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Percutaneous irreversible electroporation of locally advanced pancreatic carcinoma using the dorsal approach: A case report

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Abstract

Irreversible electroporation (IRE) is a novel image-guided ablation technique that is increasingly used to treat locally advanced pancreatic carcinoma (LAPC). We describe a 67-year-old male patient with a 5cm stage III pancreatic tumor who was referred for IRE. Because the ventral approach for electrode placement was considered dangerous due to vicinity of the tumor to collateral vessels and duodenum, the dorsal approach was chosen. Under CT-guidance, six electrodes were advanced in the tumor, approaching paravertebrally alongside the aorta and inferior vena cava. Ablation was performed without complications. This case describes that when ventral electrode placement for pancreatic IRE is impaired, the dorsal approach could be considered as an alternative.
Introduction

Pancreatic adenocarcinoma is the fourth leading cause of cancer-related death. It has a dismal prognosis, with a 5-year survival rate of 6% and a case-fatality rate among the highest of any malignancy. Unfortunately, at the time of diagnosis only 15 to 20 per cent of patients are eligible for surgical resection with curative intent. Forty per cent have locally advanced pancreatic carcinoma (LAPC) (stage III; AJCC TNM Staging System for Pancreatic Cancer). For these patients, chemotherapy or chemoradiation with palliative intent is the treatment of choice, leading to a modest increase in survival and improved quality of life. However, with a median survival of 6 to 11 months, the prognosis remains extremely poor.1

The past two decades, image-guided tumor ablation has received substantial attention when surgical options are precluded. The aim of pancreatic ablation is cytoreduction, leading to better symptom palliation, improved quality-of-life and prolonged survival. However, due to the vulnerability of pancreatic tissue and its vicinity to critical structures, local treatment in this area risks pancreatitis and injury of duodenum, vessels and common bile duct. Thermal ablation using radiofrequency or microwave ablation to treat LAPC is therefore associated with a high complication rate, but without a clear benefit in survival.2

Recently, irreversible electroporation (IRE) has been introduced as a novel ablation technique. With IRE, multiple short, high-voltage electrical pulses are delivered to malignant tissue. The electrical pulses destabilize the existing cellular membrane potential and lead to the formation of 'nano-pores' in the lipid bilayer, irreversibly damaging the cell's homeostatic mechanism which ultimately leads to cell death through apoptosis.3 IRE only affects the membranes of living cells, whilst preserving the extracellular matrix constituents that are responsible for the patency of major vascular and ductal structures and other vulnerable tissues, without the generation of heat.4 With these characteristics, IRE may be suitable to treat LAPC. Several studies have investigated the safety and efficacy of open as well as percutaneous IRE using the ventral approach for this indication. Although results are still preliminary, the technique seems to be tolerated well and early results of efficacy appear promising.5-7

The shortest pathway and therefore the most commonly used route for CT-guided ablation of lesions in the pancreatic head is the ventral, or anterior, approach. However, in certain cases it can be extremely challenging to reach the desired position for all electrodes without having to traverse overlying intestinal, ductal and vascular structures. In this case the conventional ventral epigastric approach of needle placement can be complicated and concerns about the safety of the procedure arise. Here, we present a case of percutaneous IRE for LAPC using the dorsal approach for electrode placement.

Case report

A 67-year-old male patient presented with intermittent abdominal pain. Computed tomography (CT) imaging showed a 5.0x5.0x4.2cm mass in the head and corpus of the pancreas with >180° encasement of the celiac axis, splenic and hepatic artery, and abutment of the superior mesenteric artery of 180°. The main portal vein was completely obliterated, which had led to extensive collateral vessel formation ventrally from the tumor (figure 1A and 1B). The tumor was also located in proximity to the duodenum. There were no signs of lymph nodal or metastatic spread. A transgastric biopsy of the lesion confirmed the diagnosis.
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pancreatic adenocarcinoma. Due to its vascular encasement the tumor was considered surgically incurable (stage III). The patient was referred to our center for irreversible electroporation of the lesion as part of the prospective PANFIRE-study (clinicaltrials.gov registration number NCT01939665) and gave written informed consent. Given the vicinity of the tumor to the common bile duct, a plastic retrievable biliary endoprosthesis was placed via endoscopic retrograde cholangiopancreatography as a precautionary and protective measure prior to the procedure. Because of the extensive network of portal collaterals that had developed anteriorly from the tumor and its vicinity to the duodenum, ventral needle placement was considered to be associated with a substantial risk of damaging the duodenum or the collateral vessels. Therefore, we opted for a dorsal approach for needle placement.

The patient was put under general anesthesia in the prone position. A contrast-enhanced (CE) CT scan (Sensation 64 slice MDCT, Siemens, Erlangen, Germany) in the arterial (triggered) and portal venous phase (70 seconds after contrast injection) was made to determine the three-dimensional measurements of the tumor and its proximity to other structures. Size and shape, including a 5mm margin, determines the number and configuration of the electrodes, which must cover the full extent of the tumor. The distance between electrode pairs should be 20mm (± 5mm), which is considered the most effective treatment distance at which the ablation zone has an oval shape. A total of six monopolar needle electrodes (NanoKnife, AngioDynamics, Latham, New York) were advanced into the central part and in the outer border of the cranial and caudal part of the tumor, approaching paravertebrally alongside the aorta and inferior vena cava under CT-guidance (figure 1C and 2). Due to the necessity to place the needles on either side of the vertebral column, exact parallel positioning of all electrode pairs was not feasible. The active working length of the electrodes was set at 2cm. Eight vectors for pulse delivery were chosen (figure 3A and 3C). All pulses were delivered in the absolute refractory period of the heart with use of electrocardiographic synchronization (Accusync, Model 72, Milford, Connecticut) to avoid the induction of cardiac arrhythmias and with deep muscle paralysis using additional rocuronium to prevent generalized muscle contractions. First, ten test pulses of 1500V/cm with a pulse length of 90\( \mu \)sec were delivered for each electrode pair to verify the delivered current, which must lie between 20-40 Amps. Subsequently, 80 treatment pulses were delivered along each vector. High current between electrodes 3 and 5 led to energy shutdown twice. With adjustment of the voltage and pulse length to 70\( \mu \)sec the ablation was continued successfully. After a 2cm pullback of all needles, an overlapping ablation was performed with use of the similar protocol. To cover the lateral parts of the tumor, the most cranial and caudal electrodes (electrodes 1 and 5) were repositioned to the lateral left and right tumor border approaching from the left paravertebral region. Next, another series of 90 pulses between four electrode pairs (figure 2 and 3A) was delivered. Mean delivered current of all electrodes was 35 Amps (standard deviation 5.7). After removal of all needles, CECT showed a spastic but patent hepatic and splenic artery. There were no signs for early complications (figure 1E). The patient awakened uneventfully in the recovery unit and was transferred to the ward. The next day contrast enhanced magnetic resonance imaging (CE MRI) showed a typical ablation zone with a non-enhancing center and a peripheral hyperintense reactive rim (figure 1F). There was a moderate increase in lipase (from 11 to 86 U/L) and amylase (from 24 to 112 U/L) that normalized to 15 U/L and 20 U/L on the third day, respectively. Pain was managed well with oral acetaminophen and tramadol and continuous intravenous morphine and ketamine. On the 4th day post-IRE
Pancreatic IRE using the dorsal approach

Figure 1: (A) Axial contrast enhanced (CE) CT image of the pancreatic tumor prior to IRE with collateral vessels anteriorly (arrow). (B) Axial CE MRI image (T1 with fat suppression) of the tumor which appears slightly hypovascular compared to normal pancreatic tissue. (C) Axial CT image of two electrodes placed alongside the vertebral column. (D) Coronal view of fused CT series depicting all electrode positions before and after needle reposition. Close proximity of the duodenum (D) to the tumor. (E) Axial CECT image obtained ten minutes after IRE demonstrating air within the ablated area but no complications. (F) Axial CE MRI image (T1 with fat suppression) with a typical ablation zone showing a non-enhancing center and a peripheral enhancing rim. (G) Axial CECT image 2 weeks after IRE showing a hypodense tumor center. (H) Axial CE MRI (T1 with fat suppression) 2 weeks post IRE depicting shrinkage of the ablation zone.
the patient was discharged with oral acetaminophen, tramadol and oxycodone. During the next two weeks he experienced moderate intermittent abdominal pain, loss of appetite and a sublebrile temperature (up to 38°C). After 2 weeks, CT and MRI showed a decreased size of the ablated area with a hypovascular center and no signs of complications (figure 1G and 1H). In the following weeks the pain significantly decreased and the patient was able to reduce his pain medication to half the amount of what he was using prior to the treatment. At 3 months, the ablated area had further decreased in size. The patient resumed his normal daily activities and remains in follow-up.

