Lightning strikes

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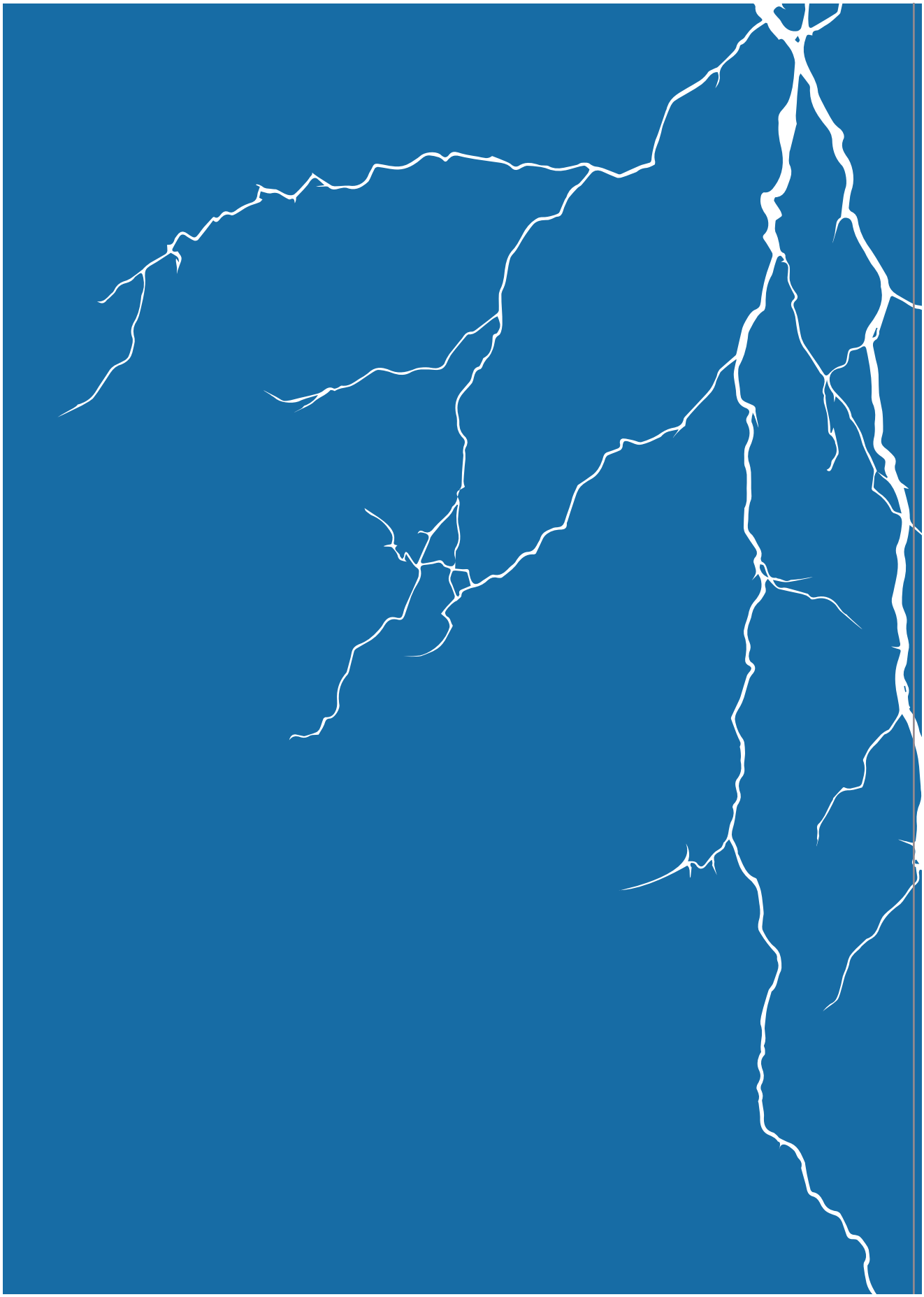

