

# Anaesthetic management during open and percutaneous irreversible electroporation

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## Editor's key points

- Irreversible electrocorporation is a novel tumour ablation technique involving repeated application of electrical energy.
- The electrical pulses have the potential to cause seizures, arrhythmias, and muscle contractions.
- The authors report the incidence of complications among 28 patients undergoing the technique.
- They found no major complications and a low incidence of minor complications.

**Background.** Irreversible electroporation (IRE) is a novel tumour ablation technique involving repetitive application of electrical energy around a tumour. The use of pulsed electrical gradients carries a risk of cardiac arrhythmias, severe muscle contractions, and seizures. We aimed to identify IRE-related risks and the appropriate precautions for anaesthetic management.

**Methods.** All patients who were treated with IRE were prospectively included. Exclusion criteria were arrhythmias, congestive heart failure, active coronary artery disease, and epilepsy. All procedures were performed under general anaesthesia with complete muscle relaxation during ECG-synchronized pulsing. Adverse events, cardiovascular effects, blood samples, cerebral activity, and post-procedural pain were analysed.

**Results.** Twenty-eight patients underwent 30 IRE sessions for tumours in the liver, pancreas, kidney, and lesser pelvis. No major adverse events occurred during IRE. Median systolic and diastolic blood pressure increased by 44 mm Hg (range –7 to 108 mm Hg) and 19 mm Hg (range 1–50 mm Hg), respectively. Two transient minor cardiac arrhythmias without haemodynamic consequences were observed. Muscle contractions were mild and IRE caused no reactive brain activity on a simplified EEG. Pain in the first 24 h after percutaneous IRE was generally mild, but higher pain scores were reported after pancreatic treatment (mean VAS score 3; range 0–9).

**Conclusions.** Side-effects during IRE on tumours in the liver, pancreas, kidney, and lesser pelvis seem mild and manageable when current recommendations for anaesthesia management, including deep muscle relaxation and ECG synchronized pulsing, are followed. Electrical pulses do not seem to cause reactive cerebral activity and evidence for pre-existing atrial fibrillation as an absolute contra-indication for IRE is questionable.

**Keywords:** ablation techniques; anaesthesia, general; EEG, electroencephalography; electroporation, methods; liver neoplasms, surgery; pancreatic neoplasms, surgery

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Irreversible electroporation (IRE) is a novel tumour ablation technique based on the local application of an electrical field between two or more electrodes inserted around a tumour. Multiple cycles of short, extremely high-voltage electrical pulses alter the transmembrane potential of tumour cells, leading to the creation of nanoscale defects in the lipid bilayer of the cell membrane, increasing membrane permeability. With the appropriate electrical parameters (90 pulses of 70  $\mu$ s; electric field strength 1500 V cm<sup>-1</sup>; delivered current 20–50 A), the membrane permeability becomes permanent and the cell eventually dies because of loss of

homeostasis.<sup>1,2</sup> Because cell death in IRE is based on electrical energy rather than thermal energy, the technique has two advantages over thermal ablation techniques like radiofrequency ablation (RFA). First, whilst IRE effectively destroys all cells within the ablation area, the extracellular matrix is preserved. As a consequence, vascular, biliary, and nervous structures rich in extracellular collagenous and elastic structures remain intact.<sup>3,4</sup> Secondly, IRE is unaffected by the so-called heat-sink effect, in which incomplete tumour ablation may occur near large vessels as a result of loss of heat via blood flow.<sup>5</sup> Therefore, IRE may represent an effective alternative

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for tumours that cannot be resected or thermally ablated because of unfavourable location. In light of the promising results of the first trials investigating the safety and efficacy of IRE in different organs, we anticipate that the therapeutic use of IRE will expand rapidly in the near future.<sup>6–9</sup>

