

Irreversible electroporation: state of the art

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Abstract: The field of focal ablative therapy for the treatment of cancer is characterized by abundance of thermal ablative techniques that provide a minimally invasive treatment option in selected tumors. However, the unselective destruction inflicted by thermal ablation modalities can result in damage to vital structures in the vicinity of the tumor. Furthermore, the efficacy of thermal ablation intensity can be impaired due to thermal sink caused by large blood vessels in the proximity of the tumor. Irreversible electroporation (IRE) is a novel ablation modality based on the principle of electroporation or electropermeabilization, in which electric pulses are used to create nanoscale defects in the cell membrane. In theory, IRE has the potential of overcoming the aforementioned limitations of thermal ablation techniques. This review provides a description of the principle of IRE, combined with an overview of in vivo research performed to date in the liver, pancreas, kidney, and prostate.

Keywords: irreversible electroporation, IRE, tumor, ablation, focal therapy, cancer

Introduction

The past decades have yielded significant developments in the field of focal ablative therapy for the treatment of primary tumors or organ-confined distant metastases. Among the practiced techniques are cryoablation, radiofrequency ablation (RFA), microwave ablation, and high-intensity focused ultrasonography. These thermal ablative techniques provide a minimally invasive treatment option in selected tumors in multiple organs such as the liver, lung, pancreas, kidney, and prostate.¹⁻⁶

Focal tumor ablation requires precisely dosed and accurate targeting of the tissue to be ablated while preserving surrounding healthy tissues and vital structures such as blood vessels, nerves, and neighboring organs.^{7,8} The unselective destruction inflicted by thermal ablation modalities can result in damage to vital structures in the vicinity of the tumor. Furthermore, the efficacy of thermal ablation intensity can be impaired due to “thermal sink”. Close proximity of large vessels, bile ducts, or the renal collecting system can cause thermal fluctuations, leading to inconsistent ablation results.^{4,8}

Irreversible electroporation (IRE) is a novel ablation modality with the potential of overcoming the aforesaid limitations of thermal ablation techniques. This review provides a description of the principle of IRE, combined with an overview of in vivo research performed to date in tumors of the liver, pancreas, kidney, and prostate (Table 1). It has to be noted that the development of IRE is simultaneous to that of related techniques based on the same principle, such as electrochemotherapy (ECT), which combines electroporation with chemotherapy.^{9,10} This review is confined to IRE as an ablation technique and does not go into detail on ECT.

Evidence acquisition

For this nonsystematic review, we performed a literature search of PubMed for original and review articles written in English using the search terms “Irreversible

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Table 1 Overview of clinical trials focusing on IRE in liver, pancreatic, kidney, and prostate tumors

