the procedure. Total sample size was planned on 20 SRMs according to the study protocol.

2.2. IRE procedure

Ablation was performed using the IRE device (Nanoknife, AngioDynamics, Queensbury, NY, USA) under general anesthesia with deep muscle relaxation [14]. The console comprises a low energy direct current generator, a foot switch, and 19G monopolar needle electrodes (15 or 25 cm length). IRE electrodes were placed percutaneously under CT guidance by an interventional radiologist experienced in IRE in conjunction with a urologist. A full neuromuscular blockade was achieved to prevent muscle contraction. Renal mass biopsy (RMB) was performed during the diagnostic workup or during the procedure prior to the ablation. The electrodes were placed to delineate the border between tumor tissue and normal renal parenchyma. Three to 6 electrodes with an active tip exposure of 10 mm to 25 mm, depending on the size of the tumor, were used to deliver pulses. The delivery of pulses was synchronized with the patients' ECG. First, 10 test pulses of 90 μs using 1,500 V/m^3 were administered, after which the voltage was adjusted to achieve 20 to 40 A. Second, when sufficient amperage was reached, 90 pulses of 90 μs were administered. When the depth of the tumor exceeded 20 mm, a pullback (retraction of electrodes) was performed or the active tip length was adjusted in order to cover the entire tumor. Immediately after ablation, a contrast-enhanced CT was performed to assess the absence of ablation zone enhancement. Ablation time (beginning of the test pulses until the end of the 90 treatment pulses), procedural time (the time for scanning, performing RMB and placing electrodes), and anesthesia time (from induction of anesthesia until the anaesthesiologist transfers the care of the patient to the postanesthesia care unit) were recorded. Additionally, perioperative complications and technical success were recorded.

2.3. Feasibility and safety

The safety of IRE was assessed by evaluating the device and procedural adverse events (AEs) using the Clavien-Dindo (CD) and Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 grading systems postoperatively and during the follow-up [15−17]. Tumor characteristics were described using the Renal and Padua classification [18,19]. Patient comorbidities were described according to the age-adjusted Charlson comorbidity index (ACCI) [20]. The feasibility of IRE was assessed by recording the technical success of the ablation, determined by obtaining a contrast-enhanced CT immediately after IRE. As instructed by guidelines, technical success was established when ablation was able to treat the tumor according to protocol, and when the ablation zone covered the whole tumor [21].

Serum creatinine was measured preoperative, and at 1 week, 3 months, 6 months, and 12 months post-IRE. Pain

Table 1
Patient characteristics and tumor characteristics, IRE data and technical feasibility.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10
Patient data										
Age	72	60	68	66	60	60	77	77	70	73
Male	x	x		x	x	x			x	x
Anticoagulant med	x*	x*		x	x*	x*			x	
ACCI	6	7	10	12	5	5	5	10	7	5
Solitary kidney		x	x	x						
Serum creatinine (mg/dl)	88	194	85	144	77	82	70	82	122	112
Tumor data										
Size lesion (cm)	1.8	1.5	1.8	1.7	2.7	2.8	3.9	2.3	2	1.1
dimensions lesion (cm)	1.8 × 1.8 × 2.0	1.5 × 2.0 × 1.0	1.8 × 1.7 × 2.1	1.7 × 1.7 × 1.8	2.7 × 2.4 × 2.4	2.8 × 2.8 × 2.6	3.9 × 3.9 × 3.7	2.3 × 2.3 × 2.3	2 × 2.1 × 2.5	1.1 × 1.4 × 1.4
Side; Location pole	L; middle	R; lower	L; upper	R; middle	R; upper	L; lower	L; central	R; upper	L; lower	L; upper
a/p/x	a	p	p	a	p	p	p	p	a	x
Padua	9	8	9	8	9	8	10	7	6	6
Renal	7	6	6	5	8	6	8	5	5	4
Biopsy	ccRCC F2	ccRCC F2	ccRCC F3	ccRCC F2	pRCC T1 F1	ND	ND	ccRCC F2	ccRCC F2	ccRCC F1
Tumour Node Metastasis (TNM)	cT1aG2cN0cM0	cT1aG2cN0cM0	cT1aG3pN1pM1	cT1aG2cN0pM1	cT1aG1cN0cM0	cT1aGxcN0cM0	cT1aGxcN0cM0	cT1aG2cN0cM0	cT1aG2cN0cM0	cT1aG1cN0cM0
In proximity to	1 mm calyx 12 mm colon	5 mm calyx	na	na	na	5 mm calyx	1 mm spleen 1 mm calyx	2 mm liver 2 mm calyx	5 mm calyx	5 mm colon