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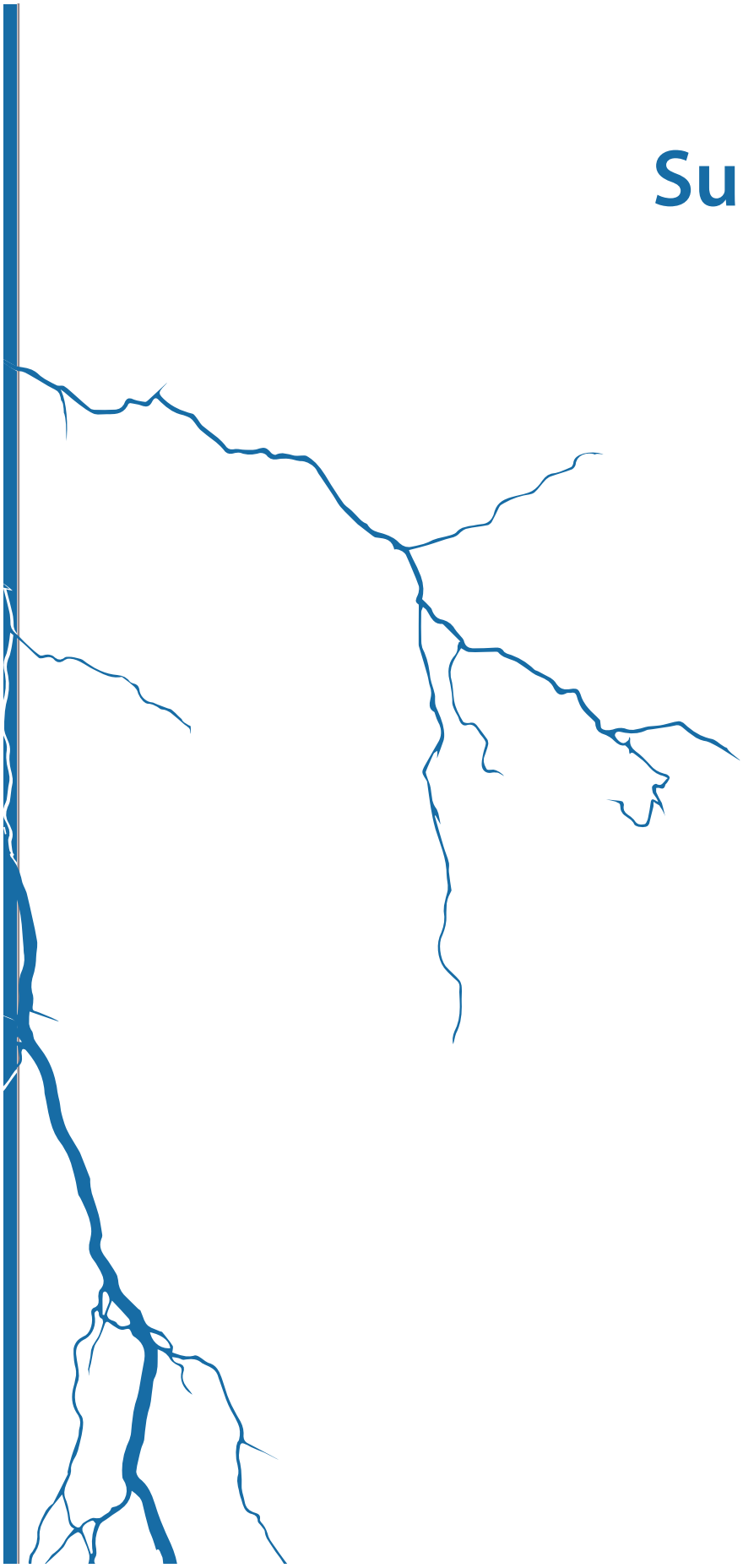
Summary



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There is a rapidly growing acceptance, if not excitement, that image-guided tumor ablation adds a new dimension to the therapeutic oncologic armamentarium. Only 10 years ago, patients with surgically incurable tumors in for example the liver used to rely on palliative chemotherapy, aimed at prolonging life expectancy. Since a certain maturity of thermal ablation techniques has been achieved in the past 10 years, ablation of these tumors using MWA and RFA is now considered common practice, and this has led to improved survival.[1,2] Referrals from oncologists, surgeons, and radiation therapists to interventional oncologists are now customary. However, when surgically incurable tumors are located near certain heat-susceptible structures such as bile ducts, large blood vessels and nervous structures, thermal ablation has a high risk of damaging these vital structures, or of incomplete ablation due to the heat-sink effect, and is therefore contra-indicated. Up until a few years ago, these patients faced no other option than to be treated with palliative chemotherapy.