For the anaesthesiologist, the pulsatile application of electrical pulses with a very high voltage presents specific challenges, including the possible triggering of cardiac arrhythmias caused by increased cell membrane permeability of electroporated tissue, which opens a path for ion transport.<sup>10</sup> Also, severe muscle contractions and epileptic seizures could occur because of stimulation of muscular or nervous tissue.<sup>11</sup> Therefore, specific precautions in intraprocedural management are required in order to safely perform IRE. For example, as complete muscle paralysis is necessary to prevent muscle contractions, all IRE procedures require general anaesthesia and the use of neuromuscular blocking agents. Furthermore, to prevent arrhythmias, the electrical pulses must be administered synchronously to the heart rhythm, because external electrical stimuli delivered during the absolute refractory period of the heart are incapable of inducing an action potential.<sup>10</sup>

Current literature on anaesthetic management for IRE procedures is limited to a single publication by Ball and colleagues, who reported their initial experience in 21 patients treated with CT-guided percutaneous IRE for hepatic, renal, and pulmonary tumours and formulated guidelines for this procedure.<sup>11</sup> In our study, we aimed to broaden the experience of open and percutaneous IRE to an additional patient population with different tumour types and to confirm previous formulated guidelines for anaesthetic management. To this end, we specifically focused on IRE-related side-effects and the appropriate precautions with respect to anaesthetic management of open and percutaneous procedures in different organs.

## Methods

This study was conducted with the approval of the Medical Ethics Committee of the VU University Medical Center. The study was designed and conducted in accordance with Good Clinical Practice and the principles of the Declaration of Helsinki. All patients provided written informed consent.

## Patients

All patients treated with open or percutaneous IRE between August 2012 and September 2013 were prospectively included in a database and analysed. This included patients participating in the COLDFIRE-I trial, in which patients who were already undergoing surgical resection of colorectal liver metastases (CRLM) were treated with IRE during surgery 60 min before resection (Clinicaltrials.gov registration number: NCT01799044). All other patients underwent IRE in the liver, pancreas, kidney, or lesser pelvis on clinical indication, because of proximity of the tumour to vital structures precluding surgical resection or thermal ablation. A designated multidisciplinary board determined local treatment. All patients had a histologically proven malignancy and underwent appropriate pre-procedural imaging. Inclusion criteria were ASA classification III or more

and adequate bone marrow, hepatic, and renal function. Exclusion criteria were cardiac arrhythmias requiring anti-arrhythmic therapy or pacemaker/implantable cardioverter-defibrillator, a history of congestive heart failure (NYHA class higher than II), active coronary artery disease, uncontrolled hypertension, and epilepsy.

## Anaesthetic management

Preoperative screening was performed with specific emphasis on contra-indications for IRE. Patients undergoing laparotomy received a thoracic epidural before surgery. The anaesthesia technique used was standardized to avoid bias. Based on personal preferences and also a practical issue (not all anaesthesia machines in the radiology department of our institution are equipped with proper scavenging systems that allow the use of volatile anaesthetics), total i.v. anaesthesia was induced with propofol (2 mg kg<sup>-1</sup>), sufentanil (0.3 µg kg<sup>-1</sup>), and rocuronium (0.6 mg kg<sup>-1</sup>) and maintained with propofol and remifentanyl.

The Accusync ECG-gating device (model 72; Milford, Connecticut) was connected to a 5-lead ECG to allow IRE pulses to be synchronized with the refractory period of the heart to avoid arrhythmias. Two defibrillation pads were placed and connected to a defibrillator as a precautionary measure. Immediately before IRE, complete muscle relaxation was confirmed by a train-of-four (TOF)-ratio of 0, using a peripheral nerve stimulator (TOF-Watch<sup>®</sup>, MIPM, Mammendorfer, Germany) to assess neuromuscular transmission. When necessary, an additional dose of rocuronium was administered.

After laparotomy, the epidural stayed *in situ* for at least 3 days. Pain control after percutaneous procedures was managed with acetaminophen combined with an NSAID (diclofenac) and an opioid (piritramide) if needed.