Author, year	Organ	Number of IRE ablations	FU method	FU term	Findings	Type of study	Level of evidence
Thomson et al, ³⁶ 2011	Liver Kidney	63 11	CT	Directly, 1 mo and 3 mo	In humans, IRE of liver and kidney tumors is safe if pulses are synchronized with ECG	Prospective cohort	4
Kingham et al, ³⁸ 2012	Liver	65	CT/MRI	Directly, 1/3/6 mo	IRE is safe for the treatment of liver tumors; one persistence and one recurrence observed	Retrospective cohort	4
Cannon et al, ⁴⁰ 2013	Liver	48	CT/MRI/PET, tumor markers	Directly, 3-monthly	Initial ablation success in 100% of cases, local recurrence-free survival 60% at 1 year; nine low-grade AEs, all resolved	Prospective cohort	4
Silk et al, ⁶¹ 2014	Liver	15	CT	Directly, 1–2 mo	Local tumor recurrence in six of eleven patients (55%); one biliary stent placed, possibly due to contact of IRE electrode with bile duct	Retrospective cohort	4
Cheung et al, ⁴¹ 2013	Liver	18	CT	1 mo, 3-monthly	Complete ablation in 13 (72%) lesions; no recurrences at mean FU of 18 mo; no serious complications	Prospective cohort	4
Scheffer et al, ⁶² 2014	Liver	10	Resection	Ablation–resection	Macroscopic vitality staining, nonviable IRE lesion covering complete tumor in eight of ten patients; microscopically, irreversible cell damage in the tumor-free margin of all specimens	Prospective cohort	4
Cheng et al, ⁴² 2015	Liver	6	CT, resection	1 mo, 3-monthly until liver transplant	Imaging: complete response in all cases; pathology: five lesions with complete necrosis, one lesion with viable tumor cells <5%	Retrospective cohort	4
Niessen et al, ³⁹ 2015	Liver	79	CT/MRI	Directly, 1.5/3/6 mo	Incomplete ablation in two cases; FU of 6 mo in 48 patients, 14 (29%) of whom showed local recurrence; risk factors for local recurrence: tumor volume and tumor type	Prospective cohort	4
Sugimoto et al, ³⁷ 2015	Liver	6	CEUS/CT/MRI	Directly, 1 wk, 1 mo, 3-monthly	Complete IRE ablation in five (83%) tumors; residual tumor in one case at 1 week; no serious complications	Prospective cohort	4
Narayanan et al, ⁴⁵ 2012	Pancreas	15	CT	Directly, 1 day, monthly	CT directly and 24 hours post-IRE showed patent vasculature in all cases; no severe complications or mortality occurred; grade 2 pancreatitis in one case, resolving spontaneously	Retrospective cohort	4
Paiella et al, ⁴⁶ 2015	Pancreas	10	CT	Directly, 1/2/3 mo	All cases treated successfully; overall survival: 7.5 mo; complications: pancreatic abscess (n=1) and pancreaticoduodenal fistula (n=1)	Prospective cohort	4
Martin et al, ⁴⁷ 2012	Pancreas	27	CT/MRI/PET	Discharge, 3-monthly	At 90 days, no signs of local recurrence in all patients; 17 possible IRE-related complications; grade 4/5 complications: bile leak (n=2) and portal vein thrombosis (n=2); one mortality at 70 days	Prospective cohort	4

(Continued)

Table 1 (Continued)

Author, year	Organ	Number of IRE ablations	FU method	FU term	Findings	Type of study	Level of evidence
Martin et al, ⁴⁸ 2013	Pancreas	54	CT/MRI/PET	Discharge, 3-monthly	Improvement IRE vs standard therapy: local PFS 14 vs 6 mo, distant PFS 15 vs 9 mo; and overall survival of 20 vs 13 mo; a total of 57 AEs: bile leakage (n=2) and duodenal leakage (n=2); one mortality occurred	Prospective cohort	4
Martin et al, ⁴⁹ 2015	Pancreas	200	CT/MRI/PET	Discharge, 3-monthly	Median overall survival 24.9 mo (range: 4.9–85 mo); complication rate of 37% (median: grade 2, range: grades 1–5); local recurrence in six (3%) patients	Prospective cohort	4
Pech et al, ¹⁸ 2011	Kidney	6	Resection	Ablation–resection	No changes in laboratory blood results or cardiac function; pathology (H&E), swelling of the ablated cells but no actual dead cells; no viability staining performed	Prospective cohort	4
Trimmer et al, ⁵² 2015	Kidney	20	CT/MRI	6 wk, 6 mo, 10 mo	Residual tumor at 6 wk in two of 20 cases; 6 mo FU available in 15 cases, no signs of recurrence; 1 y FU available in six cases, recurrence in one case; no major complications observed	Retrospective cohort	4
Wendler et al, ⁵³ 2015	Kidney	3	Resection	4 wk	IRE lesions covering all tumors completely, no residual tumor in margins; very small tumor residues of unclear malignancy observed within the ablation zone, requiring additional investigation using viability staining	Prospective cohort	4
Onik and Rubinsky, ⁵⁸ 2010	Prostate	16	Biopsy	3 wk	All patients remained continent and potent patients remained so after IRE; no evidence of cancer in ablated area in 15 cases; one patient refused biopsies	Prospective cohort	4
Valerio et al, ⁵⁹ 2014	Prostate	34	MRI	1 wk and 6 mo	Suspicion of residual disease in six patients, confirmed with biopsies in one case; complications: urinary retention (n=2), debris/hematuria (n=6), dysuria (n=5), urinary tract infection (n=5)	Retrospective cohort	4
Van den Bos et al, ²⁹ 2015	Prostate	16	Resection	4 wk	Complete ablation of tissue within the IRE electrode configuration, no skip lesions; IRE ablation zone 2.5–2.9 times larger than IRE needle configuration	Prospective cohort	4

Notes: Levels of evidence assigned according to *Oxford Centre for Evidence-based Medicine* – Levels of Evidence (March 2009); Howick et al (<http://www.cebm.net/?o=1025>).¹¹

Abbreviations: AE, adverse event; CT, computed tomography; ECG, electrocardiogram; FU, follow-up; H&E, hematoxylin and eosin; IRE, irreversible electroporation; MRI, magnetic resonance imaging; mo, months; PET, positron emission tomography; PFS, progression-free survival; wk, weeks; y, years; CEUS, contrast enhanced ultrasound.