**Discussion**

The advantage of percutaneous ablation over ablation during laparotomy is the less invasive nature, which generally implies a lower risk for complications and faster recovery. However, using the ventral approach, intervening structures like stomach and intestines can obstruct access to the lesions, which requires transgression of the gastrointestinal tract. Acute pancreatitis is an uncommon but severe complication of pancreatic biopsy. Because bowel transgression can potentially contaminate a sterile biopsy procedure, it is best avoided to preclude even a small risk of infection or leakage of bile and pancreatic juices. In their series of 184 pancreatic biopsies Mueller et al found an 8% risk of pancreatitis after transintestinal biopsy as opposed to a 1.3% risk after normal biopsy. With IRE, multiple electrodes are inserted in the pancreas and remain in situ for a substantial period of time, so the risk of bowel transgression leading to pancreatitis and infection of the ablation zone can be considered higher. Another issue that can preclude the ventral approach is pre-existing portal vein thrombosis with subsequent formation of collateral circulation vessels. Although uncommon, major hemorrhage with pancreatic biopsy resulting from the inadvertent puncture of mesenteric or pancreatic vessels has been reported. To overcome abovementioned difficulties, alternative routes for pancreatic biopsies such as the transhepatic and transsplenic approach, have been reported. Posterior transcaval and paracaval biopsy have also been investigated and have proven relatively safe. In our case, we considered the posterior approach to have the lowest risk of complications. To the best of our knowledge, this approach for pancreatic IRE has not been previously described.

Although the vertebrae impeded exact parallel positioning of the electrodes, we eventually succeeded to place all needles in the desired position with the required inter-electrode distances and to properly deliver all planned pulses within the desired current range. The maximum allowed angulation as advised by the manufacturer is 20°, since beyond this angle the strength and distribution of the electric field could become unreliable. However, whether

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![Figure 2: 3D image with electrodes placed within the tumor. Pink electrodes representing electrode position during the first ablation. Orange electrodes representing repositioned electrode 1 and 5 prior to the second ablation (marked with *). Biliary endoprosthesis in the common bile duct in situ (long arrow). Prominent pancreatic duct due to tumor obstruction (short arrow).](image)
Pancreatic IRE using the dorsal approach

Exceeding this angle can truly result in a less effective ablation has not been investigated. For the electrode pairs that were placed on the ipsilateral side of the vertebral column the largest angulation was 22°. To cover the full extent of the tumor, ablation was also performed between electrode pairs that traversed the spine on either side, with the midpoint of the active tips in a crossed position (figure 3B). The maximum angulation for these pairs was 62°. In clinical practice, a slight deviation from exact parallel electrode placement is common. It could be argued that as long as the distance between two electrodes remains between the required 1.5-2.5cm over the entire length of the active tips, this should result in effective ablation. Still, validation of the consequence of out-of-plane electrode placement on the strength and distribution of the electric field is of great importance and should be a focus of future research on IRE.

Current published data on safety and feasibility of IRE for LAPC is limited. One study of open IRE for locally advanced pancreatic tumors in patients who had undergone standard induction chemotherapy for a minimum of 4 months did show greater local palliation and potential improved overall survival (20 vs. 11 months, \( p = 0.03 \)) compared to standard chemoradiation or chemotherapy regimens. A Percutaneous pancreatic IRE also seems...
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relatively safe and feasible with the important additional benefit of providing a less invasive treatment option. The largest series has been reported by Narayan et al who performed 14 procedures using the percutaneous ventral approach. No major (CTCAE grade ≥3) complications were observed and three minor complications occurred (pneumothorax, subcutaneous hematoma and mild pancreatitis). The observed palliation of pain after pancreatic IRE may be explained by a reduction of tumor load, diminishing pain caused by tumor obstruction or celiac plexus invasion. Theoretically, given the vicinity of the celiac plexus to pancreatic head tumors, the treatment may also induce a temporary or permanent celiac plexus block, which may further contribute to reduced pain perception. This would be a desirable side effect of the treatment.

Our imaging findings post-IRE are in concordance with the available literature, which describes that 24 hours after IRE, T1-weighted CE MRI of the ablated region typically shows a non-enhancing center, surrounded by a hyper-intense reactive rim. The radiologic ablation zone measurements show a high correlation with the histologically confirmed ablation zone in a study on IRE in rodent liver (P < .001 for both T1- and T2-weighted measurements) and could therefore be used as an indication for complete or incomplete ablation and for follow-up evaluation of clinical outcome. The increased uptake of contrast at the periphery of the ablated region may be due to an initial inflammatory response increasing metabolic activity at the targeted region as the cellular debris is removed from the targeted site. However, whether all tumor cells in this region have truly been destroyed must become evident during follow-up.

In the hours after IRE, a margin of reversibly electroporated tissue exists between the ablation zone and the untreated tissue, where the electrical field strength stayed below the critical threshold. The cell membranes of the cells in this zone are temporarily permeable during this period, allowing drugs such as chemotherapeutics to travel freely into the cells. Reversible electroporation has been used for decades to promote uptake of chemotherapy into the cell, a process known as electrochemotherapy. Capitalizing on this principle, the addition of systemic chemotherapy immediately after IRE could eradicate marginal reversibly electroporated tumor cells, which would improve treatment effect. This approach warrants further study and may contribute to the multidisciplinary treatment approach of cancer in the near future.

In conclusion, this case report describes a technically successful IRE procedure of a locally advanced pancreatic carcinoma using the dorsal approach. This case illustrates that if a pancreatic tumor is enclosed by organs or vessels which impedes ventral needle placement, clinicians could consider alternative routes for needle placement, such as the dorsal approach.
References


“You can always tell when the groove is working or not

Prince
Chapter 6

Niche indications
6.1

Irreversible electroporation to treat malignant tumor recurrences within the pelvic cavity

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Submitted for publication
Abstract

Objective
To describe the initial clinical experience with irreversible electroporation (IRE) to treat locoregional tumor recurrences within the pelvic cavity.

Materials and methods
A retrospective single-center analysis was performed of patients treated with IRE for malignant local tumor recurrences within the pelvic cavity that were unsuitable for established treatment options due to the vicinity of major nerves, prostate or ureter. Adverse events were recorded using CTCAE 4.0. The clinical outcome was determined using pain- and general symptom assessment, including Seddon's peripheral nerve injury (PNI) scores. Radiological outcome was evaluated by comparing baseline with three-monthly 18F-FDG PET-CT follow-up.

Results
Eight patients (9 tumors) underwent percutaneous IRE to treat recurrences of primary rectal (n=4), anal (n=1), sigmoid (n=1), cervical (n=1), and renal cell carcinoma (n=1). Overall, one CTCAE grade III adverse event (hemorrhage) and eight CTCAE grade II complications occurred in 6/8 patients: lower limb motor loss (n=3; PNI score II) with partial recovery in one patient, hypotonic bladder (n=2; PNI scores I and II) with complete recovery in one patient, and upper limb motor loss (n=2; PNI score II) with partial recovery in both patients. After a median follow-up of 14 months (range 2-36), local progression was observed in 5/9 lesions, of which 4/5 were > 3cm pre-IRE; one lesion was successfully retreated. Debilitating preprocedural pain (n=3) remained unchanged in one, and improved slightly and considerably in two patients.

Conclusion
IRE may represent a suitable technique to treat tumor recurrences within the pelvic cavity, although permanent neural function loss can occur. Radical ablation seems realistic for smaller lesions; for larger lesions symptom control should be the focus of future clinical studies.
IRE of pelvic tumor recurrences

Introduction

Malignancies that are notorious for their recurrence within the pelvic cavity following radiotherapy and/or surgery are both female and male urogenital tract tumors and locoregional recurrences from gastro-intestinal origin such as anorectal carcinomas.\textsuperscript{1,2} Due to ingrowth in or compression on peripheral nerves, these relapsing malignancies can cause aggravating pain and neural function loss. The presence of extensive adhesions induced by previous surgical procedures and the risk of radiation-induced toxicity in a previously irradiated area precludes radical local treatment options such as repeat surgery\textsuperscript{3} and stereotactic ablative body radiation therapy (SABR).\textsuperscript{4-6} The risk of severe treatment-induced morbidity does not seem to outweigh clinical benefit.\textsuperscript{2,7,8} In general, therapy for this specific patient population primarily aims at prolonging the - preferably quality-preserved - life span, and most patients will be referred to medical oncologists for either palliative chemotherapy or best supportive care.\textsuperscript{9,10}

Yet, selected patients can be offered other local treatment modalities such as radiofrequency ablation (RFA) or cryotherapy.\textsuperscript{11-13} One important drawback of these thermal treatment modalities is the high risk of inducing thermal damage to important neural structures like the sciatic nerve or perisacral plexus, as well as to the intestines, ureters and large pelvic vessels.\textsuperscript{14,15}

Irreversible electroporation (IRE) is an emerging ablation technique that is based on the application of an electric field across cells that alters the transmembrane potential. On reaching a sufficiently high voltage, the phospholipid bilayer structure of the cell membrane is permanently disrupted, inducing apoptosis.\textsuperscript{16-18} Electroporation is regarded to leave supporting tissue largely unaffected, so the structural integrity of large blood vessels, and intestines is relatively preserved.\textsuperscript{17,19} Moreover, initially damaged axons may regenerate with complete recovery of function, according to preclinical animal studies.\textsuperscript{20-23} For these reasons, IRE may prove a safe and feasible treatment option for patients with malignant tumor recurrences within the pelvic cavity that are considered unsuitable for established focal therapies.\textsuperscript{20,21,23}

This retrospective study describes the preliminary single-center experience of eight patients (nine lesions) with locoregional malignant tumor recurrences within the pelvic cavity that were treated with percutaneous IRE.