In the past years a new ablation modality has emerged, based on a different energy form: irreversible electroporation (IRE). Irreversible electroporation uses electrical energy to induce cell death. The application of high-voltage, but low frequency electrical pulses, applied through electrode pairs placed around a tumor, distorts the pre-existing cellular membrane potential, leading to disruption of the lipid bilayer, after which the cell loses its homeostatic properties and dies.[3–6]

Preclinical studies showed that within the ablation zone IRE mostly affects cells, leaving the supporting extracellular matrix structures relatively intact.[7–9] This preservation of gross anatomic architecture allows unresectable tumors near vascular and biliary structures to be ablated safely.[10,11] After demonstrating this advantage of preservation of extracellular matrix structures in the absence of thermal coagulation in animal studies, IRE was introduced in the clinical setting. The first paper on the clinical application of IRE was published in 2011 by Thomson and colleagues who performed IRE on 38 patients with 96 separate unresectable and not thermally ablative tumors in the liver, kidney and lung, with overall satisfactory results.[12] From this moment on, interventional radiologists around the world started using IRE for hepatic, pancreatic, renal and pulmonary tumors. At the same time, as IRE was increasingly used in the clinical setting, treatment protocols were adjusted and more aggressive energy regimens were applied, with higher voltage and higher pulse number protocols. Although the preclinical pulse protocols were able to create cell death with negligible thermal effects, these new high-energy regimens have shown to be able to generate potentially harmful thermal effects.[4,9,13–15] Given the fact that the underlying rationale for the clinical application paradigms of IRE are based in large part on the assumption of the nonthermal mechanism of cell death, characterization and quantification of the thermal effects of IRE is necessary to ensure both safe and effective ablations.

The aims of this thesis were twofold: in the first – preclinical - part of this thesis we tried to get a better understanding of the secondary heat that is produced when performing IRE using clinical ablation protocols and different clinical scenarios, such as variable voltage and interelectrode distance, and the presence of a metal stent. In the second – clinical - part we presented the results of the studies in which IRE was performed in the clinical setting: the COLDFIRE-1 study for colorectal liver metastases, the PANFIRE study for locally advanced pancreatic cancer, and for current niche indications such as locoregional recurrences in the

lesser pelvis and perihilar cholangiocarcinoma.

Chapter 1: where do we stand?

The first chapter (**Chapter 1.2**) provides an overview of the current evidence for IRE in the clinical setting. We conducted a systematic review in which all in-human literature on IRE reporting safety, efficacy, or both was included. To establish the safety, all adverse events were recorded and to assess oncologic efficacy, tumor response on follow-up imaging from 3 months onward was evaluated. The search resulted in sixteen studies, in which 221 patients had 325 tumors treated in the liver (n = 129), pancreas (n = 69), kidney (n = 14), lung (n = 6), lesser pelvis (n = 1) and lymph node (n = 2), from August 2010 to November 2013. No major adverse events occurred during the IRE-procedure. Post-IRE, only minor complications occurred in the liver, but three major complications occurred with pancreatic IRE. With respect to efficacy, 67% - 100% of the hepatic tumors were effectively eradicated at three months, and this percentage was even higher for tumors <3 cm (93% - 100%). Pancreatic IRE also seemed promising: IRE combined with surgery led to prolonged survival compared with control patients (20 versus 13 months), and significant pain reduction. Percutaneous pancreatic IRE also suggested a survival benefit. However, we also established that the current literature on IRE is subject to important limitations, such as the retrospective character of most studies, the lack of a control group, low patient numbers, and a generally short follow-up period. We acknowledged that the level of evidence of the currently available studies is low. Nevertheless, we concluded that despite these limitations, the first clinical results of IRE with respect to safety and early efficacy appear encouraging, especially considering that most patients were heavily pretreated, and IRE was performed as a 'last-resort' treatment.