Electroporation”, combined with “liver”, “pancreas”, “kidney”, and “prostate”. This search resulted in 203 hits, from which we selected 20 articles based on relevant contribution to clinical evaluation of IRE (Table 1). Case reports

were excluded. The selected articles had been published from 2011 to 2015, and 40% of the papers were published in 2015. Levels of evidence were assigned to the selected articles according to the Oxford Centre for Evidence-based

Medicine's "Levels of Evidence".¹¹ The reference lists of the selected papers were scrutinized for additional relevant articles (yielding 41 articles).

IRE principle

IRE is based on the principle of electroporation or electroporomeabilization, in which electric pulses are used to create nanoscale defects in the cell membrane. These defects, termed "nanopores" or "conductive pores", permeate the cell membrane, permitting molecules to pass into the targeted cells.^{8,12,13} Nanopore formation can be temporary (reversible electroporation), as used in the fields of gene transfection or ECT.^{9,14,15} Above a certain electrical threshold, the "nanopores" become permanent, causing cell death due to the inability to maintain homeostasis (IRE), as used in the food industry for sterilization and, more recently, in medicine for tumor ablation.^{16–18} The occurrence of IRE was initially considered an unwanted treatment side effect during reversible electroporation procedures. In the past decade, however, the focus has turned to IRE as an ablation modality, resulting in the development of a commercially available IRE console designed specifically for tissue ablation.^{8,19}

The presence of nanopores following the delivery of electrical pulses has been visualized using electron microscopy, showing temporary and permanent nanopores.^{12,13} The pulse-induced disturbances of the cells as a whole were studied using fluorescence microscopy.^{20,21} Because direct visualization of cell poration is difficult to follow over time, researchers have used indirect measures to quantify the effect of electroporation, such as changes in electrical conductivity or the uptake of dye following the admission of electrical pulses.^{22,23} However, visualization of membrane pores following the application of pulses does not definitively prove them to be the cause of IRE-induced cell death. Furthermore, *ex vivo* and animal research results have shown that IRE using the current clinically practiced treatment settings causes substantial increase in temperature in the targeted tissue.^{24–26} This secondary temperature development raises the question regarding the extent of the IRE effect that is caused by the temperature change versus that due to cell membrane poration. Therefore, as the field of tumor ablation using IRE progresses at a rapid pace, its underlying mechanism remains a subject of debate.^{16,24,27}

If we assume instead of temperature development, the theory of cell membrane poration, IRE is not dependent on thermal energy and is therefore not influenced by "thermal sink", promising consistent results in the vicinity of large vessels or the renal collecting system. Furthermore, IRE should

be defined so as to limit damage of the cell membrane, spare tissue architecture, and minimize damage to blood vessels, nerves, and the renal collecting system.²⁸ IRE lesions show a sharp demarcation between ablated and nonablated tissues, whereas thermal ablation techniques show a transitional zone of partially damaged tissue wherein insufficient temperatures were reached for definitive ablation.²⁹ This indicates that IRE ablation boundaries can potentially be planned more precisely compared to conventional techniques.