## Safety analysis

All adverse events were graded according to the Common Terminology Criteria for Adverse Events (NCI CTCAE v4.0). Cardiac rhythm, blood pressure, and saturation were continuously monitored. ECGs were monitored continuously until discharge from the recovery ward, and another 12-lead ECG was made 1 day post-IRE. Blood samples were evaluated with a special emphasis on serum electrolytes, renal function, and hepatic or pancreatic enzymes that could identify biochemical disturbances possibly caused by cellular destruction. These samples were drawn within 7 days before IRE, within 5 min after IRE and at least 1 day after the procedure. To monitor brain activity and the effect of pulses on the cerebrum before and during IRE, a simplified electroencephalogram (EEG) was made in six patients using the Thymatron System IV (Schwind Benelux Medical Electronics BV, Oosterbeek, The Netherlands). Post-procedural pain was scored three times a day during hospital admission, using the visual analogue scale (VAS).

## Intervention

All procedures were performed by a board-certified interventional radiologist trained in IRE. Before IRE, the size and shape of the target lesion, including a 1 cm tumour-free

margin, were defined; this determined the number and configuration of the electrodes. Two or more insulated 15 cm needle electrodes with an exposure length of 2 cm (liver, kidney, and lesser pelvis) or 1.5 cm (pancreas) were placed in the outer border of the tumour with an interprobe distance of 2.0 cm (0.2 cm). During laparotomy, intraoperative ultrasound (Alpha7, Hitachi Aloka Medical, Ltd, Tokyo, Japan) was used to aid electrode placement. For percutaneous procedures, the electrodes were advanced under CT fluoroscopy (Volume Zoom, Siemens, Erlangen, Germany), with or without ultrasound (Fig. 1). To allow needle placement under CT fluoroscopy, ventilation was briefly stopped.

After confirmation of correct electrode position, the appropriate parameters for voltage ( $1500 \text{ V cm}^{-1}$ ), number of pulses (90), and pulse interval ( $70 \mu\text{s}$ ) were set, and ablation was started using the NanoKnife, a low-energy direct-current ablation device (AngioDynamics, Latham, NY). The pulses were synchronized with the heart rhythm, as detailed above. The delivered current should lie between 20 and 50 A, and in the case of overcurrent ( $>50 \text{ A}$ ) a safety mechanism automatically turns off energy delivery to prevent thermal injury. If necessary, electrodes were repositioned for renewed ablation until the ablation zone fully covered the tumour.

### Statistical analysis

All data were described and analysed; continuous variables were presented as mean and *SD* (normal distribution), median and range (non-normal distribution), or frequencies and percentages (categorical variables). A *P*-value of  $<0.05$  was considered significant. Analysis was performed using SPSS 20.0 (SPSS, Inc., Chicago).

### Results

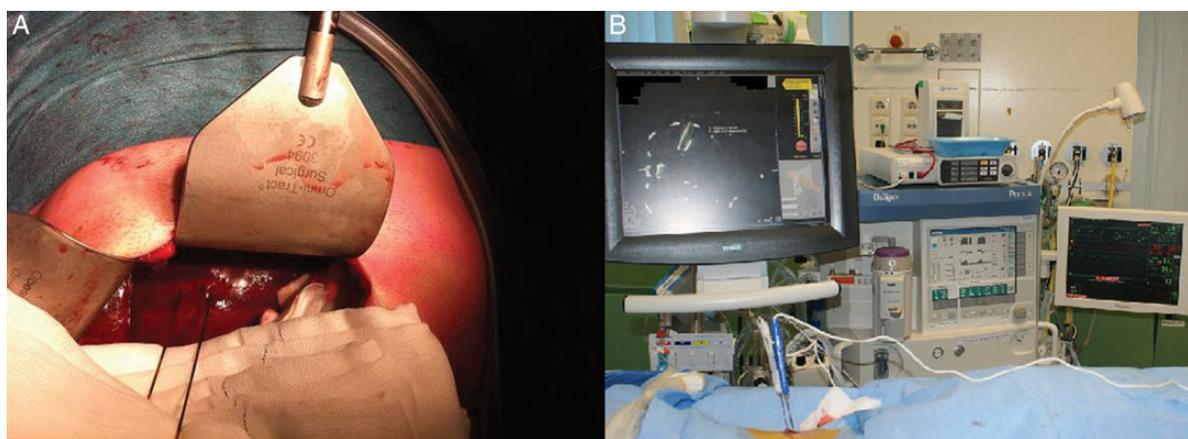
A total of 28 patients with ASA classification I ( $n=4$ ), II ( $n=23$ ), and III ( $n=1$ ) were treated with IRE in 30 sessions. Thirteen patients were treated during laparotomy for CRLM; of whom, 10 patients participated in the COLDFIRE study. All these