Materials and methods

A retrospective analysis was performed of all patients treated with IRE for malignant pelvic tumor recurrences that were considered unsuitable for additional resection, re-radiation, or other local therapies due to the vicinity of major nerves, prostate, ureter, or intestines. Further systemic chemotherapy was considered unfavorable. All patients were discussed in our weekly multidisciplinary oncology board, which consisted of at least a medical oncologist, radiation therapist, surgical oncologist, diagnostic abdominal and interventional radiologist, and pathologist. IRE was only performed in curative setting if the oncology board unanimously agreed on the indication. Histopathological proof of recurring malignancy was required and the lesions were proven \textsuperscript{18}F-FDG PET avid prior to IRE. A history of ventricular cardiac arrhythmias, epilepsy and an American Society of Anesthesiologists (ASA) performance
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status >3 were considered exclusion criterias. Patients gave written informed consent for both the treatment and the use of their data. Local review board approval was obtained on an individual patient basis. The study was conducted conformal to the guidelines for Good Clinical Practice.

**IRE procedure**

All procedures were performed under general anesthesia with propofol, sulentanil and rocuronium, and maintained with propofol and remifentanil. To define the three-dimensional measurements of the tumor and its vicinity to vital structures, a contrast enhanced (ce) CT scan was performed, using multiplanar image reconstruction. The size and shape of the tumor, including a 5mm tumor-free margin, determined the number and configuration of the needle electrodes. Needle electrodes with an exposure length of 15 mm were percutaneously positioned in and around the tumor under CT-fluoroscopy guidance, aiming at an inter-electrode distance of 15-24 mm. The NanoKnife (AngioDynamics Inc, Latham, NY) was used to perform the procedure. A total of 100 pulses of 1500 V/cm with a 90 microseconds pulse length were delivered for each electrode pair. For larger tumors, the electrodes were repositioned or pulled back for one or more overlapping ablations.

### Table 1. Seddon’s classification

<table>
<thead>
<tr>
<th>Score</th>
<th>Tissue injured</th>
<th>Clinical findings</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Myelin</td>
<td>Profound motor loss, paralysis lasting days-months AND normal to minimal sensory involvement</td>
<td>Excellent</td>
</tr>
<tr>
<td>II</td>
<td>Myelin, axon</td>
<td>Complete motor loss with sensory involvement OR complete motor loss with normal sensation</td>
<td>Fair</td>
</tr>
<tr>
<td>III</td>
<td>Connective sheath damage ranging from partial disruption of the endoneurium to complete disruption of the involved nerve</td>
<td>Complete motor loss AND complete sensation loss</td>
<td>Poor</td>
</tr>
</tbody>
</table>

**Safety assessment**

Immediately after the procedure, a second ceCT scan was acquired to assess the ablation zone and to detect early complications such as perilesional bleeding. All direct and indirect procedure-related complications were scored according to the Common Terminology Criteria of Adverse Events (CTCAE), version 4.0. Pain assessment was determined using the Visual Analog Scale (VAS) scores prior to IRE, and 24h and three months after the procedure. Neurological impairment was evaluated using Seddon’s classification. This classification defines three types of neural damage – neurapraxia, axonotmesis, and neurotmesis - based on the severity of the nerve injury, the prognosis, and the recovery time. Neurapraxia describes the mildest type and refers to a block to conduction of nerve impulses but without interruption of the axon or perineurium. Axonotmesis is the second type and refers to an injured axon, whereas the surrounding connective tissue remains intact. Neurotmesis is considered the most severe injury type in which the axon as well as the connective framework are damaged (Table 1).

**Oncological outcome**

Outcome was evaluated comparing baseline with three-monthly ^18^F-FDG PET-CT, using both the revised Response Evaluation Criteria In Solid Tumors (RECIST) and the PET Response Criteria In Solid Tumors (PERCIST) to obtain primary and assisted efficacy rates, time to local progression (TLP) and time to distant progression (TDP). Based on imaging features,
the parameters for local site recurrence (LSR) were (a) tumor lesion increase of at least 20% in longest diameter compared to the baseline scan at 3 months post-IRE, or (b) clear increase in tracer uptake on \textsuperscript{18}F-FDG PET, without signs indicative for inflammation or abscess formation. Primary efficacy rate was defined as the percentage of lesions without signs for LSR at least 3 months after the initial IRE procedure, according to the abovementioned criteria. Assisted efficacy rate was defined as the percentage of tumors completely eradicated at least 3 months after the last procedure, including tumors that underwent repeat ablation(s).\textsuperscript{29}

Table 2. Patient and tumor characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Primary tumor</th>
<th>Histopathology primary tumor</th>
<th>Treatment primary tumor</th>
<th>Number of lesions</th>
<th>Longest diameter (mm)</th>
<th>Vulnerable structures at risk</th>
<th>Treatment(s) prior to IRE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pt. 1</td>
<td>Male</td>
<td>70</td>
<td>Rectal</td>
<td>Adenocarcinoma</td>
<td>Rectum resection</td>
<td>1</td>
<td>60</td>
<td>Bladder wall, ureter, lumbosacral nerve plexus</td>
<td>Neo-adjuvant chemoradiation</td>
</tr>
<tr>
<td>Pt. 2</td>
<td>Female</td>
<td>57</td>
<td>Anal</td>
<td>Squamous cell carcinoma</td>
<td>Chemoradiation + perineal resection</td>
<td>1</td>
<td>50</td>
<td>Sciatic nerve</td>
<td>Radiotherapy</td>
</tr>
<tr>
<td>Pt. 3</td>
<td>Female</td>
<td>63</td>
<td>Cervical</td>
<td>Unknown</td>
<td>Chemoradiation</td>
<td>1</td>
<td>70</td>
<td>Sciatic nerve</td>
<td>Radiotherapy</td>
</tr>
<tr>
<td>Pt. 4</td>
<td>Male</td>
<td>74</td>
<td>Rectal</td>
<td>Adenocarcinoma</td>
<td>Radiotherapy + perineal resection</td>
<td>1</td>
<td>29</td>
<td>Ureter, sciatic nerve</td>
<td>Neo-adjuvant chemoradiation + SBRT</td>
</tr>
<tr>
<td>Pt. 5</td>
<td>Male</td>
<td>58</td>
<td>Rectal</td>
<td>Adenocarcinoma</td>
<td>Resection</td>
<td>1</td>
<td>51</td>
<td>Sacral plexus (in particular, S3 and S4)</td>
<td>Neo-adjuvant chemoradiation + SBRT</td>
</tr>
<tr>
<td>Pt. 6</td>
<td>Male</td>
<td>48</td>
<td>Rectal</td>
<td>Adenocarcinoma</td>
<td>Chemoradiation + rectum resection</td>
<td>2</td>
<td>17 + 14</td>
<td>Prostate, ureter, pelvic splanchnic plexus</td>
<td>Neo-adjuvant chemoradiation</td>
</tr>
<tr>
<td>Pt. 7</td>
<td>Female</td>
<td>66</td>
<td>Sigmoid</td>
<td>Adenocarcinoma</td>
<td>Resection</td>
<td>1</td>
<td>12</td>
<td>Ureter</td>
<td>Re-resection (2x)</td>
</tr>
<tr>
<td>Pt. 8</td>
<td>Male</td>
<td>52</td>
<td>RCC</td>
<td>Chromophobe carcinoma</td>
<td>Nephrectomy</td>
<td>1</td>
<td>30</td>
<td>Intestines</td>
<td>Resection and RFA</td>
</tr>
</tbody>
</table>

Results

Between December 2012 and November 2015, eight patients (9 tumors) underwent percutaneous CT-guided IRE to treat recurrences of primary rectal (n=4), anal (n=1), sigmoid (n=1), cervical (n=1), and renal cell carcinoma (n=1). Needle insertion and pulse delivery was successful in all procedures. Median longest tumor diameter was 3.7 cm (range 1.2–7.0). Patient and tumor characteristics are displayed in table 2. Pre- per- and post-procedural images of a successful IRE-procedure are shown in figure 1.

Complications

There were no deaths within 90 days post-IRE. One patient experienced a delayed hemorrhage after restarting anticoagulation therapy three days after the procedure (CTCAE grade-III). Eight CTCAE grade-II complications occurred in 6/8 patients. Three patients showed lower limb motor loss (all PNI score: II [axonotmesis]), with partial recovery in one patient. Two patients developed a hypotonic bladder (PNI score: I [neurapraxia], and PNI score: II [axonotmesis]) with complete recovery in one patient. Two patients showed upper limb motor loss, with partial recovery in both patients (PNI score: II [axonotmesis]). Procedure-related details including complications are summarized in table 3.