A = anterior; ACCI = age-adjusted Charlson comorbidity index; AZ = ablation zone; ccRCC = clear cell renal cell carcinoma; IRE = irreversible electroporation; p = posterior; pRCC = papillary renal cell carcinoma; RMB = renal mass biopsy.

x: Middle. x*: Anticoagulant medication stopped before ablation and restarted after ablation. TNM was uniformly used according to the seventh edition of the TNM 2009 classification system.

was measured preoperative, at 1 day, 1 week, 3 months, and 12 months post-IRE.

3. Results

From September 2016 until January 2018, 10 SRMs were included and treated in 10 treatment sessions (9 patients, 6 male, 3 female; mean age 68 years old [60−77]). Patient and tumor characteristics are described in Table 1. The median follow-up was 6 months (range 3−12 months). Fig. 1 shows the MRI pre-IRE and post-IRE, and a picture of the procedure. RMBs demonstrated 7 clear cell RCCs, 2 nondiagnostic cases, and 1 papillary RCC. One patient was diagnosed with bilateral SRMs and underwent bilateral ablation on 2 separate treatment sessions (SRM 5 and 6). In total 9 out of 10 SRMs (8 out of 9 patients) were discharged the day after the IRE procedure.

3.1. IRE procedure

Ablationand operative data are displayed in Table 2. Mean anesthesia time was 3.7 hours (range 3−4 hours). The mean ablation time was 50 minutes (range 20 minutes −1 hour 45 minutes).

3.2. Safety

All AEs are depicted in Table 3. Five AEs occurred in 4 patients within the first month after ablation. The 5 AEs consisted of 1 CD grade 3b (95% CI 0.0179−0.4041), 1 CD grade 2 (95% CI 0.0179−0.4041), and 3 CD Grades 1 (95% CI 0.1078−0.6032).

Case 2 had a single kidney and developed an increase in creatinine 1 day after the IRE procedure due to a blood clot that partially obstructed the ureter. A double J ureteric stent was inserted under general anesthesia and admission was prolonged with 6 nights. Subsequently, the renal function returned back to preoperative level 3 weeks after the procedure. Hence, the double J ureteric stent was removed (CD grade 3b, CTCAE grade 3). The patient did not require dialysis and did not have any lasting symptoms.

Case 8 developed a perinephric hematoma during the procedure, which was observed on the CT made immediately after ablation (Grade 1 CD, Grade 1 CTCAE). There were no signs of active bleeding. The hematoma resolved on imaging within 3 months. Case 8 also developed pyelonephritis 17 days after the IRE procedure, which required admission and IV antibiotics (CD grade 2, CTCAE grade 3). Case 9 experienced painful micturition during 3 days after the procedure (Grade 1 CD, Grade 1 CTCAE), which resolved spontaneously within a week after the IRE. Case 7 had an episode of painless hematuria without passage of clots 5 days after ablation, which lasted for 2 days and resolved spontaneously (Grade 1 CD, Grade 1 CTCAE). All patients recovered without any permanent sequela.

In total, 9 out of 10 cases returned back to preoperative renal function 1 week after ablation. All the cases retained preoperative renal function within 3 weeks after ablation. There was no urinary leakage or retention. No patient required dialysis.

3.3. Technical feasibility

The mean procedural time was 2.1 hours (range 1 hour 45 minutes−2 hours 30 minutes). Technical success was