patients underwent resection and RFA of additional lesions. The remaining 15 patients were all treated percutaneously for CRLM ( $n=5$ ), pancreatic carcinoma ( $n=5$ ), cholangiocarcinoma ( $n=1$ ), hepatic adenoma ( $n=1$ ), renal cell carcinoma ( $n=1$ ), and presacral metastasis of colorectal carcinoma ( $n=2$ ). Two patients were treated twice because of local recurrence (presacral metastasis and cholangiocarcinoma). Two to six electrodes were used for each procedure, depending on the size of the target lesion. Median ablation time, defined as the interval between the first and the last pulse, was 14 min (range 4–120) and was determined by lesion size and the need for needle repositioning for overlapping ablations. The median total procedure time was 206 min (range 90–315) and the median length of hospital admission was 8 days after laparotomy (range 5–12 days) and 4 days after percutaneous IRE (range 2–20). Patient and procedure characteristics are given in Table 1.

### Cardiovascular effects: hypertension and arrhythmias

During electroporation, an elevation of systolic and diastolic blood pressure was observed in most patients, with a median of 44 mm Hg (range  $-7$  to 108 mm Hg) and 19 mm Hg (range 1–50 mm Hg) compared with baseline. This was most pronounced during pancreatic IRE (60 and 30 mm Hg) (Table 1). This elevation was easily managed with additional propofol and remifentanyl, and blood pressure returned to baseline within minutes after IRE. Heart rate showed a moderate increase during electroporation (median  $10 \text{ min}^{-1}$ , range  $-7$  to 32), and seemed more profound during IRE of the pancreas ( $18 \text{ min}^{-1}$ ) than of the other organs ( $8 \text{ min}^{-1}$ ), although this difference was not significant (Table 1).

During two IRE procedures, a minor self-limiting cardiac arrhythmia was observed. Ventricular extrasystole was observed during open IRE apical in the liver near the left diaphragm. Cardiac rhythm normalized after abortion of the procedure and could be continued after the removal of the electrode that was closest to the heart. The second arrhythmia, bigeminy



**Fig 1** Open (A) and percutaneous (B) IRE procedure of the liver with electrodes *in situ*.

**Table 1** Patient and IRE procedure characteristics. HD, haemodynamic; VAS, visual analogue score; SBP, systolic blood pressure; DBP, diastolic blood pressure; bpm, beats per minute; perc., percutaneous

	Liver (open)	Liver (perc.)	Pancreas	Kidney	Sacrum	Total
Number of patients	13	7	5	1	2	28
Number of lesions	19	8	5	1	3	36
Number of IRE procedures	13	8	5	1	3	30
Median tumour size (mm) (range)	20 (5–53)	28 (14–50)	40 (33–50)	32	48 (34–50)	28 (5–53)
Muscle movement	–	+/-	+	–	++	
HD parameters (n, or median and range)						
Arrhythmias	1	–	1	–	–	2
Increase SBP (mm Hg)	29 (–7–54)	45 (10–80)	60 (30–108)	60	50 (42–50)	44 (–7–108)
Increase DBP (mm Hg)	16 (1–23)	30 (5–50)	30 (25–38)	20	25 (18–28)	19 (1–50)
Heart rate (bpm)	2 (–7–20)	6 (0–32)	18 (10–22)	2	10 (0–15)	10 (–7–32)
Maximum VAS (median, range)	4 (0–10)	3 (0–8)	4 (2–9)	0	2 (0–5)	3 (0–9)

with premature ventricular complex, occurred during pancreatic ablation but disappeared within 5 min of the end of the procedure. Neither minor arrhythmia led to haemodynamic instability. All ECGs made 1 day after IRE were without abnormalities and similar to the ECG made before the intervention.