Follow-up
**Chapter 6.1**

**Table 3. Procedure details, clinical and radiologic outcome**

<table>
<thead>
<tr>
<th># probes</th>
<th># pullbacks</th>
<th>CTCAE grade</th>
<th>Complication type</th>
<th>Seddon's classification</th>
<th>Affected nerve(s)</th>
<th>Function recovery</th>
<th>Follow-up (months)</th>
<th>Time to progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pt. 1</td>
<td>5</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>36 ± 1</td>
<td>4 ± 3</td>
</tr>
<tr>
<td>Pt. 2</td>
<td>6</td>
<td>2</td>
<td>II</td>
<td>Lower limb motor + sensory involvement</td>
<td>Axonotmesis</td>
<td>Sciatic nerve</td>
<td>Partial 11 ± 1</td>
<td>5 ± 1</td>
</tr>
<tr>
<td>Pt. 3</td>
<td>6</td>
<td>2</td>
<td>II</td>
<td>Hypotonic bladder</td>
<td>Neurapraxia</td>
<td>Pudendal plexus S2-S4</td>
<td>Complete 21 ± 1</td>
<td>5 ± 1</td>
</tr>
<tr>
<td>Pt. 4</td>
<td>4</td>
<td>1</td>
<td>II</td>
<td>Mild deterioration of pre-existing lower limb motor + sensory loss</td>
<td>Axonotmesis</td>
<td>Sciatic nerve</td>
<td>None 12 ± 1</td>
<td>6 ± 6</td>
</tr>
<tr>
<td>Pt. 5</td>
<td>6</td>
<td>1</td>
<td>II</td>
<td>Hypotonic bladder</td>
<td>Axonotmesis</td>
<td>Pudendal plexus S2-S4</td>
<td>None 17 ± 1</td>
<td>7 ± 1</td>
</tr>
<tr>
<td>Pt. 6</td>
<td>4</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9 ± 1</td>
<td>- ± 1</td>
</tr>
<tr>
<td>Pt. 7</td>
<td>4</td>
<td>0</td>
<td>II</td>
<td>Upper limb motor + sensory involvement</td>
<td>Axonotmesis</td>
<td>Femoral nerve</td>
<td>Partial 5 ± 1</td>
<td>- ± 1</td>
</tr>
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<td>Upper limb motor + sensory involvement</td>
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ILP = Time to local progression; TDP = time to distant progression; * Patient developed a marginal recurrence which was successfully retreated with percutaneous IRE (see text); † deceased

After a median follow-up of 14 months (range 2-36), three patients were still alive and four had deceased, respectively 11, 12, 21 and 36 months after IRE. Although no local site recurrences have been objectified according to conventional RECIST so far, unequivocal LSR was observed in five patients (5 lesions) using PERCIST criteria. For lesions with a largest tumor diameter of ≤3 cm (5/9), up until now, one LSR has been detected (29 mm; patient 4). Contrarily, all (4/9) lesions with a largest diameter of >3 cm have recurred. CT-guided core biopsy confirmed tumor relapse in one patient who was successfully retreated with percutaneous IRE 16 months after the initial treatment; hereafter, no local recurrence was detected until he died due to cerebral metastases (patient 1, figure 2). Tumor recurrence distant from the pelvic treatment site developed in 4/9 patients: cerebral (n=1), pulmonal (n=2) and in a different site in the pelvic cavity (n=1). Lesion-based primary efficacy rate was 33% (3/9) and assisted efficacy rate was 44% (4/9). One day post-IRE, the reported pain was moderate with a median VAS score of 3 (range 0–5); pain could easily be controlled with acetaminophen combined with NSAIDs and opioids if needed. Prior to IRE three patients reported debilitating pain; 3 months after IRE pain perception had remained unchanged in one patient (VAS score 5; patient 2), and had improved slightly (VAS score from 5 to 4; patient 5) and considerably (VAS score from 6 to 3; patient 3) in the other two patients.

**Discussion**

Despite advances achieved in the radical treatment of primary colorectal and urogenital cancer, locoregional relapse remains a major therapeutic concern 1–6. This case series demonstrates the feasibility of IRE to achieve local tumor control (4/9 lesions; respectively after one [n=3] or two [n=1] procedures) for heavily pretreated pelvic tumor recurrences.
IRE of pelvic tumor recurrences

Lesion size seems key in predicting outcome with only 1/4 local site recurrences for lesions ≤ 3 cm. While safety should be confirmed in larger series, no major life-threatening complications occurred. Conversely, the number of patients suffering from permanent ablation-induced neural function loss should be considered high (6/8), which contradicts earlier animal studies. 20,22,23,30

While tumor recurrences within the pelvic cavity encompass a broad disease category, it is widely recognized that selected patients may benefit from intensive local therapy. 31–33 Surgical resection, often with curative intent, remains the treatment of first choice. However, the number of eligible patients is relatively small because the presence of adjacent crucial anatomical structures renders them unsuitable for complementary radical procedures. 36,37 Generally, the maximum tolerable radiation dose has already been reached during treatment of the primary tumor. In these cases, re-radiation is precluded due to the high risk of radiation-induced complications. 4 In the past two decades, thermal ablation has worked its way into everyday clinical practice. Apart from the (potentially) curative possibilities, thermal ablation can be valuable in the palliative setting to achieve cyto-reduction and pain relief. 11–13 For example, palliative CT-guided RFA for painful pelvic recurrences of rectal cancer is considered a feasible and effective treatment in selected cases where the recurrence is located at a safe distance from major nerves, intestines and urogenital tract structures. 15,38–41 In one study, twelve patients who underwent RFA for pain reduction were pain free at the end of follow-up. 11 With one rectovesical fistula (8%) and one rectal abscess (8%), complication rate was considered acceptable. Since all lesions in our series were deemed unsuitable for thermal ablation, a fair comparison to these reports cannot be made.

One case report of a 56-year-old woman who was referred for IRE treatment of a large advanced local recurrence of endometrial tumor (maximum tumor diameter 14.9 cm) with infiltration of the sacral bone and nerve plexus described only minor temporary impairment of neural function after the procedure. 42 No other studies regarding IRE for pelvic tumors in humans, outside the prostate, have been published.
Chapter 6.1

Figure 2: (A) ¹⁸F-FDG PET-CT image of a 70-year-old male patient with an ¹⁸F-FDG avid 60mm pathologically proven locoregional recurrence (arrows) of primary rectal adenocarcinoma in the left parasacral area. (B) Histopathology confirmed malignancy (C) Nonenhanced CT scan showing three of the inserted needle electrodes prior to pulse delivery. (D) ¹⁸F-FDG PET-CT image 16 months after IRE showing a local site recurrence (D) Histopathology confirming local recurrence (E). (F) Nonenhanced CT scan during re-treatment of local recurrence. (G, H, I) ¹⁸F-FDG PET-CT image, histopathology and ceCT 4 months after the second IRE procedure showing no signs for residual or recurring disease.

The discrepancy between the preclinical animal experiments and our results regarding neural damage remains largely unclarified. One explanation could be a variation in the applied electric fields, as these are key in determining IRE-outcome.⁶⁵ Although the parameters used in the animal studies were in accordance with ours, the induced potential depends on the ohmic characteristics of the tissue, which can differ in heterogeneous tissues.⁶⁴ The actual working mechanism of IRE is based on a non-thermal effect, nonetheless, the development of some heat seems inevitable. Van den Bos et al found a temperature rise of 19.6 °C at 5mm distance from the electrodes (using 1500 V/cm) in a non-perfused gelatin tissue model.⁶⁵ According to animal studies, transient nerve dysfunction starts at temperatures as low as 40 °C and permanent nerve injury at 51 °C.⁶⁶,⁶⁷ Since the conductivity and the electric field distribution may differ between healthy and tumor tissue, this may have resulted in focal areas with a greater temperature rise in our study, resulting in permanent thermal damage to the nervous structures.⁶⁸ In the future, sequential pulsing may prove to reduce the maximum tissue temperature gradient and therefore the extent and volume of thermal damage.⁶⁵ However, further research is needed to assess whether this is factual and whether this does not compromise oncologic efficacy. Furthermore, as opposed to healthy sciatic nerves and surrounding tissues in the animal experiments, the neural and perineural structures in the presented patients may well have been injured to some extent by earlier treatments or by tumor compression; by undergoing the IRE procedure, they may have lost their neural
IRE of pelvic tumor recurrences

function completely. Li et al explored the effect of IRE on nerves in a rat model and observed that nerve continuity was preserved postprocedurally.26 However, studies have shown that the regeneration process of nerves in larger animals is better comparable to neural regeneration in humans and might therefore be more suitable to study longer distance nerve regeneration.49,50 Schoellnast et al assessed the acute, subacute, and delayed effects of IRE on the sciatic nerve in a pig model and concluded that IRE potentially damaged neural structures.22,23 Though, they also hypothesized that the observed preservation of the endoneurium architecture and the Schwann cell proliferation could potentially enable axonal regeneration. Within this study, most animals did not exhibit symptoms of lameness one month post-IRE although nerve conduction studies revealed limited function of the sciatic nerve in half of the animals. These inconsistent results might be explained by compensation for the loss of function of the sciatic nerve by addressing muscle groups that are not affected by sciatic nerve palsy, such as the gluteal muscles and the extensors and adductors of the thigh. In contrast to healthy individuals, cancer patients are generally less physically active and have less capacity to use other muscles to compensate the loss of neural function. In addition, pre-existing (partial) neural function loss and pain complaints might hinder optimal recovery and abovementioned compensation mechanism post-IRE. Recently, Tam et al.51 investigated the post-ablation effects of IRE in the epidural space of the porcine spine and concluded that even at low electric field strengths nerve root injury can occur (p = <0.05). To recognize impending nerve injury and to prevent irreversible damage, intraoperative neurophysiologic monitoring (IONM) might be helpful during percutaneous IRE, since neural structures adjacent to the target area are often poorly visible.52

There are inherent limitations to this study. Besides the limited number of cases, retrospective study design, heterogeneity of tumor type and tumor size, anatomical location and treatment indication (symptom palliation or disease control) was high. Another limitation was the inability to precisely quantify the level of nerve palsy after the ablation. To overcome this drawback in a prospective future study, general neurological examination and nerve conduction studies could be performed to objectify the neural function pre- and post-IRE.