IRE device and procedure

The first, and at the time of writing only, commercially available IRE console for clinical use in tissue ablation is the NanoKnife™, also registered as the HVP-01 Electroporation System (Angiodynamics Inc, Queensbury, NY, USA). The system carries a CE mark and has US Food and Drug Administration approval for soft tissue ablation. The NanoKnife™ platform consists of a low-energy direct current generator interfaced with a computer system equipped with user-friendly treatment planning software (Figure 1A and B). The system has the capability of connecting up to six monopolar needle electrodes, 16 G in diameter and covered in a retractable insulation sheath, allowing for the adjustment of the active tip length (Figure 1C). Bipolar IRE electrodes are available; however, these are not commonly used after early animal research showed bipolar IRE to result in lower ablation volumes, combined with a higher risk of collateral damage.³⁰

Further parameters to be adjusted in IRE ablation are voltage, pulse number, pulse length, electrode number, and electrode spacing. The parameters can be entered into the IRE console, which subsequently generates a two-dimensional (2D) representation of the ablation shape, perpendicular to the direction of the inserted needle electrodes (Figure 1B). Knowledge on how to tailor IRE settings to specific tissue/tumor types remains limited. Research into simulation of the IRE ablation zone, in order to aid IRE ablation planning, is under way but has not yet yielded accurate results.³¹ Except for slight variations, IRE settings are similar for most research into tumor ablation. Currently practiced IRE settings for tumor ablation are voltage 1,500 V/cm, 70–90 pulses of 70–90 μ s, electrode spacing 1.5–2 cm, and active electrode tip length 1–1.5 cm.

In order to prevent complications as a result of the administration of high-intensity electrical pulses, two main precautions are generally taken during IRE procedures. First, to prevent severe muscle contractions, IRE procedures take place under general anesthesia with additional

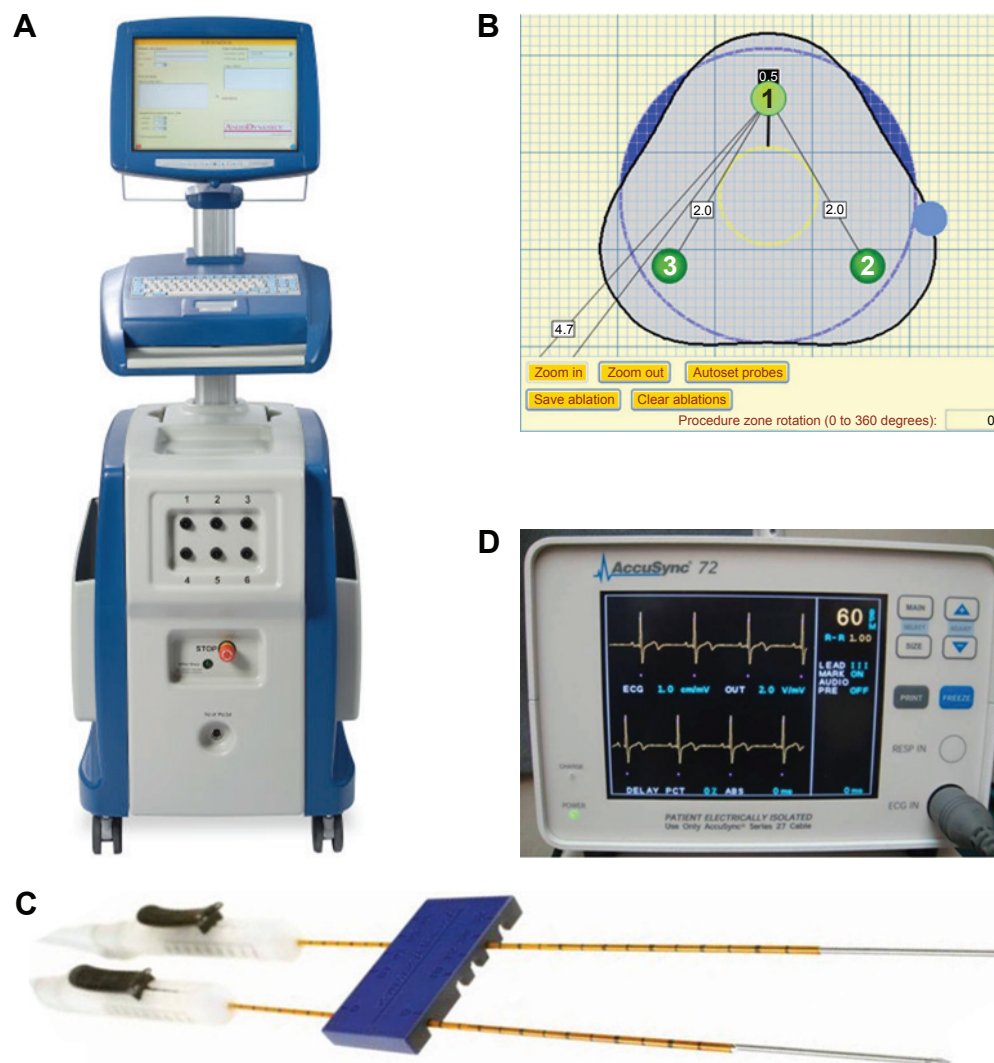


Figure 1 IRE equipment.