Chapter 2: preclinical studies

Characterization and quantification of the thermal effects during clinical IRE is necessary to ensure safe but effective ablations. We conducted a study in which we could visualize the development and distribution of thermal energy during IRE using a thermal camera, and investigated the influence on thermal outcome of different ablation parameters: voltage (500-2500 V/cm), pulse length (50-90 µsec), active electrode tip length (5-25 mm), interelectrode distance (5-30 mm), and consecutive versus sequential pulse delivery (**Chapter 2.1**). IRE was delivered through electrodes positioned just underneath the surface of a transparent polyacrylamide gel with characteristics that mimic soft biologic tissue with respect to electrical and thermal conduction. The surface temperature of the tissue-mimicking gel was measured using an infrared camera. A temperature gradient, starting at the tips of both electrodes and expanding toward each other, developed immediately with pulse delivery. Temperatures increased with increasing voltage (ΔT 2.5 – 40.4 °C), pulse length (ΔT 5.3 – 9.8 °C), active tip length (ΔT 5.9 – 17.6 °C), and interelectrode distance (ΔT 7.6 – 21.5 °C), in accordance with higher energy

"IRE produces substantial heat that increases with higher energy deposition. Sequential pulsing reduces the extent and volume of thermal damage and may prove beneficial with respect to procedural safety"

delivery. Continuous pulsing resulted in a temperature increase of almost 12 °C, but when pulses were delivered sequentially, the temperature decreased during each break, resulting in a significant reduction of ΔT.

Patients with central liver tumors or with locally advanced pancreatic carcinoma (LAPC) can develop biliary obstruction, for which a bare metal Wallstent is often placed to resolve obstructive jaundice. In Chapter 2.2 we investigated the effect of a metal stent on the distribution of thermal energy. We performed IRE with and without a metal stent placed between the electrodes using the same setup as in chapter 2.1, and in vivo in a porcine liver. Temperatures were measured using an infrared camera and with fiber-optic probes. We did not observe direct heating of the stent, but the presence of a stent between the electrodes caused a higher increase in median temperature near the electrodes (23.2 vs 13.3 °C; p = 0.021). In vivo tissue examination revealed a rim of vital tissue around the stent, whereas ablation without stent resulted in complete tissue avitality. These findings reinforce the appeal to place plastic biliary endoprostheses rather than metal stents in case of biliary obstruction and, if already in situ, to remove metal stents prior to IRE whenever possible.

"A metal stent results in incomplete ablation in which a small rim of viable tissue remains immediately surrounding the stent"

Chapter 3: anesthetic management

Relying on multiple cycles of short, 3000 Volt electrical pulses to eradicate tumor cells, IRE is a challenging procedure for the anesthesiologist's team. Through stimulation of cardiac, muscle or nervous tissue, potential complications are the induction of cardiac arrhythmias, severe muscle contractions and epileptic seizures, repsectively. To prevent severe muscle contractions, IRE must be performed under general anesthesia with complete muscle paralysis; to prevent cardiac arrhythmias, the electric pulses should be synchronized with the absolute refractory period of the cardiac cycle using R-wave detection. Chapter 3.1 describes our initial experience with IRE from the anesthesiologist's perspective. In this prospective registry twenty-eight patients underwent thirty IRE sessions for tumors in the liver, pancreas, kidney and lesser pelvis. During pulse delivery a significant rise of systolic (~40 mmHg) and diastolic blood pressure (~19 mmHg) occurred. Two self-limiting benign cardiac arrhythmias occurred, which resolved immediately after aborting pulse delivery. Muscle contractions were mild with adequate administration of rocuronium. A simplified EEG revealed that no reactive cerebral activity occurred during pulse delivery, from which we concluded that the absolute contraindication for epilepsy is probably unsubstantiated and should not withhold patients from receiving IRE treatment.