In conclusion, IRE may represent a suitable technique to treat well-selected locoregional tumors within the pelvic cavity. However, as opposed to preclinical animal studies, permanent neural function loss can occur. Although radical ablation seems achievable for smaller lesions (< 3cm), this currently seems unrealistic for patients with larger tumors. For these patients, treatment with IRE might be useful to decelerate tumor progression or to accomplish symptom prevention; this should be the focus of future clinical studies.
Chapter 6.1

References
IRE of pelvic tumor recurrences

Chapter 6.1


IRE of pelvic tumor recurrences
6.2

Percutaneous irreversible electroporation of unresectable hilar cholangiocarcinoma (Klatskin tumor) - a case report

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Abstract

Irreversible electroporation (IRE) is a novel image-guided ablation technique that is rapidly gaining popularity in the treatment of malignant tumors located near large vessels or bile ducts. The presence of metal objects in the ablation zone, such as Wallstents, is generally considered a contraindication for IRE, because tissue heating due to power conduction may lead to thermal complications. This report describes a 66-year-old female with a Bismuth-Corlette stage IV unresectable cholangiocarcinoma with a metallic Wallstent in the common bile duct who was safely treated with percutaneous IRE with no signs for relapse one year after the procedure.
Introduction

Cholangiocarcinoma accounts for approximately 2% of all cancer diagnoses, with an overall incidence of 1.2/100,000 individuals.\(^1\) Two-thirds of cases occur in patients over the age of 65, with a near ten-fold increase in patients over 80 years of age.\(^1\) Hilar cholangiocarcinomas (Klatskin tumors) account for up to 25% of all cholangiocarcinomas.\(^1\) Complete tumor resection (Bismuth–Corlette type I and potentially type II and III) offers the only hope for long-term survival, with 5-year survival rates ranging from 10 to 40 percent.\(^1\) However, because most tumors become symptomatic at a late stage, less than half of the cholangiocarcinomas are resectable at time of presentation with a median survival of less than 6 months for those patients.\(^1,3\) No clear clinical benefit has been demonstrated for neoadjuvant and adjuvant therapies. There is no established standard palliative chemotherapeutic regimen.\(^2\)

Recently, irreversible electroporation (IRE) has been introduced as a novel technique for image-guided tumor ablation. With this technique, multiple short, high-voltage electrical pulses are delivered to the tumor tissue, which disrupt the cellular membrane and ultimately lead to cell death through apoptosis.\(^4\) Although results are still preliminary, for pancreatic and liver tumors the technique appears to be tolerated well and early results of efficacy are promising.\(^5,7\) Clinical studies seem to confirm preclinical animal studies where IRE near the portal triad rarely leads to biliary complications.\(^8\)

The presence of a metallic Wallstent within the ablation zone is generally considered to be an absolute contra-indication for IRE. If the electric current passes through the stent, the predicted electric field distribution may be compromised and extreme current concentration may result in stent-induced tissue heating, leading to undesirable thermal damage to sensitive structures such as intestines and bile ducts.\(^9-10\) Also, redistribution of the electric field may result in an unpredictable shape of the ablation zone, leading to an incomplete ablation. Commercial electroporation pulse-generators are typically limited to a 50 Ampere maximum current and surpassing this threshold leads to a generator hard-reset for recalibration or component restabilization.\(^8\)

Despite this contraindication, uncomplicated IRE-procedures in previously stented patients with locally advanced pancreatic carcinoma have been reported (data presented at CIRSE 2013 by G. Narayanan, University of Miami, Miller School of Medicine). Here, a case of percutaneous IRE is presented in a patient with an unresectable and growing hilar cholangiocarcinoma for which a palliative metallic Wallstent was previously placed.

Case presentation

A 66-year-old female presented with silent icterus (bilirubin 89 µmol/L, alkaline phosphatase U/L). Computed tomography (CT) imaging showed a 30x 30x 38 mm mass in the liver hilum surrounding the common and the left and right main bile ducts (Bismuth–Corlette type IV) (figure 1A-B). There was no sign of lymph nodal or metastatic spread and all the bloodvessels were patent. An endoscopic ultrasound (EUS) guided core needle biopsy of the lesion confirmed the diagnosis hilar cholangioadenocarcinoma. Because of biliary obstruction, a plastic retrievable endoprosthesis was placed and renewed several times, but due to repeated congestion of the endoprosthesis it was eventually replaced for a metallic Wallstent
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and bilirubin levels normalised (14 μm/L). After establishing local disease progression at 3 months she was referred to our centre.

The patient was discussed in our weekly multidisciplinary hepatobiliary tumor board consisting of a radiologist, interventional radiologist, hepatobiliary surgeon, medical oncologist, hepatogastroenterologist, radiotherapist and nuclear radiologist. All potential risks and benefits of IRE near the portal triad with a metallic stent in situ were carefully outweighed against best supportive care. Since the stent did not reach into the duodenum the risk of damaging the duodenal wall was considered low. After careful deliberation, the patient opted for IRE and gave written informed consent.

First, to allow repeated and real-time visualization of both the tumor and the vessels within the celiac trunk, a catheter was placed within the common hepatic artery (figure 2). To determine the three-dimensional measurements of the tumor and its proximity to other structures a 40mL bolus of 1:1 saline diluted contrast material was injected at 4mL/sec with a scan delay of 7 and 30 seconds for

Figure 1: (A) Coronal ceCT image pre IRE with a hilar cholangiocarcinoma (arrow) surrounding a metallic Wallstent present in the common bile duct. (B) ceMRI image demonstrating an enhancing mass in the liver hilum surrounding the common bile duct. (C) Axial CT image of two electrodes placed alongside the Wallstent. (D) Coronal CT view demonstrating all six electrodes and eight electrode pairs during the ablation (red lines). (E) ceCT immediately after IRE demonstrating patent vessels and gas bubbles in the ablated area (arrow). (F) ceMRI 1 day post IRE with no signs of complications. (G-H) ceCT six months and one year after IRE demonstrating no tumor progression.
the arterial and portal venous phase CT respectively (Sensation 64 slice MDCT, Siemens, Erlangen, Germany). Size and shape, including a 5mm margin, determined the number and configuration of the electrodes. With the patient under general anaesthesia in the supine position, a total of six monopolar needle electrodes (NanoKnife; AngioDynamics, Latham, New York) were placed alongside the metallic Wallstent under CT-fluoroscopy guidance, three on each side (figure 1C-D and 2). The active working length of the electrodes was set at 2cm. Eight vectors for pulse delivery were chosen with a minimum and maximum interprobe distance of 1.6 and 2.5 cm (Fig 1D). All pulses were delivered in the absolute refractory period of the heart with use of electrocardiographic synchronisation (Accusync, Model 72; Milford, Connecticut) to elude the induction of cardiac arrhythmias. To avoid generalized muscle contractions additional rocuronium was given to achieve deep muscle paralysis. First, ten test pulses of 90μsec were delivered for each electrode pair with a deliberately low voltage (750 V/cm) because of the presence of the Wallstent to verify the delivered current, and avoid a potential stent-induced overcurrent, which ranged between 13 and 24 Ampere. Next, the voltage was adjusted to 1250 V/cm after which another ten test pulses were given. The delivered current appeared consistent for all electrode pairs and ranged between 24 and 40 Ampere, so subsequently 80 treatment pulses were delivered along each vector. After removal of all six needles, contrast-enhanced CT (ceCT) demonstrated a hypodense ablation zone containing gas bubbles (figure 1E). The gas bubbles are presumably caused by the electrolysis of water (H2O) into oxygen (O2) and hydrogen gas (H2) by the electric current passing through the tissue. The portal vein and the surrounding arteries were patent and the intrahepatic bile ducts appeared unremarkable.

The patient awakened uneventfully in the recovery unit and was transferred to the ward. The next day she experienced some nausea and vomiting, which was successfully treated with anti-emetics. No pain medication was required. Venous sampling showed a mild increase in transaminases (AST from 32 to 53 U/L, ALT from 26 to 52 U/L) with no signs for cholestasis (bilirubin 17 umol/L). MRI(DWI) one day post IRE showed an edematous ablation zone surrounding the Wallstent which was present in the same location. No complications to the blood vessels or bile ducts were noticed (figure 1F). On the 4th day post-IRE the patient was discharged in good clinical condition. Further recovery was uneventful. Four months later, follow-up ceCT showed no local tumor progression or metastatic disease, also no stent complications were noticed. At six, nine months and one year follow-up ceCT still showed no local tumor progression or metastatic disease (figure 1G and H). She currently remains in follow-up.

Figure 2: 3D reconstruction with a catheter in the common hepatic artery (asterisk) and six electrodes placed alongside the metallic Wallstent
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Discussion

The electrical pulses administered with irreversible electroporation destabilize the cellular membranes and lead to the formation of ‘nano-pores’ in the lipid bilayer, irreversibly damaging the cell’s homeostatic mechanism.\(^7\) IRE only affects the membranes of living cells, whilst preserving the extracellular matrix constituents that are responsible for the patency of major vascular and ductal structures and other vulnerable tissues.\(^7\) Also, ablation success is not impaired by heat-sink.\(^9\) For these reasons, the technique may be suitable to treat hilar cholangiocarcinoma.

Because hilar cholangiocarcinomas are often unresectable at presentation, in the majority of cases treatment focuses on palliation of symptoms. The preferred modality of palliation is placement of a stent in the main biliary duct.\(^9\) Both plastic endoprosthesis and metallic Wallstents are used for biliary drainage. Adverse effects, including cholangitis, stent occlusion, migration, perforation and the need for reinterventions occur more frequently with plastic stents (39.3\%) than with metal stents (11.8\%).\(^13\),\(^15\) Therefore, in spite of the high initial cost, metallic Wallstents are considered more cost-effective for patients with tumors that are considered unsuitable for surgical resection.