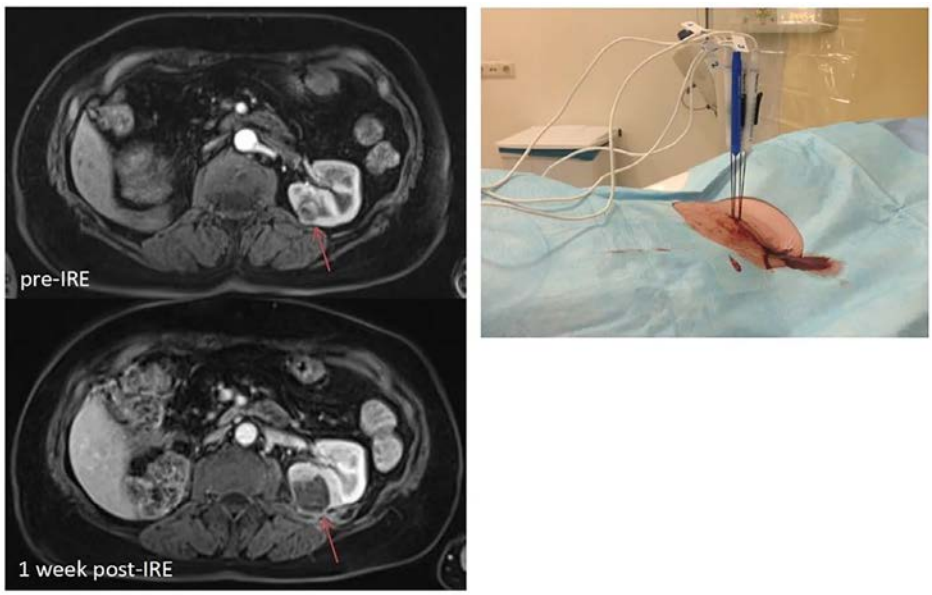

Fig. 1. Left: MRI of pre-IRE tumor (red arrow), MRI and post-IRE ablation zone (red arrow). Right: Picture of IRE electrodes (blue and white) during the procedure. They percutaneously apply high voltage to the tumor. IRE = irreversible electroporation. (Color version of figure is available online.)

Table 2
IRE data and operative data.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10
IRE data										
No. of electrodes; configuration	4; square	4; square	3; triangular	3; triangular	4; square	4; square	6; pentagonal with center	4; square	4; square	3; triangular
Pullback	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	No
Tip exposure (cm)	1.5	1.5	2.5	2.5	1.5	1.5	2.5	1.5	1.5	2.5
Pulse length (μs)	90	90	90	90	90	90	90	90	90	90
Min amperage	19	22	31	21	22	25	22	25	21	28
Max amperage	50	29	41	29	32	35	32	38	41	36
Min voltage	600	1500	2250	1650	1980	2850	2080	1650	1620	2250
Max voltage	2340	3000	2850	2400	3000	3000	2850	3000	2970	3000
Anesthesia time	4 h	4.5 h	3 h	3 h	4 h	3 h 45 min	4 h	3 h	4 h	3 hrs
Ablation time	1 h 45 min	40 min	45 min	30 min	1 h	30 min	1 h 20 min	45 min	1 h	20 min
Intervention time	2 h	3 h	2 h	2 h	2 h	2 h 30 min	1 h 45 min	2 h	2 h	1 hr 45 min
ECG-abnormalities	No	No	No	No	No	No	No	No	No	No
Technical success	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Enhancement AZ	No	No	No	No	No	No	No	No	No	No
Coverage of tumor by AZ	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes

Intervention time: Time for scanning, performing biopsy and placing IRE needles. Ablation time: Time for test pulses and treatment pulses. Anesthesia time: Time that patient was under general anesthesia. Technical success: Coverage of tumor by ablation zone and enhancement, assessed on CT performed immediately after ablation.

Table 3
Adverse events post-IRE.

Case	AE description	Treatment	Length stay	CD grade	CTCAE grade
2	Increase creatinine due to partially blocked ureter because of a blood clot. 1 d post-IRE until 7 d post-IRE.	JJ inserted under general anesthesia and prolonged admission	6 nights	3b[a]	3[a]
7	Episode of painless haematuria (light rosé color). 5 d post-IRE until 7 d post-IRE.	No treatment	NA	1	1
8	Perinephric hematoma developed during the electrode placement, which was visible on imaging until 1 wk after ablation.	No treatment	NA	1	1
8	Pyelonephritis with fever. 17 d post-IRE until 22 d post-IRE.	IV antibiotics and admission	5 nights	2[a]	3[a]
9	Painful micturition. 3 d post-IRE until 5 d post-IRE.	Urine stick and sediment was negative, hence no treatment	NA	1	1

NA = not applicable.
[a] Serious adverse event (SAE).

achieved in 9 out of 10 cases. One patient (Case 7) had a growing and enhancing lesion 3 months after ablation on CT. Retrospective evaluation by the multidisciplinary kidney tumor panel of the procedural CT scan performed immediately after ablation and the CT scan performed 1 week after ablation revealed residual tumor. This tumor was the largest of the cohort with a size of $3.9 \times 3.9 \times 3.7$ cm.