"Epilepsy should not be considered an absolute contraindication to perform IRE"

Chapter 4: the liver

Preclinical studies have shown that IRE only affects cells within the ablation zone, leaving the supporting extracellular matrix structures intact, allowing tumors near vascular and biliary

structures to be ablated safely. However, complete tumor cell death caused by IRE in *in situ* human beings has never been demonstrated, and the mechanism of cell death is still poorly understood. **Chapter 4.1** describes the results of the COLDFIRE-1 ablate-and-resect study (trial registration number NCT01799044), in which ten patients with resectable CRLM were treated with IRE during an open procedure using intra-operative ultrasound, followed by resection at least one hour later. One benign self-limiting cardiac arrhythmia occurred during IRE. Ultrasound immediately after IRE showed a sharply demarcated hypoechoic ablation zone around the tumor. After resection, the specimens were stained with TTC vitality staining for macroscopic assessment of cell death, and with immunohistochemical stainings for microscopic evaluation. Complete tumor avitality was achieved in all but one tumor, which showed residual vital tumor cells. Traversing larger portal, arterial and venous vessels and bile ducts appeared patent and intact. Results of immunohistochemistry were heterogeneous, presumably due to the short ablation-to-resection interval, but confirmed irreversible cell damage and diffuse apoptosis in the tumor-free margin of all specimens.

"IRE induces complete tumor cell death whilst preserving major vessels and bile ducts"

This 'proof of concept' study encouraged us to initiate a larger trial to investigate the safety and efficacy of IRE for unresectable and not thermally ablative CRLM. The COLDFIRE-2 study started in June 2014 (trial registration number NCT02082782). The study protocol is presented in **chapter 4.2**. In this single-arm, multicenter phase II clinical trial twenty-nine patients with 18F-FDG avid CRLM <3.5 cm are prospectively included to undergo IRE of the respective lesion. All complications will be registered. Follow-up consists of 18F-FDG PET-CT and 4-phase liver CT at 3-monthly intervals during the first year. Treatment efficacy is defined as the percentage of tumors successfully eradicated 12 months after the initial IRE procedure based on clinical follow-up using both imaging modalities, tumor marker and (if available) histopathology. To determine the accuracy of 18F-FDG PET-CT and ceCT, two reviewers that are blinded for the final oncologic outcome will individually score both imaging modalities. The results of the COLDFIRE-2 study will hopefully represent an important step forward towards the implementation of IRE for central liver tumors in the clinical setting.

After completion of the COLDFIRE-1 and halfway through the COLDFIRE-2, we assessed the lessons we had learnt so far. The review presented in **chapter 4.3** discusses different technical and practical issues of IRE for CRLM; the indications, patient preparations, procedural steps and different 'tricks of the trade' used to improve procedural safety and efficacy. An example is the optimization of target visibility with the use of transcatheter CT hepatic angiography. Imaging characteristics post-IRE using ceCT, 18F-FDG PET-CT and MRI are discussed and early efficacy results from the literature are presented. Efficacy rates vary between 55 and 93%, but are significantly better for tumors <3 cm. However, current local control rates appear inferior to thermal ablation and surgical resection. Therefore, at this time IRE for CRLM should only be reserved for small tumors truly unsuitable for resection or thermal ablation because of abutment of the portal triad or the venous pedicles.

Chapter 4 concludes with the unique case of a 28-year-old female patient with a 5 cm large, centrally located hepatocellular adenoma who wished to get pregnant (**chapter 4.4**).

Regarding the risk of growth and rupture of the adenoma caused by hormonal changes during pregnancy, treatment of the tumor was advised prior to pregnancy. However, due to its central location, the tumor was considered unsuitable for resection, thermal ablation and also embolization. Percutaneous CT-guided IRE was performed without complications and led to rapid and impressive tumor shrinkage. Subsequent pregnancy and delivery went uncomplicated. We learn from this case that the indication for IRE may extend to the treatment of benign liver tumors that cannot be treated safely otherwise.