The effect of metal on tissue temperature during IRE has recently been analyzed in porcine liver. Dunki-Jacobs et al reported a mean maximum change in temperature immediately adjacent to the electrodes of 29.3°C for ablations with metal stent in situ versus 11.3°C for ablations without metal stents (p = .007).\(^8\) The effect of smaller metallic implants on the ablation parameters was evaluated by Neal et al.\(^7\) Numerical, ex vivo and in vivo models evaluated the influence from multiple metallic brachytherapy seeds on electrical current, electric field, and temperature in tissue as well as acute histological effects.\(^7\) There was no significant impact from the presence of these small conducting seeds on the characteristics influencing the outcome of IRE.

In this specific case the potential thermal effect on tumor tissue surrounding the stent may actually have been beneficial in terms of ablation and oncological efficacy for three reasons. First, since tissue conductivity increases with an increase in temperature the zone of irreversibly electroporated tissue may be larger and more complete.\(^6\) Secondly, with an exposure length of several minutes and the before mentioned peak temperature increases surrounding the stent, the periductal tumor tissue may also have been irreversibly damaged by heat itself.\(^12\) Thirdly, although in large part unknown, an increase in tumor temperature during ablation coincides with a stronger immune response, therefore a potential systemic abscopal response may have been elucidated.\(^14\) It remains unclear to what extent the metal influences the electric field, which can also lead to a less effective or less predictable ablation zone. To avoid thermal damage to the duodenal wall, the use of IRE should be discouraged if the metallic Wallstent extends into the duodenum.

In conclusion, this case report describes a technically successful percutaneous IRE procedure of a hilar cholangiocarcinoma in the presence of a metallic Wallstent in the main bile duct. However, before IRE for this indication can be implemented in the clinical setting, the biophysical effects of metallic objects within the zone of electroporation, as well as its safety and efficacy needs to be confirmed in future translational and clinical studies.
IRE for a Klatskin tumor

References

6.3

Percutaneous irreversible electroporation for recurrent thyroid cancer - a case report

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Abstract

A 74-year-old man presented with a small locoregional, histopathologically proven, fluorodeoxyglucose positron emission tomography/computed tomography–avid recurrence of follicular thyroid carcinoma in the left subglottic space after extensive surgical resection, adjuvant radioactive iodine therapy, and external beam radiation therapy. Because all established focal therapies were considered contraindicated, percutaneous irreversible electroporation was performed without complications. Follow-up imaging at 7 months showed a small ablation scar without signs for residual vital tumor tissue. Irreversible electroporation may be a viable treatment option for selected cases of recurring head and neck tumors that are unsuitable for other local treatments.
Introduction

Thyroid cancer is the most common endocrine malignancy with 465,000 new cases identified each year within the European Union and the United States. Differentiated thyroid carcinoma comprises 90% of the cases, including papillary and follicular subtypes. Approximately 10%–30% of patients with localized differentiated thyroid cancer develop a recurrence, of which approximately 80% are localized to the neck region. The prognosis for these patients is promising, with an approximate 50% cure with reoperation regardless of cell type. Clinically unapparent local and regional recurrences that are detected by iodine-131 (\textsuperscript{131}I) scan can be treated with \textsuperscript{131}I ablation and have an excellent prognosis. However, 25% of recurrences from well-differentiated thyroid cancer do not show \textsuperscript{131}I uptake. In these cases, external beam radiation therapy (EBRT) or intraoperative radiation therapy can be useful in controlling symptoms related to local tumor recurrences. Intensity modulated radiation therapy has been proven feasible and effective in selected patients, although the potential acute toxicity is a drawback. Radiofrequency (RF) ablation and ethanol ablation also can be applied in specific cases of locoregional recurrence. However, thermal and toxic injuries to surrounding structures have been described.\textsuperscript{5,6}

Irreversible electroporation (IRE) is a newer ablation technique that uses ultrashort but strong electric fields to create permanent nanopores in the cellular membrane, which disrupt cellular homeostasis and eventually lead to cell death. IRE is particularly useful for the ablation of tumors in regions where preservation of the extracellular matrix, blood flow, and nerves is important. This case report describes a technically successful percutaneous IRE procedure of a locoregional recurrence from follicular thyroid carcinoma.

Case presentation

A 74-year-old man presented with a third consecutive recurrence of follicular thyroid carcinoma. A left-sided hemithyroidectomy had been performed 8 years earlier for a tumor that was originally thought to represent an adenoma. He presented 4 years after primary surgery with an extensive 5-cm local recurrence, which was treated by partial tracheal resection and complete thyroidectomy. Revision of the histopathology of the recurrence and the primary tumor showed follicular carcinoma. Because of tumor-positive resection margins, he received adjuvant radioactive \textsuperscript{131}I therapy (total dose 150 mCi). A second recurrence was treated 6 years after the initial presentation with a total laryngectomy, partial pharyngectomy with placement of a voice prosthesis, and bilateral neck lymph node dissection (level II–IV). Histopathologic examination showed positive resection margins and one positive lymph node, for which he received adjuvant EBRT (2 x 33 Gy). Because of persistent general malaise combined with an elevated thyroglobulin and thyroglobulin-antibody and negative radioactive iodine scan, a contrast-enhanced computed tomography (CT) scan of the neck and chest was performed. This scan revealed a new 17-mm small solid mass in the left paratracheal submucosal visceral space. The lesion was fluorodeoxyglucose (\textsuperscript{18}F-FDG) avid on positron emission tomography (PET-)CT, indicative for a third consecutive recurrence (figure A, B). Ultrasound-guided fine-needle aspiration cytology confirmed follicular thyroid carcinoma, the cell type matching the original tumor type. The mass was considered unsuitable for surgical resection, and because it did not show \textsuperscript{131}I uptake, it was unsuitable for \textsuperscript{131}I ablation. Also, because of its vicinity to the tracheoesophageal fistula, the risk of complications associated with additional EBRT and thermal or chemical ablation was deemed
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too high. The multidisciplinary tumor board unanimously opted for experimental treatment with IRE. Because IRE has CE clearance for use in soft tissue ablation, the local review board waived formal approval. The patient gave written informed consent.

With the patient under general anesthesia in the supine position, two monopolar needle electrodes (NanoKnife; AngioDynamics, Latham, New York) were placed alongside the cranial and caudal margins of the mass using CT fluoroscopy guidance (figure C). The active working length of the electrodes was set at 2.0 cm; interelectrode distance was 2.0 cm. Pulses were delivered in the absolute refractory period of the heart with use of electrocardiographic synchronization (AccuSync 72; AccuSync Medical Research Corporation, Milford, Connecticut) to prevent the induction of cardiac arrhythmias and with deep muscle paralysis using additional rocuronium to avoid generalized muscle contractions. First, 10 test pulses of 90 ms were delivered to verify correct energy delivery. Subsequently, 80 additional treatment pulses were delivered. After removal of both needles, CT showed a nonenhancing ablation zone with typical gas inclusions (figure D). The patient recovered uneventfully in the recovery unit and was transferred to the ward. There were no signs of injury to vital structures, and the patient was discharged in a good condition 2 days after the procedure. No late complications occurred in the ensuing months. A small scar lesion (figure E) with minimal residual tracer uptake was seen on 18F-FDG PET-CT 7 months after IRE, presumably representing inflammation (figure F).

Discussion

Advances in the field of minimally invasive image-guided tumor ablation have led to a solid position of these techniques within treatment guidelines for malignancies in the abdominal and thoracic cavity.8 The use of thermal ablation methods such as RF ablation, microwave ablation, laser ablation, and cryoablation in the head and neck region has been limited because of the delicate anatomic structures and the unpredictable distribution of heat.8 This report describes a technically successful and uneventful case using (predominantly) nonthermal IRE to eradicate a small follicular thyroid carcinoma recurrence. In general, the outcome of patients with locally recurring thyroid cancer is fair. In a single series of 289 patients with recurrences after initial surgery, 16% died of their disease after a median period of 5 years.11 The selection of additional treatment depends on many factors, including cell type,131I uptake, prior treatment, site of recurrence, and individual patient considerations. Complete remission is achieved with a second operation in approximately 50% of patients.2 Patients with locoregional recurrence visible on 131I scan have a better prognosis.3 Surgery with or without 131I ablation can be useful in controlling local recurrences, regional node metastases, or occasionally metastases at other localized sites.4 Systemic chemotherapy was reported to induce an occasional objective response, usually of short duration.12 Retrospective studies showed that adjuvant EBRT may prevent locoregional recurrence of papillary carcinoma after surgery.13 Patients with presumed microscopic residual disease who received EBRT had better 10-year local relapse-free rates (93% vs 78%) and disease-specific survival rates (100% vs 95%) than patients who did not receive EBRT.14 However, complications of EBRT, such as esophageal, tracheitis, neck fibrosis, xerostomia, osteo-radionecrosis, tracheal stenosis, and dental decay, are common. Also, EBRT may preclude further surgery for recurring tumors. To reduce morbidity, new radiation techniques such as intensity-modulated radiation therapy are increasingly used.5 With a reported therapeutic success
IRE for recurring thyroid carcinoma

rate of 70%–98%, RF ablation and ethanol ablation also should be considered important nonsurgical treatment options for recurrent thyroid cancer in high-risk patients. However, various lower grade complications such as discomfort, pain, skin burning, and permanent changes in voice have been reported. In electrochemotherapy, the local application of short and intense electric pulses temporarily permeabilizes the cell membrane, as opposed to permanent permeabilization in IRE; this allows the temporary transmembrane transport of non-permeable drugs such as bleomycin into the cell interior. Electrochemotherapy appears to be an efficacious treatment; however, it should be used with caution in the treatment of head and neck cancer. Whether the simultaneous administration of chemotherapeutics such as bleomycin can enhance the effect of IRE by exploiting the reversibly electroporated