Notes: (A) The NanoKnife™ IRE console. (B) User-friendly treatment planning software generates a 2D representation of the ablation zone, perpendicular to the direction of the inserted needle electrodes. (C) Monopolar needle electrodes (16 G), covered in a retractable insulation sheath, allowing for adjustment of the active tip length. The blue spacer allows for parallel external fixation of the IRE needles. (D) AccuSync ECG synchronizer, allowing for synchronization of the IRE pulses with the cardiac rhythm.

Abbreviations: ECG, electrocardiogram; IRE, irreversible electroporation; 2D, two-dimensional.

muscle relaxation.³² Second, the administered IRE pulses could potentially cause cardiac arrhythmia, depending on the distance of the ablation spot to the heart.³⁶ Therefore, synchronization of the IRE pulses with the cardiac rhythm is advised. A synchronization device can be interfaced to the IRE console to ensure accurate pulse timing (Figure 1D). The IRE electrodes are positioned under computed tomography (CT) and/or ultrasound guidance in a similar manner to RFA or cryoablation probes. In order to guarantee an equal distribution of the electrical field, the electrodes need to be placed exactly parallel. External spacers are available to interlock the electrodes (Figure 1C). In prostate ablations, a brachytherapy grid can be used for needle targeting and fixation.²⁹

In vivo IRE results

Liver

Conventional thermal ablation techniques, specifically RFA, have been proven effective in the treatment of hepatic tumors in selected patients.^{33,34} Thermal ablation in the liver is limited by the risk of thermal damage to large vessels, bile ducts, gall bladder, hepatic capsule, and extrahepatic organs.³⁵ Furthermore, the presence of large vessels may lead to heat sink, impairing ablation results.

IRE of tumors of the liver is the most extensively investigated, with nine trials reporting on its efficacy and safety (Table 1). In terms of safety, all nine studies concluded that IRE was well tolerated by patients, and that IRE is safe for treating liver tumors under the condition that the procedure

is electrocardiographically synchronized to the cardiac rhythm.^{36,37} IRE was especially feasible in tumors with close proximity to major vital structures, for instance, bile ducts, portal veins, and arteries.^{38,39}

The tumor response rate varied from 50% to 98.1%.^{36–38,40–42} Highest response rates were described in patients with a median tumor size of 1 cm in high-risk locations, such as perivascular regions and positions close to major biliary structures, investigated by Kingham et al.³⁸ Lowest response rates were demonstrated in patients with liver metastasis from numerous different primary tumors, fluctuating from 1.7 to 6.3 cm in size.³⁶ The overall local recurrences at 6-month follow-up varied from 0% to 55%.^{38–41}

The aforementioned response rates and recurrences vary widely across studies, which is probably due to the heterogeneity of patient populations, ablation protocols, and tumor characteristics.

In conclusion, success of IRE in the liver mainly depends on lesion size. Thomson et al³⁶ reported that liver metastases >5 cm did not show any response with regard to tumor control. When four or more unipolar electrodes are required to ablate one lesion, the overall response rate decreases drastically. This is imaginable because it is technically challenging to place a multiple-needle array. Additionally, the field of electrical impulses is wider and therefore less controllable. A further risk factor associated with local recurrence after IRE is tumor type, with hepatocellular carcinoma (HCC) being less associated with recurrence than metastatic disease ($P=0.023$ for HCC, cholangiocellular carcinoma, or metastatic disease).³⁹

Early results of IRE appear to be promising for small liver lesions close to vital structures, as no complications that were directly related to the IRE ablation were described. Nonetheless, comparative studies with conventional thermal ablative therapies need to be carried out to prove its oncological efficacy.