Chapter 5: the pancreas

Pancreatic adenocarcinoma is among the most aggressive of all cancers with a 2-year overall survival rate of less than 10%. About 30-40% of the patients present with surgically incurable disease due to tumor involvement of major abdominal vasculature (locally advanced pancreatic cancer [LAPC], AJCC stage III). **Chapter 5.1** reports the results of the PANFIRE-study, which investigated whether percutaneous IRE for LAPC is safe and effective (trial registration number NCT01939665). From January 2014 to June 2015, twenty-five patients with LAPC were included. Thirteen of twenty-five patients had undergone previous chemotherapy (10 folfirinox, 2 gemcitabine, 1 gemcitabine and nab-paclitaxel). There were no deaths within 90 days post-IRE. Twelve minor (grade I/II) and eleven major complications (9 grade III; 2 grade IV: severe pancreatitis and bleeding of duodenal wall ulcer) occurred in 10/25 patients. After a median follow-up period of 12 months (IQR 7-16), median event-free survival from IRE was 8 months (95%CI 4-12); median time to local progression from IRE was 12 months (95%CI 8-16). Median overall survival was 11 months from IRE (95%CI 9-13) and 17 months from diagnosis (95%CI 10-24). The complication rate we encountered was higher than in previous studies, which is partly explained by the prospective nature of our study. Our survival-data are encouraging, especially considering that half of our patients did not receive chemotherapy prior to IRE. The recent advent of folfirinox and the addition of nab-paclitaxel to gemcitabine are now showing improved survival compared to gemcitabine alone. We believe that the best strategy to achieve better survival in LAPC may be the combination of obtaining local tumor control using ablation, whilst gaining control of metastatic spread using the new systemic therapy regimens. To validate our findings we have recently started the multicenter phase-III trial comparing IRE with stereotactic ablative body radiotherapy after neoadjuvant folfirinox (CROSSFIRE-study, clinicaltrials.gov registration number NCT02791503).

"Although preliminary survival data are encouraging, serious adverse events can occur with pancreatic IRE"

Besides investigating the safety and efficacy of IRE in the PANFIRE-study, we assessed the specific imaging characteristics of the tumor and ablation zone before and after IRE with multiphasic ceMRI and ceCT, and investigated whether there was a correlation between differences in attenuation and the development of local recurrence (**chapter 5.2**). The imaging characteristics of the 25 patients treated in the PANFIRE-study were assessed

"DWI-b800 and postcontrast T1-weighted MRI imaging characteristics may be useful to predict successful ablation and early recurrence."

over a 6-month follow-up period. Post-IRE, diffusion-weighted imaging (DWI) b800 signal intensities decreased in all cases ($p<0.05$). Both ceMRI and ceCT revealed absent or decreased contrast enhancement, with a hyperintense rim on ceMRI. An initial increase of the ablation zone volume was noted on both modalities in the first six weeks caused by posttreatment edema, followed by a decrease at three months ($p<0.05$). In the patients developing a local recurrence, a focal DWI-b800 hyperintense spot at six weeks predated the unequivocal recurrence on CT. We concluded that DWI-b800 post-IRE may be useful to establish technical success and to predict treatment outcome. However, whether focal areas of non-altered diffusion restriction truly indicate residual tumor requires longer follow-up and should be the focus of future work.