Figure: (A) Transaxial contrast-enhanced CT slices show a small enhancing mass (arrow in A, D–F) in the left paratracheal groove with (B) \(^{18}\)F-FDG tracer uptake on PET-CT. (C) Sagittal multiplanar reconstruction shows the two needle electrodes encompassing the mass on the cranial and caudal sides, just before IRE. (D) Immediately after IRE, the lesion was nonenhancing with gaspockets in the ablation zone. (E) 7 months after IRE, a small scar lesion with minimal residual tracer uptake on PET/CT (F) presumably represents inflammation.
Chapter 6.3

marginal zone should be the focus of future studies. Because all established definitive focal therapies were either contraindicated or exhausted in our case, we opted for experimental IRE treatment with curative intent and reserved chemotherapy for palliation in the event the treatment failed. IRE treatment was technically successful, and follow-up CT performed at 7 months did not show signs of residual vitality. Although PET-CT detected minimal residual FDG uptake in the ablated area, this likely represented treatment-induced inflammation rather than residual disease. However, in the case of a late recurrence, retreatment with IRE will be strongly considered. Should larger series confirm its safety and efficacy, IRE may prove a viable treatment option for selected cases of recurring head and neck tumors that are unsuitable for repeat surgical resection or established ablation techniques.
References

“Can I get a witness to testify?
  Open your eyes, realize, electrify.

*Beastie Boys, Electrify*
General discussion and future perspectives
Modern medicine is constantly developing less invasive methods for treatment of disease. While some of the research regarding tissue ablation was documented over 100 years ago, the majority of the investigative efforts have taken place within the past 20 years. Since its first introduction in 1990, the efficacy of thermal ablation techniques, such as radiofrequency ablation (RFA) and microwave ablation (MWA), has greatly improved due to technological advancements in image-guidance, resulting in real-time tumor localization and accurate needle targeting. Technical advances of the thermal devices such as the development of more powerful generators and better-quality probe designs have further improved the efficacy, creating larger, more spherical and more predictable ablation zones.

In the rapidly changing climate of tumor ablation, irreversible electroporation (IRE) is the newest kid on the block. Over the past years, IRE has been increasingly used in clinical practice because the hypothetical advantages over thermal ablation seem intuitive and self-evident. However, hard evidence regarding the actual working mechanism and more importantly - regarding the established safety and efficacy is lacking and conclusions drawn from the available data may very well be prejudiced.

In this thesis, we were able to demonstrate proof-of-concept that IRE is capable of creating complete cell death of in situ malignant tumors in humans, without creating major thermal coagulation necrosis. Based on our results we can further conclude that IRE has an acceptable safety profile, considering the treatment of difficult-to-reach tumors that are not suitable for surgical resection and thermal ablation. The toxicity profile, the focal treatment site efficacy and the currently reported oncological outcome after IRE mandates the setup of larger phase II and III clinical trials for tumors within the liver, biliary tract, pancreas and prostate.

Nonetheless, many aspects of IRE still need to be unraveled. IRE suffers from several growing pains that need to be addressed in the following years in order to improve its efficacy and further decrease the risk for collateral damage.

**Knowledge gaps in irreversible electroporation**

One of the difficulties encountered in clinical practice is the lack of properly validated tumor-specific standardized treatment protocols, since the current ablation protocols are mainly based on animal studies investigating the effect of IRE on healthy liver tissue. Recent papers have questioned IRE’s ability to destroy tumor tissue in the same way it destroys normal tissue. Qin et al found that even at 1,300 V/cm with 99 pulses, a pulse duration of 100 μs, and 10 Hz, there were still islands of viable tumor cells seen.¹ This brings into question a potential flaw in the assumption that tumor tissue will have the same response to IRE as normal tissue. The mechanism of cell death following IRE relies on cell apoptotic responses to loss of homeostasis from pore formation. Tumor cells, known to be resistant to apoptotic pathways, may require higher thresholds to be adequately treated, analogous to increased chemotherapy levels required for tumor cell death.² Electric field dose-response studies for tumor-specific tissues are scarce, and much remains unknown about the clinical possibilities to destroy malignant tissues with irregular geometries and heterogeneous properties. An interesting topic to this extent is the study from Appelbaum and colleagues, who showed that multiple shorter cycles of energy application create larger ablation zones.³ The authors hypothesized
that the increase in electrical conductivity induced by an IRE pulse persists after the initial pulse, and that longer overall exposure results in an increased shift of cellular contents caused by the membrane permeabilization, thereby enhancing the ablation zone. Apart from their findings, we showed that sequential pulsing simultaneously leads to a lower temperature increase, which improves procedural safety. The model of sequential pulsing needs to be validated in further animal and clinical studies, but could represent a big step forward towards improved safety and efficacy of IRE.

“Researchers are faced with the challenging task to identify the optimal treatment algorithms of different tumor types with heterogeneous electrical properties; strong enough to create complete tumor cell death, whilst avoiding thermal damage in areas where this can have detrimental effects”

Another shortcoming of IRE that likely reduces procedural efficacy is the lack of well-defined intraprocedural endpoints that can be used to confirm effective ablation. With RFA, tissue necrosis is achieved as the tissue gradually desiccates and eventually loses its ability to conduct current, which is signaled by a precipitous rise in impedance (‘roll-off’), which has been shown to be a significant predictor of local control. With IRE, the current should lie between 20-40 A during pulse delivery, but there is no reliable feedback to inform the clinician whether all tissue has been effectively electroporated. Especially with pancreatic IRE, exact delineation of the irreversible damaged ablation zone with intraprocedural ultrasound or CT is not feasible because of the development of edema and gas pockets. Since it has been postulated that increased current is a direct derivative of increased membrane permeabilization, the group of Martin and colleagues advises a current increase of 12 to 15 A from baseline for each electrode pair. If this increase is not reached after the initial 90 pulses, the protocol should be repeated until the desired current change is achieved. However, since we showed in chapter 2.1 that there is a steady temperature rise during IRE that is also accompanied by a rise in amperage – in an acellular model –, caution should be taken when repeating the electroporation protocol, as the accumulated energy may cause thermal damage to the heat-susceptible structures in the vicinity of the ablated region.

“IRE would benefit from the establishment of solid intraprocedural endpoints that can be used to confirm effective ablation”

A third issue that needs to be addressed is the difficulty of planning the desired 3-dimensional geometry of the ablation zone, and subsequent electrode placement. At the moment, the NanoKnife® generator converts the 3-dimensional tumor measurements (width, height and depth) into a 2-dimensional oval or circle, reducing the tumor to a perfect oval- or circle-shaped 'tube', in which the planned electrode configuration is then drawn. In reality, the shape and size of deep-seated tumors and the subsequent planning of electrode placement is much more complex, and the current software does not take this into account. Recently, a web-based treatment-planning software tool of electroporation-based treatments was developed, including algorithms for automatic tissue segmentation and generation of a 3D model of the tissue. The procedure allows the user to define how the electrodes will be inserted. Finally, electric field distribution is computed, the position of electrodes and the voltage to be applied are optimized using the...
3D model and a downloadable treatment plan is made available to the user. This new software tool may improve treatment planning and subsequent accuracy of IRE delivery.

Last, the geometry of zones of cell death produced by IRE is a complex issue. Placement of multiple electrodes at a 1.5 – 2.0 cm interelectrode distance whilst carefully manoeuvring past vessels and bile ducts has proven laborious and time-consuming. Misplacement of the probes by a margin of millimeters can already result in residual tumor. Placement of larger probe-arrays with multiple repositionings to treat larger tumors has proven even more difficult, and local failure rates of tumors >3 cm are too high. As has been successfully done with thermal ablation, emphasis should be put on the development of electrodes that are capable of creating larger ablation zones, resulting in fewer electrode repositionings, thereby reducing the risk of misplacement. The bipolar probe that is currently being developed, is therefore eagerly awaited.

**IRE and cancer care – where do we go?**

**Colorectal liver metastases**

In the COLDFIRE-1 study we were able to demonstrate that IRE was able to destroy in situ colorectal liver metastases. As mentioned before, the safety of IRE in the liver has been well documented in the literature; however, local control remains relatively low compared to thermal ablation techniques, especially for lesions > 3cm.\(^6\)\(^-\)\(^13\) On the other hand, considering that these patients represent a group for which no curative treatment option used to be available, a fair chance of complete tumor destruction already has major implications. Results of the COLDFIRE-2 study are eagerly awaited and will be published at the beginning of 2017. Until local control rates improve, IRE should be reserved for well-selected patients with relatively small hepatic tumors that are truly unsuitable for resection and thermal ablation. In general this means tumors abutting the portal triad or the hepatic venous pedicle, where thermal ablation is considered unsafe and less effective. A study comparing IRE to stereotactic body radiation therapy for small-size colorectal liver metastases is currently being constructed (COLDFIRE-3).