### Muscle contractions during IRE

Muscle relaxation was verified before the start of IRE in all patients, expressed as TOF=0. While generalized contractions of skeletal muscles were successfully prevented with rocuronium, mild contractions confined to the treatment area were still visible. During open IRE, this was noticed through minimal pulsatile movement of the electrodes. Local contractions were more profound during percutaneous procedures, especially when electrodes were inserted through large muscles to achieve optimal positioning. Isolated contractions of the gluteus maximus and the rectus abdominus muscle were remarkable during IRE in the lesser pelvis (dorsal approach) and in the pancreas, respectively. The muscle contractions never resulted in dislocation of the electrodes. The median duration between the last pulse and termination of the procedure was 20 min for percutaneous (range 3–89) and 113 min for open procedures (range 32–172). In 11 of 15 percutaneous procedures a median dosage of 400 mg sugammadex (range 200–1600 mg) and in 6 of 13 open procedures 200 mg were used to reverse neuromuscular block.

### Laboratory values

Significant electrolyte abnormalities were not observed in any patient. Serum pH was measured during open procedures, but no disturbances were noted. Renal function remained unremarkable during IRE and in the postoperative period, except for a clinically insignificant decline in glomerular filtration rate in the patient who was treated in the kidney ( $69-59 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$ ). Further analysis revealed elevation of hepatic and pancreatic enzymes in all patients directly after IRE of the liver and pancreas, respectively. This was most pronounced on the first postoperative day and decreased

thereafter. One patient developed a pancreatitis with bile leakage, characterized by a persistent increase in pancreatic enzymes, pain, and fever. These values normalized after antibiotic treatment and drainage. The postoperative elevation of transaminases in the 13 patients who underwent additional RFA and liver segment resection (COLDFIRE study) could not be solely attributed to IRE, because these additional procedures are commonly associated with such increases.

### Cerebral monitoring

Before induction of general anaesthesia, normal cerebral activity was registered. After induction, brain activity became minimal in five (5/6) patients. During IRE, each electrical pulse was clearly registered as an artifact in all six patients (Fig. 2). Importantly, no reactive (epileptic) activity was observed.

### Complications

Apart from the previously mentioned minor arrhythmias, no adverse events occurred during the procedures. In the postoperative period after open IRE, five complications occurred in four patients (4/13), two of which were major (re-laparotomy because of alleged persisting haemorrhage; postoperative pain). None of these complications were considered directly related to IRE but most likely to the surgical procedure.

Post-procedural complications after percutaneous IRE also occurred in five patients (5/17) after hepatic, pancreatic, renal, and lesser pelvic tumour ablation (Table 2). Of these, two were considered major complications (CTCAE grade  $\geq 3$ ).

### Postoperative pain

Because all patients who underwent open IRE of the liver also had additional resection or thermal ablation, postoperative pain was unlikely to be solely related to IRE. In all but one patient, pain was well managed with thoracic epidural analgesia.

Post-procedural pain after percutaneous IRE in the liver, pancreas, kidney, and lesser pelvis was mild, with a mean



**Fig 2** Simplified EEG registration ( $100 \mu\text{V cm}^{-1}$ ). (A) Cerebral activity before induction of general anaesthesia. (B) Baseline cerebral activity after induction of general anaesthesia. (C) Cerebral activity during IRE, with artifacts seen during actual IRE delivery and a return of brain activity to baseline thereafter.

**Table 2** Complications during and after IRE

Treatment site	Complication	N	Grade	Intervention
Liver (open)	Arrhythmia	1	I	Removal of one electrode
	Postoperative haemorrhage	1	III	Re-laparotomy
	Pain	2	II, III	Oral, i.v. and intrathecal analgesics
	Pneumonia	1	II	Antibiotics
	Peripheral oedema	1	II	Compression stockings
Liver (percutaneous)	Pneumothorax	2	II	Chest tube
Pancreas	Arrhythmia	1	I	None
	Pancreatitis + bile leakage	1	III	Drainage, antibiotics
Kidney	Haematuria	1	I	None
Pelvis	Nerve function loss	1	II/III	Rehabilitation, physiotherapy

maximum reported VAS score of 3 during hospital admission (range 0–9). Of these sites, pain after pancreatic IRE was the most severe with a mean maximum VAS of 4 (range 2–9) (Table 2).