The paucity of spontaneous antitumor immune responses in pancreatic cancer - in part explaining its aggressive and therapy-resistant behavior - may be partly caused by the local and systemic immune suppression caused by tumor-derived factors. There is growing evidence in the literature that beside the induction of local tumor destruction, IRE may also induce a systemic antitumor response through the priming or boosting of tumor specific immunity. We hypothesized that since pancreatic IRE results in apoptosis and a decrease in tumor mass, this could lead to reduction of tumor-associated immune suppression and the simultaneous release of immunogenic apototic tumor cell remnants. In **chapter 5.3** we investigated this hypothesis by performing an immune monitoring pilot study in the first ten patients enrolled in the PANFIRE-study. Flowcytometric analysis was performed of the frequency and activation state of various lymphocytic and myeloid subsets in the peripheral blood of the patients, at baseline, 2 weeks and 3 months post-IRE. Systemic T cell responses were determined to the pancreatic cancer associated antigens mesothelin and Wilms Tumor (WT)-1 after *in vitro* stimulation in an IFNy Elispot essay. Our data showed a transient decrease in systemic regulatory T cell frequencies and a simultaneous transient increase in activated $CD8^+$ T cells, consistent with the temporary lifting of regulatory T cell imposed immune suppression after the IRE procedure. Importantly, , in line with the observed post-IRE increase in CD8+ T cell proliferation, we found post-IRE boosting of a pre-existing WT-1 specific T cell response in two out of three patients as well as the *de novo* induction of these responses in another two patients. These WT-1 T cell responses were related to longer overall survival ($p=0.055$). Although the pilot study was not powered to draw definitive conclusions, our findings suggest a systemic immune stimulatory effect of IRE.

"IRE of pancreatic cancer elicits a specific immune-stimulatory response, that supports the combination of percutaneous IRE with therapeutic immune stimulation"

All except one procedure in the PANFIRE-study was performed via the ventral approach. However, in one patient this approach was considered dangerous due to the vicinity of the tumor to collateral vessels and the duodenum, so we opted for the dorsal route. The case report presented in **chapter 5.4** illustrates that when ventral electrode placement for IRE is impaired, the dorsal approach can be considered alternatively.

Chapter 6: niche indications

Although IRE has mostly been applied for pancreatic cancer and centrally located liver and renal tumors, virtually any tumor closely related to vulnerable tissue is potentially suitable for IRE. In chapter 6 we describe our clinical experience of IRE for these so-called niche indications.

"Contrary to animal studies, permanent neural function loss can occur when IRE is performed around peripheral nerves in the clinical setting"

One of these indications is locoregional tumor recurrence within the lesser pelvis from urogenital or gastro-intestinal origin. Due to ingrowth or compression on peripheral nerves, these local recurrences can cause aggravating pain and loss of neural function. Animal studies have shown that after CT-guided IRE of peripheral nerves in pigs, the preservation of architecture of the endoneurium and the proliferation of Schwann cells might enable axonal regeneration with full or partial nerve function recovery. With thermal ablation, nerves are certainly permanently damaged. In **chapter 6.1** we investigated the safety and efficacy of percutaneous IRE in a prospective cohort of 7 patients with local tumor recurrence of rectal, anal and cervical cancer. Median tumor size was 4.5 cm (range 4.1 - 5.0). All tumors were closely related to or invading the peripheral nerves such as the sciatic nerve, sacral plexus and pudendal plexus. IRE was performed with palliative intent for cytoreduction and for palliation of pain. In five of seven patients peripheral nerve injury was present 24 hours after IRE (4 lower limb motor loss; 1 hypotonic bladder). At three months follow-up, neural function had partially recovered in two patients, but persisted in the other three. After nine months progressive disease was observed in three patients. We concluded that IRE may be preferred over other techniques to treat tumors near nervous structures, although, as opposed to animal studies, permanent neural function loss can occur.

Chapter 6.2 describes the case of a 74-year-old male who presented with a third consecutive recurrence of follicular thyroid carcinoma in the left subglottic space after extensive surgical resection, adjuvant radioactive iodine therapy and external beam radiotherapy. Because all established focal therapies were contraindicated, percutaneous IRE was performed without complications. Follow-up imaging at 7 months showed no signs of recurrence.

Chapter 6.3 reports the case of a 66-year-old female who presented with a stage IV unresectable hilar cholangiocarcinoma with a metal Wallstent in the common bile duct. Although little is known about the redistribution of the electric field with a metal stent in situ, the patient preferred IRE treatment over best supportive care. IRE was performed successfully with 3 electrodes placed on either side of the stent. No complications occurred. After one year follow-up, ceCT showed no signs of local progression or metastatic disease.

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