Pancreas

Pancreatic tumors are aggressive in nature. Furthermore, they are generally complicated to treat due to close proximity to vital structures, such as the portal vein, the celiac trunk, and the superior mesenteric vein.⁴³ In patients with unresectable locally advanced pancreatic cancer (LAPC), RFA has been shown to improve survival. However, RFA treatment is characterized by a high rate of complications.⁴⁴

Narayanan et al⁴⁵ evaluated the safety of percutaneous pancreatic IRE in 15 ablations in 14 patients. No severe complications or mortality occurred. One patient developed a grade 2 pancreatitis, which resolved spontaneously.

Similarly, Paiella et al⁴⁶ reported on the safety and feasibility of pancreatic IRE in ten patients diagnosed with unresectable LAPC. Two complications were observed, namely, a pancreatic abscess and a pancreaticoduodenal fistula, both in the same patient.

A considerable amount of experience in pancreatic IRE has been obtained by the research of Martin et al.^{47–49} Starting with a pilot study in 27 patients, aimed at studying the safety and feasibility of pancreatic IRE,⁴⁷ 17 possible IRE-related complications were reported in four patients, ranging from grades 1 to 5. Grade 4 and grade 5 complications consisted of bile leak ($n=2$) and portal vein thrombosis ($n=2$). One mortality occurred at 70 days post-IRE. This was due to portal vein thrombosis, which was presumably induced or worsened by the IRE treatment. At 90-day follow-up, none of the patients showed signs of local recurrence.⁴⁷ In a subsequent study, Martin et al reported on pancreatic IRE in a group of 54 unresectable LAPCs.⁴⁸ When comparing IRE patients to those on standard therapy, an improvement in local progression-free survival was observed (14 vs 6 months; $P=0.01$), distant progression-free survival (15 vs 9 months; $P=0.02$), and overall survival (20 vs 13 months; $P=0.03$). A total of 67 adverse events were reported in 32 patients of the IRE group, including two cases of bile leakage and two cases of duodenal leakage. One mortality occurred post-pancreatic IRE.⁴⁸ A recent analysis of 200 LAPC stage III patients treated with IRE in addition to conventional chemotherapy and radiation therapy showed equally promising results.⁴⁹ Median overall survival in these patients was 24.9 months (range: 4.9–85 months), at a complication rate of 37% (median: grade 2, range: grades 1–5). In six (3%) patients, a local recurrence was observed.⁴⁹

According to these studies, IRE has proven to be an effective treatment in pancreatic carcinomas, with an improvement in progression-free survival and overall survival when compared to chemotherapy or chemoradiation therapy. However, a few limitations deserve consideration. Sample sizes are small and therefore confine the clinical evidence. We recommend that trials should be repeated with larger populations. Additionally, complication rates are high and severe in nature. A major part of the aforementioned studies included unresectable pancreatic carcinomas, a population that is known for its high morbidity and mortality. Due to high complication rates and the aggressive nature of these tumors, it might be difficult to determine the overall effect of IRE in pancreatic carcinomas. However, first results indicate that IRE is a suitable option and should be considered in patients diagnosed with unresectable pancreatic carcinoma.

Kidney

The alternative for nephron-sparing surgery is the use of RFA or cryoablation in selected patients presenting with a small renal mass (≤ 4 cm). Oncologic outcomes of ablative therapies are slightly lower compared to the results from conventional surgery; this is, however, balanced by a lower complication rate and a preservation of renal function.^{50,51} Thermal ablative treatments are contraindicated for tumors in close proximity to the renal collecting system, the large blood vessels, or the abdominal organs. IRE could potentially extend the application of focal therapy in kidney cancer if proven safe and reliable in these high-risk locations.

The first-in-human study into the feasibility and safety of IRE ablation of renal cell carcinoma was performed by Pech et al.¹⁸ This “ablate-and-resect” pilot study included six patients with a renal mass requiring radical nephrectomy. IRE was performed under anesthesia immediately before resection of the kidney. In one patient, a single intraoperative supraventricular extrasystole was encountered, without any further electrocardiographic abnormalities during follow-up. Histopathological examination, using hematoxylin and eosin staining, of the resected tumors showed swelling of the ablated cells, but no actual dead cells were observed.¹⁸ No additional viability staining was performed.