### Discussion

IRE is a promising new technique for the local treatment of tumours ineligible for surgical resection or thermal ablation. The local application of an extremely high voltage presents

several challenges in anaesthetic management that need to be anticipated.<sup>10 11</sup> Results of the present study indicate that adverse effects may include cardiac arrhythmias, a transient increase in blood pressure and muscle contractions. However, these adverse effects were generally mild and easily managed. Although the size of our population precludes definitive conclusions, our results are in concordance with previous observations that IRE appears safe and feasible when a dedicated anaesthetic team takes the proper precautions.

Strong electrical currents are known to have the potential to cause arrhythmias, including ventricular tachycardia or even ventricular fibrillation.<sup>12</sup> Without the use of cardiac synchronization, Ball and colleagues observed brief runs of ventricular tachycardia in seven patients, which seemed to occur more frequently in close proximity to the heart.<sup>11</sup> Of these, four were associated with a decrease in arterial blood pressure, but immediately after completion of the 10-pulse treatment cycle blood pressure and ECG rhythm returned to normal. These and other ventricular arrhythmias should be prevented by synchronizing IRE pulse delivery with the absolute refractory period of the cardiac cycle (microseconds after the R-wave) using R-wave detection.<sup>9 10</sup> As the use of synchronized pulsing, only minor arrhythmias have been reported in the literature, all of which resolved spontaneously after the procedure was aborted.<sup>7 9 13</sup> In our study, a mild and self-limiting cardiac arrhythmia was observed in two patients, one of which occurred during IRE near the left diaphragm, which is in line with previous results. According to the manufacturer, IRE is contraindicated in patients with pre-existent cardiac arrhythmias, as R-wave detection may be less reliable here, although there is no literature to support this. As other applications such as electrical cardioversion to treat atrial fibrillation also rely on accurate R-wave detection for synchronized defibrillation shock application, this contra-indication may be relative and needs to be further investigated.<sup>14</sup>

A transient increase in blood pressure during electroporation, usually without a simultaneous increase in heart rate, was observed in all but one patient, confirming previous observations.<sup>11</sup> In our study, the increase in blood pressure was effectively treated with additional propofol and remifentanyl. Although the median values for the changes in blood pressure were moderate, the maximum individual response can be considered dangerous in a patient with a history of cardiovascular disease. The exact mechanism behind this increase is unclear, but stimulation of the autonomous nervous system is a likely explanation. Whether this autonomous stimulation is caused by direct stimulation or by pain perception and how it is best prevented remains to be clarified before patients with major cardiovascular disease can be treated.

When applying high-voltage pulses, neuromuscular block is required to avoid uncontrolled severe contractions. Ball and colleagues reported that inadequately paralysed patients developed contractions of the entire upper body with each pulse, similar to a grand mal seizure.<sup>11</sup> In our study, even after confirmation of complete medicinal neuromuscular block (TOF=0), the electric pulses induced at least mild muscle contractions confined to the treatment area in all percutaneous procedures. These contractions were probably because of leakage

current inducing a regional electromagnetic field causing direct muscle depolarization, which is not prevented by non-depolarizing neuromuscular blocking agents.

Another contra-indication for IRE, and noted by the manufacturer, is epilepsy or previous seizure activity, because the electrical discharges could theoretically trigger a seizure through pulsatile brain stimulation. Electrical pulses used in electroconvulsive therapy for severe depression induce seizure activity if a frequency of >5 Hz is reached, but whether IRE can induce seizures has not been firmly established.<sup>15</sup> Therefore, we analysed the effect of IRE on the brain in non-epileptic patients by monitoring cerebral activity with a simplified EEG. We found an absence of background brain activity during IRE in 5 of 6 patients. This can be attributed to the use of propofol, which is a known suppressor of cerebral activity.<sup>16</sup> The high voltage seen during an electrical pulse was never followed by a reactive cerebral response in any of the patients. Indeed, the depth of anaesthesia may entirely preclude seizures. The likelihood of seizure induction by IRE is also reduced by the synchronization of pulses with the heart rhythm, meaning that they will never reach the minimum frequency of 5 Hz required to provoke a seizure.<sup>17</sup> Based on these results and arguments, epileptic seizure risk during IRE is probably very low. If IRE were indicated in a patient with epilepsy, we suggest that the use of cerebral monitoring during the procedure would allow quick seizure recognition and treatment initiation.