**Pancreatic cancer**

Although ablation of unresectable CRLM is nowadays considered standardized practice, pancreatic tumor ablation raises more questions. Rather than pursuing cure, pancreatic ablation aims to prolong life expectancy whilst preserving quality of life. Previous studies investigating the safety of IRE reported relatively low complication rates,\(^13\)\(^-\)\(^15\) but in the PANFIRE-study significantly more complications occurred, with a major complication rate of 44% including a wide diversity of gastrointestinal problems. Although a few suggestions were given to reduce IRE-associated morbidity, these complications weigh heavily when considering IRE for LAPC. On the other hand, in line with the literature, our results show a promising event-free and overall survival. Whether the assumed survival benefit truly outweighs the morbidity associated with pancreatic IRE - in a patient population that is considered technically incurable – needs to be further assessed. Importantly, the possible role of immune induction yields promise for further improved survival.

Besides the introduction of IRE, the traditional cornerstones of LAPC treatment – chemotherapy and radiation - are also subject to alterations. Recently, the landscape for
General discussion and future perspectives

systemic therapy for pancreatic cancer has improved with the advent of folfirinox. In LAPC, folfirinox with or without additional chemoradiation showed improved survival, and in some instances even led to downstaging to resectability.\textsuperscript{16,17} Additionally, a study in 2013 revealed a survival benefit when nab-paclitaxel was combined with gemcitabine as compared to gemcitabine alone.\textsuperscript{18} Improving chemotherapeutic options for pancreatic adenocarcinoma remains an active area of research with multiple ongoing studies.

Although the standard treatment regimen of LAPC generally includes radiation, survival data of randomized trials regarding the role of external beam radiation therapy for patients with LAPC have been conflicting.\textsuperscript{19} Besides, the use of large radiation fields inevitably delivers a high percentage of the radiation dose to the surrounding tissue, leading to significant toxicity. This limits the delivery of the intended radiation dose to the tumor, increasing the chance for local failure.\textsuperscript{20} In order to maximize survival benefit and minimize toxicity, stereotactic ablative body radiotherapy (SABR) recently came on stage. SABR is capable of delivering higher doses of radiation with improved precision using four-dimensional diagnostic imaging, resulting in decreased toxicity and dose-escalation to the tumor.\textsuperscript{21-22} In a disease with so many systemic manifestations, it is hard to see the impact of localized therapy on survival without obtaining some control of metastatic spread with systemic therapy. Besides, there is growing body of literature that suggests that a multimodal approach combining systemic chemotherapy with focal tumor destruction offers great promise to improved survival of LAPC.\textsuperscript{23,24} The next step towards implementation of IRE in the treatment of LAPC is therefore to compare it with the current standard of care, which consists of folfirinox and radiation. This is the aim of the CROSSFIRE-trial, a multicenter randomized study with overall survival as the primary endpoint, and safety and progression-free survival as secondary endpoints, started in May 2016. In the CROSSFIRE-trial, patients with de novo LAPC will receive 4 cycles of folfirinox, after which 73 patients will be randomized to SABR, and 73 to IRE. After completion of local treatment, additional folfirinox will be given until progressive disease or maximum toxicity (see appendix A for the flowchart of the CROSSFIRE study).

**Perihilar cholangiocarcinoma**

As we have shown in chapter 6, the indications for IRE may extend beyond the liver and the pancreas. A disease in which IRE might also show potential is perihilar cholangiocarcinoma (PHC). The location of PHC in the liver hilum and proximal bile ducts causes biliary obstruction with concomitant jaundice. Despite palliative treatment with biliary stenting to relieve cholestasis, patients eventually die of cholangitis, sepsis or liver failure. As with LAPC, approximately 50% of tumors are considered locally advanced because of unreconstructable vascular or extensive biliary involvement and during exploratory laparotomy another 40% have locally advanced or metastasized tumors.\textsuperscript{25,26} Liver transplantation is the only chance for cure for these patients but has strict selection criteria.\textsuperscript{27} Several ablative strategies for the treatment of PHC have been investigated, such as photodynamic therapy, intraductal RFA, brachytherapy and MWA, but without great success, mostly due to the heat-sink effect. The
successful case presented in chapter 6.3 stimulated us to develop the ALPACA-trial, a joint effort between the VU University Medical Center and the Academic Medical Center. In this trial, 10 patients with upfront unresectable PHC will be treated with percutaneous IRE whereas another 10 patients that are found to have advanced PHC intraoperatively are treated with IRE during the same surgical exploration session. Rather than placing a metal stent for biliary protection, which may leave a rim of vital tissue behind as shown in chapter 2.2, percutaneous biliary drainage using plastic stents will be performed prior to IRE for biliary protection. The primary aim of the ALPACA-trial is to investigate the safety and feasibility of IRE for advanced PHC; secondary endpoints are progression-free and overall survival, and quality of life (see appendix B for the flowchart of the ALPACA study).

**Future perspectives**

As interventional oncologic therapies evolve, they are combined with other treatments in a multimodality approach to treat cancer. Combined therapy of ablation with embolization, radiation with embolization, or chemotherapy with ablation are just a few examples of treatment options that show the promise of this multifaceted approach to increase treatment effect. Similarly, directly after IRE a margin of reversibly electroporated tissue exists between the irreversibly damaged ablation zone and the normal tissue. During this temporary permeability of the cell membranes, macromolecules such as chemotherapeutics can travel freely into the cells within this zone, a process known as electrochemotherapy. Capitalizing on this principle, if IRE were combined with systemic or intratumorally-injected chemotherapy, marginal remnant viable tumor cells within this zone could be eradicated with electrochemotherapy. The therapeutic advantage of combinational irreversible electroporation and electrochemotherapy is the focus of current studies.\(^2^8\)

On another level, we have proven that besides inducing local tumor destruction, the mechanism through which IRE operates also results in a systemic effect. This local immune response could result in the destruction of micrometastases in the affected lymph nodes, which could positively affect survival. More importantly, locally generated antitumor T cell responses could ultimately provide protection against outgrowth of distant metastases and may lead to memory responses, potentially providing long-term immune protection against tumor outgrowth. Our data suggest that IRE offers an attractive and effective *in situ* vaccination platform to combine with immunotherapeutic approaches. In the coming years, this approach will be further investigated.

A similar potential to recruit the immune system has been suggested for RFA.\(^2^9\) Therefore, although it is paramount that the thermal effect of IRE should not exceed the threshold for thermal damage near heat-susceptible structures, the thermal and the electrical element of IRE may have a synergistic effect and may induce the greatest antitumor effect together. The immunologic potential of electrical and thermal ablation is the current focus of several trials. Harnessing the immune system to enhance both local and systemic treatment effect is yet another approach that warrants study and may one day offer the bridge between local and systemic treatment.

\[ \text{"IRE may offer an attractive therapeutic platform for the induction of immunogenic tumor cell death, combined with further immune stimulation"} \]
General discussion and future perspectives

Other indications for IRE that show promise but which are not covered in this thesis are prostate cancer \textsuperscript{30,31} and intracerebral gliomas.\textsuperscript{30} The feasibility of using pulsed electric fields to permeabilize the endothelial cells of the blood-brain barrier was recently demonstrated. This allows for increased drug transport across the blood-brain barrier through the transcellular pathway and may be used in combination with IRE for brain tumors.\textsuperscript{32} The chapter on niche indications exposes an ethical flaw in the generally accepted dogma that we should only treat patients according to guidelines or in the setting of clinical trials. Strictly obeying to this concept would inhibit any advances in knowledge for these rare entities. If there is a scientific foundation for the assumption that a patient might benefit from an experimental treatment, it may be worth taking the risk. After all, the only way to find a new way is to leave the beaten track.

Conclusion

The aims of this thesis were 1) to provide better insight in the working mechanism of IRE with respect to the thermal component simulating different clinical scenarios, and 2) to obtain solid data through prospective trials investigating the safety and efficacy of IRE in the liver and pancreas. To this extent we can conclude that the clinical treatment protocols for IRE generate considerable heat and every physician should take this into account when performing IRE. IRE is capable of creating irreversible cell death and to achieve macroscopic complete tumor eradication without inducing thermal coagulation necrosis of in situ human colorectal liver metastases. For patients with locally advanced pancreatic cancer, percutaneous IRE proved to have an acceptable toxicity profile and promising survival. The reported case-series and case-reports of IRE for pelvic tumor recurrences, perihilar cholangiocarcinomas, and recurring thyroid cancer show promise and endorse the setup of clinical trials to establish safety and effectiveness.

As with any new technique, more questions have been raised than answers have been given. The technique is still in its infancy, and we are just starting to understand the exact working mechanism of IRE and its side effects. Technical improvements of the ablation device and increasing knowledge about tissue-specific electrical properties should result in improved efficacy in the future. Furthermore, the demonstration of detectable and durable T cell responses in point to a protective antitumor immune response induced by IRE. Combining IRE with immune stimulation may represent another therapeutic platform for improved survival and will be the focus of future studies.

With this thesis, the foundation has been laid for the next grand challenge for IRE: to prove its efficacy in large randomized controlled trials. Until then, the technique should be reserved for well-selected patients with relatively small tumors that are truly unsuitable for resection and thermal ablation.

Based on this thesis and on the available literature, we expect IRE to prove a valuable fortification in the armory of interventional oncologists treating patients with cancer in the near future.

"IRE has the potential to become a valuable fortification in the armory of interventional radiology in the fight against cancer"
References


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