Thomson et al³⁶ investigated the safety of IRE in renal masses in their multiple organ (liver, lung, and kidney) IRE study. IRE of the kidney was performed in ten tumors of seven patients. One patient developed an obstruction of the ureter, which previously had been obstructed as a result of RFA ablation treatment. None of the remaining patients showed signs of stricture while the ureter or collecting system was within the ablation zone. Two patients suffered transient hematuria, both of whom had received IRE treatment extending into the central portion of the kidney. Two patients required a second IRE treatment after 3 months of follow-up.³⁶

Trimmer et al⁵² reported on 20 cases of IRE in small renal masses, with 1 year of imaging follow-up. Two out of the 20 cases presented with residual tumor at 6-week follow-up imaging and were treated with salvage RFA. Six-month follow-up was available in 15 cases showing no signs of recurrence. One-year follow-up was available in six cases, showing recurrence in one case, which was treated by partial nephrectomy. No major complications were observed.⁵²

The most recent report on renal mass IRE is from Wendler et al,⁵³ providing preliminary results of a trial in which the IRE lesions are resected 4 weeks postablation. This interim report describes the results in the first three patients and gives

a detailed report on the histopathology of an IRE ablation zone. The IRE lesions cover all three tumors completely, with no residual tumor in the margins. Very small tumor residues of unclear malignancy have been observed within the ablation zone. The viability, and with that the oncological consequence, of these small residues is unclear. The authors aim to perform additional viability staining in more patients to further investigate this issue.⁵³

It is concluded that IRE is safe and feasible in the treatment of kidney tumors. No major complications occurred in any of the studies. Nonetheless, the golden standard, a laparoscopic partial nephrectomy, is a highly effective minimally invasive treatment, which is accompanied by very low complication rates and side effects. Therefore, we consider that IRE should be considered in patients diagnosed with renal tumors close to vital structures as only a second-line treatment.

Prostate

Prostate cancer is the most prevalent form of cancer in men, with an increase in detection of localized disease in the Western world due to the use of prostate-specific antigen testing and improved imaging techniques.^{29,54} Conventional therapies in prostate cancer (prostatectomy and radiotherapy) are associated with high incidence of treatment side effects. Common side effects resulting from the destructive nature of conventional treatment include urinary incontinence (0%–20%), bowel problems (22%–36%), and erectile dysfunction (19%–74%).^{55–57} Focal therapies, including IRE, have the potential to reduce these burdens by sparing vital structures such as the urethra and the neurovascular bundles.

The first to report on the use of IRE in prostate cancer were Onik and Rubinsky,⁵⁸ treating 16 patients with localized cancer for whom preservation of potency and continence was a major concern. All patients were continent immediately upon removal of the catheter 0–3 days posttreatment. Patients who were potent before remained so after IRE treatment. However, two patients who received bilateral IRE treatment required 6 months for full return of potency. Treatment success was determined after 3 weeks by transperineal biopsies. Fifteen patients showed no evidence of cancer in the targeted area, with one patient refusing follow-up. In one patient, a microfocus Gleason 6 cancer was found outside the targeted area.⁵⁸

Valerio et al⁵⁹ performed IRE of prostate cancer in 34 patients, assessing safety and feasibility. A total of 12 grade 1 complications and ten grade 2 complications occurred. Follow-up consisted of multiparametric magnetic

resonance imaging (MRI) at 1 week and 6 months post-IRE. Complications included urinary retention (n=2; 6%), debris/hematuria (n=6; 18%), dysuria (n=5; 15%), and urinary tract infection (n=5; 15%). Six patients (18%) showed suspicion of residual disease, four of whom underwent a secondary treatment. Only one patient had histological confirmation of treatment failure, through transperineal biopsies, and decided to undergo a radical prostatectomy.⁵⁹

Recently, Van den Bos et al²⁹ performed an ablate-and-resect study, performing IRE in 16 prostate cancer patients 4 weeks prior to radical prostatectomy. Their study focused on safety and feasibility, not specifically targeting the prostate cancer, and therefore did not present results on cancer-free rates. However, pathology results showed complete ablation of tissue (necrosis and fibrosis) within the IRE electrode configuration. Furthermore, the IRE ablation zones were found to extend beyond the IRE needles, with three needle ablations being 2.9 times larger than the needle configuration and four needle ablations being 2.5 times larger. Importantly, no skip lesions were observed within the needle configuration.²⁹

In theory, focal treatment in prostate cancer is a promising approach as current conventional therapies have a lot of limitations. Radical prostatectomy and radiotherapy both have poor functional outcomes, with high rates of urinary incontinence and erectile dysfunction. It is believed that IRE has the potential to overcome these side effects. However, to date, there is little evidence on oncological outcome and no long-term results of IRE in prostate cancer are available. To our knowledge, there is sufficient evidence to say that IRE is a safe and effective focal treatment modality in prostate cancer, but a large trial is needed to warrant its oncological efficacy.