Post-procedural pain was previously investigated after percutaneous IRE of the kidney, lung, and liver.<sup>11</sup> Pain was well managed with oral analgesics in almost all patients, if treatment was necessary at all. Another study showed that post-procedural pain in patients treated with either RFA or IRE for hepatocellular carcinoma was comparable, with no significant difference in analgesic requirements and without the need for epidural analgesia in any of the patients.<sup>18</sup> This was confirmed by our results, which showed that percutaneous IRE of the liver, kidney, and lesser pelvis did not cause much discomfort. After percutaneous IRE of the pancreas, a previous study found that most patients experienced (CTCAE) grade I pain.<sup>19</sup> Here, pancreatic ablation was associated with the greatest pain in the first 24-h post-IRE, with maximum VAS scores up to 9, which may be explained by the anatomic location of the pancreas near the coeliac plexus, combined with the induction of a reactive pancreatitis caused by the treatment. This pain was still effectively managed using a multimodal pain treatment consisting of acetaminophen in combination with an NSAID and opioid. The past years the relationship between opioid use and cancer recurrence has been investigated. So far, no significant differences can be identified in most studies between the postoperative use of opioids or other analgesic techniques.<sup>20</sup> These data are extracted from conflicting results from retrospective analyses after resection of primary cancers and not from treatment of metastases. Prospective trials are awaited to draw distinctive conclusions on the role of opioids in cancer recurrence. The relatively mild postoperative pain and limited opioid use after (percutaneous) IRE in most of our patients may be beneficial in this respect, but the numbers treated are too low to make any hard statements. On the

other hand, the relatively long duration of the procedure may have confounded the experienced postoperative pain in some patients, because continuous remifentanyl infusion is associated with hyperalgesia.<sup>21</sup>

The results in this study represent our first experience with IRE in a relatively small and heterogeneous patient group in terms of target organ and treatment approach, which permitted evaluation of IRE-related anaesthetic challenges in different organs than were reported previously. Overall, perioperative management of the patients was similar. The absence of serious cardiac arrhythmias and muscle contractions supports the assumption that they can be prevented by ECG-synchronized pulsing and profound neuromuscular block. Epilepsy could be regarded as a relative rather than an absolute contra-indication if IRE were considered the only local treatment option. However, our conclusions should be regarded with care because of the small sample size, which is a limitation of this study. Future studies should focus on long-term follow-up, including long-term adverse events, local control, and survival rates. From an anaesthetic perspective, it may be worthwhile to further explore the more generalized physiological consequences of IRE, because IRE is intended to induce only local effects. For example, it would be interesting to investigate the mechanism of the increase in blood pressure during IRE and whether localized muscle contractions caused by leakage currents can be prevented by using a depolarizing neuromuscular blocking agent, like succinylcholine.

In conclusion, our study suggests that adverse effects during IRE of the liver, pancreas, kidney, and lesser pelvis are generally mild and easily manageable if specific perioperative precautions are taken. These include general anaesthesia with deep muscle relaxation and ECG-synchronized pulsing.

## Authors' contributions

K.N.: study conception and design, collection and analysis of the data, drafting and revising the article, final approval. H.J.S.: study conception and design, collection and analysis of the data, drafting and revising the article, final approval. J.M.V.: study conception, collection and analysis of the data, interpretation of the data, revising the article, final approval. A.A.J.M.v.T.: design of the database, analysis of the data, revising the article, final approval. S.M.: study conception and interpretation of the data, revising the manuscript, approval of final version. C.v.K.: study design, interpretation of the data, revising the manuscript, approval of final version. M.P.v.d.T.: co-initiator of this research-project, data collection, corrected and discussed all results and all versions of the manuscript, approval of final version. M.R.M.: co-initiator of this research-project. Study conception and collection of the data, data interpretation and revisions of the manuscript, approval of final version. R.A.B.: co-initiator of this research-project and supervisor of all data-management, writing the first draft and revising the article, final approval.

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## Declaration of interest

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