One technical problem was encountered during the procedure of Case 1. Throughout the ablation, the IRE console measured a high current error between 1 electrode pair during the pullback. Hence, the device was shut down twice during the procedure. The voltage was reduced to 600 v/cm^3 and the pulses were divided into 3 times 30 pulses instead of 1 time 90 pulses. After this, the procedure was completed without problems.

3.4. Functional results

The average creatinine serum was not significantly different pre-IRE vs. 1 week, 3 months, 6 months, and 12 months post-IRE (Fig. 2). In total, 2 out of 10 cases experienced mild to moderate pain at 1 day post-IRE (Case 2 and Case 8). Case 2 had an obstructed ureter by a blood clot (Grade 3 CD) and Case 8 had a perinephric hematoma (Grade 1 CD). In both cases, the pain was resolved 1 week post-IRE.

4. Discussion

IRE is characterized by high-voltage delivery of electrical pulses, proposing a potential safe treatment for centrally located tumors, and overcoming limitations of thermal

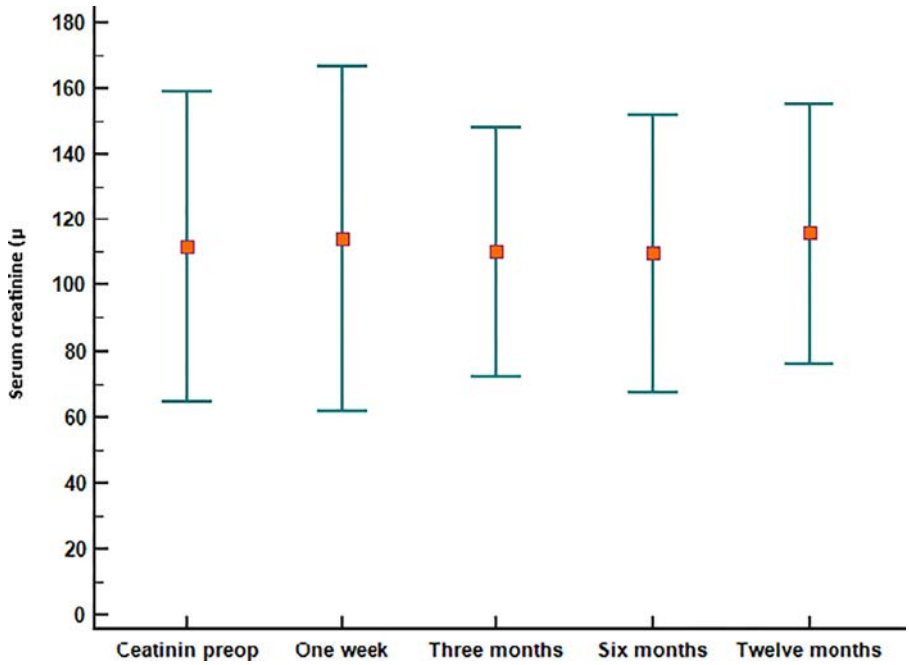

Fig. 2. The serum creatinine (Y axis) and the timeline (X axis). Mean creatinine preoperative was 112 (std dev 19.3, CI 62.0−161.3), mean creatinine 1 week post-IRE was 114.2 (std dev 21.4, CI 59.1−169.2), mean creatinine 3 months post-IRE was 110.2 (std dev 15.4, CI 70.4−149.9), mean creatinine 6 months post-IRE was 109.7 (std dev 17.3, CI 65.3−154.1), and mean creatinine 12 months post-IRE was 115.7 (std dev 16.2, CI 74.1−157.2). Preoperative vs. 1 week post-IRE, 3 months post-IRE, 6 months post-IRE, and 12 months post-IRE were not significantly different. std dev = standard deviation.

ablation. We report feasibility and safety of renal IRE in a prospective IDEAL phase 2 study. IRE was feasible for treating SRMs, with a high immediate technical success rate. IRE was well tolerated by patients, even in central SRMs.

RCC patients become increasingly more comorbid and older. Shared decision making and patient preferences result in the increased use of ablation. A recent meta-analysis has demonstrated similar recurrence rates and distant metastasis rates for partial nephrectomy vs. thermal ablation. However, the study was limited by heterogeneity among studies and the lack of randomized trials [22]. IRE has been proposed to overcome the heat sink limitation of thermal ablation. Additionally, centrally located SRMs that face a radical nephrectomy and consequently an impaired renal function can potentially be treated less invasively and in a nephron-sparing manner if IRE proves to be a safe and effective technique [23]. For these SRMs, IRE could potentially be a suitable treatment.