Considerations and future perspectives

The introduction of new treatment techniques should adhere to a standardized methodology, such as the IDEAL recommendations.⁶⁰ Following such guidelines will result in a stepwise, safe, and scientifically valid evaluation of the new technique at hand. Research into *in vivo* IRE is focusing on several different organs simultaneously, with progress being at a different stage for each field. Although IRE research in liver and pancreas is leading the way, it is important to not take these results as evidence for the safety and efficacy of IRE in other organs, that is, skipping ahead in the organ-specific evaluation of IRE.

Several trials are expected to provide additional evidence on *in vivo* IRE in the near future. The COLDFIRE-II trial

(NCT02082782) is aimed at including 29 patients with colorectal liver metastasis for treatment with percutaneous CT-guided IRE, with follow-up by positron emission tomography (PET)-CT and PET-MRI. The same research group is finalizing the results of the PANFIRE trial (NCT01939665), having included 15 patients with locally advanced pancreatic adenocarcinoma, treated with percutaneous IRE and subsequently followed by cross-sectional imaging (CT/MRI) and blood tumor markers. Two further trials focusing on IRE in pancreatic cancer are the IMPALA trial (NL44713.018.13) and the pancreatic IRE trial (NL45048.058.13) at the Leiden University (the Netherlands).

Although the evidence on IRE in different organs is rapidly expanding, most results remain in the form of low-quality cohort studies, to be graded as level 4 of evidence.¹¹ Different groups are collaborating by pooling IRE data in registries. Uniform and central collection of data will result in larger data sets, allowing for more substantial evaluation of IRE safety and efficacy. Examples of such registries are the Soft Tissue Ablation Registry (STAR) and the prostate IRE registry (NCT02255890) of the Clinical Research Office of the Endourological Society (CROES). A considerable improvement on the available evidence will come from the CROES coordinated multicenter randomized controlled trial (RCT) (level 2b) into IRE in prostate cancer (NCT01835977). This recently started RCT will compare the IRE safety and efficacy between a focal IRE ablation and extended IRE ablation of the prostate.

For IRE to evolve into an accepted segment of standard therapy more research is needed, directed at tissue-specific device settings and ablation protocols, further evaluation of early ablation results, and follow-up methods, completed by studies focused on long-term oncological outcomes. At this phase of development, it is essential to perform IRE as much as possible in the setting of a clinical trial. As it involves the use of a medical device instead of a pharmacological product, the optimal way to proceed is following the recommendations of the IDEAL collaboration.⁶⁰ This evaluation equals surgical innovation to the different phases of pharmacological research. IRE has been described for the IDEAL stage 2a (development phase). To develop IRE into a minimally invasive treatment device, results should be compared with a standard test at use in Phase IIb and Phase III RCT trials. The best trial for the clinical evaluation of a new technique is an RCT. These trials are, however, seldom undertaken because they are time consuming and expensive. The common trial design, a prospective cohort, should consist of a strict treatment protocol in combination with a clearly

defined population. If inclusion in a trial is not possible, patient data should at least be pooled uniformly in a centrally coordinated registry.

Conclusion

IRE is showing promising results in early clinical research. The prospect of treating tumors in the vicinity of vital structures gives IRE a potential edge over conventional ablation techniques, which are mainly thermal in nature. However, for IRE to evolve into a clinically accepted ablation technique, further development is needed on multiple fronts, namely, tissue-specific device settings/protocols, ablation monitoring, and follow-up imaging, as well as long-term oncological outcomes. At this stage of development, it is essential to perform IRE in the setting of well-designed clinical trials and, if trial participation is not possible, at least to pool patients in a registry. Furthermore, as electrical properties vary among different tissue types, it is important not to interchange outcomes between organs, undermining the organ-specific evaluation of IRE.

Disclosure

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