A limitation of our study is the small sample size. This pilot study was intended to precede a larger trial which will emphasize long-term endpoints. At the start of this project IRE for kidney cancer was still in the developmental stage, warranting us to start with a pilot study to prove feasibility and short-term safety before embarking on a larger study with more inclusions. Hence, adhering to IDEAL guidelines, it would not seem ethical to include a large number of patients at this stage.

We initially planned to include 20 cases. This number did not contain a formal sample size calculation and was mainly based on previous renal IRE studies, which included 3 to 20 cases [10,11,25,26]. Considering the high immediate technical success rate in the first 10 cases, a larger sample size was not required to prove feasibility. Therefore, we will proceed to a large trial to determine long-term clinical efficacy and safety. An amendment including the reduced sample size and the reason for stopping at 10 patients has been reviewed and accepted by the Institutional Review Board.

To date, no recurrences have occurred in our study population. One patient, Case 7, had residual tumor on cross-sectional imaging at 3 months post-IRE (1/10). The residual tumor was not biopsy proven but was highly suspicious on imaging. The patient underwent additional cryoablation and 3 months afterward cross-sectional imaging showed no enhancement.

During the ablation of Case 1, a technical error occurred. Due to the input of high voltage, the amperage outcome exceeded the border of 60 amperage, hence, the device shut down. Adjusting the voltage input produced a reasonable amperage (21 amperage) and still within the borders for adequate tumor destruction. The patient has remained recurrence-free to date.

To date, renal IRE has been prospectively investigated in 2 studies [10,24]. It is well known that retrospective safety analysis underreports AEs with high inter-rater variability, and is mainly outcome-driven. Wendler et al. demonstrated in a prospective, ablate-and-resect study in 7 patients, that IRE results in major damage to tumor tissue while sparing the urine collecting system or allowing for regeneration of

the urothelium [7]. Thomson prospectively proved safety and efficacy in 7 patients with kidney tumors [10].

In our prospective study we demonstrated IRE to be safe. One postoperative CD grade 3 AE occurred (an obstructed ureter by a blood clot) which, given the nature of the event, seems to be related to the procedure of needle-based ablation, and not specifically to electricity-based ablation effect. It is thought that the electrode punctured the collecting system, causing bleeding in the collecting system. The decrease in renal function resolved within 3 weeks and the patient did not require dialysis.

Additionally, the pyelonephritis (CD grade 2) occurred 17 days after IRE ablation. Taking the long interval between the infection and the IRE ablation into account, it is uncertain if infection was a direct result of the percutaneous ablation. Nevertheless, if so, it was a consequence of the ablation, this event seems to be procedure-related and not device-related. A total of 3 CD Grade 1 events occurred and were all transient and self-limiting. The demonstrated toxicity profile seems to be comparable to the renal IRE ablation in the literature [9,10,24,25].

Comorbidity and age generally increase the risk of complications and the ACCI in our population is high (mean ACCI 7 [range 5−12]), designating a high-risk population. Comparing complications with thermal ablation cohorts is therefore challenging, given the lower comorbidity rate and the large cohorts [27].

One case showed residual tumor in retrospective. This technical failure was probably caused by incorrect electrode, not entirely covering the tumor. This tumor was also the largest of the cohort measuring 3.9 × 3.9 × 3.7 cm and adjacent to the collecting system. The patient preferred additional ablation over surgery and underwent cryoablation of the residual tumor.

The long anesthesia time and procedural time is a potential concern as described earlier by Wendler et al., as increased anesthesia time increases the risk for complications [12]. On the contrary, the ablation time in our series is short with a mean of 50 minutes (range 20 minutes−1 hour 45 minutes). It appears that placing the needles is feasible, but time consuming due to need for precise- and multi-needle placement. For IRE specifically, the electrodes have to be placed in the borders of the tumor.

5. Conclusions

Renal IRE ablation in SRMs is safe and feasible. IRE offers a high immediate technical success rate in SRMs and is well tolerated with low toxicity profile. Renal function is not affected by IRE. Pain postoperative was rare and only occurred in patients with complications. Long procedural time and anesthesia time is a disadvantage of the technique.

Conflict of interests

The authors declare no conflict of interests.

Ethical considerations

The Institutional Review Board of the Academic Medical Center approved the study. The trial was conducted in accordance to the Good Clinical Practice standards.

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