Irreversible Electroporation in Interventional Oncology: Where We Stand and Where We Go

Irreversible Elektroporation: Übersicht und Ausblick

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Zusammenfassung

Die irreversible Elektroporation (IRE) ist eine neuartige Gewebeablationstechnik zur bildgesteuerten lokoregionalen Tumortherapie. Im Gegensatz zu thermischen Methoden stellt die IRE ein überwiegend nicht-thermisches Ablationsverfahren dar, dessen Wirksamkeit folglich nicht durch den „heat sink effect" limitiert wird. Ein weiterer Vorteil ist die Anwendbarkeit der IRE in Tumoren, welche unmittelbar an sensiblen Strukturen wie Gefäßnerven-Bahnen und Gallenwegen lokalisiert sind. In bisherigen Studien konnte die Durchführbarkeit der IRE in verschiedenen Tumorentitäten erfolgreich demonstriert werden. Hinsichtlich der klinischen Wirksamkeit konnten insbesondere für die Ablation in Leber-, Pankreas- und Prostatatumoren erste vielversprechende Ergebnisse verzeichnet werden. Komplikationen waren insgesamt selten und traten am häufigsten durch Verletzung von Gallengängen oder Blutgefäßen und dabei eher bei IRE in Pankreas- als in Leber- oder Prostatatumoren auf. Die praktische Ausführbarkeit von IRE in der Niere wurde bisher nur in wenigen Studien gezeigt. Für den Einsatz des Verfahrens bei pulmonalen Raumforderungen konnten aufgrund eingeschränkter Durchführbarkeit bisher keine Vorteile gezeigt werden. Die folgende Übersichtsarbeit stellt eine strukturierte Zusammenfassung zum Stand der klinischen Forschung bereit und diskutiert potentielle Indikationen für IRE in der minimalinvasiven Ablationstherapie solider Tumoren.

Kernaussagen:
- Präklinisch gewonnene Erkenntnisse wurden erfolgreich in die klinische Anwendung der IRE übertragen.
- Durch nicht-thermische Ablation können „heat-sink-effect" und Koagulationsverletzungen unbeteiligter Strukturen umgangen werden.

Abstract

Irreversible electroporation (IRE) is the latest in the series of image-guided locoregional tumor ablation therapies. IRE is performed in a nearly non-thermal fashion that circumvents the „heat sink effect" and allows for IRE application in proximity to critical structures such as bile ducts or neurovascular bundles, where other techniques are unsuitable. IRE appears generally feasible and initial reported results for tumor ablation in the liver, pancreas and prostate are promising. Additionally, IRE demonstrates a favorable safety profile. However, site-specific complications include bile leaking or vein thrombosis and may be more severe after pancreatic IRE compared to liver or prostate ablation. There is limited clinical evidence in support of the use of IRE in the kidney. In contrast, pulmonary IRE has so far failed to demonstrate efficacy due to practicability limitations. Hence, this review will provide a state-of-the-art update on available clinical evidence of IRE regarding feasibility, safety and oncologic efficacy. The future role of IRE in the minimally invasive treatment of solid tumors will be discussed.

Key points:
- Preclinical findings of IRE have been successfully translated into clinical settings.
- Non-thermal ablation is able to prevent the "heat sink effect" and collateral damage.
- IRE should primarily be applied to tumors adjacent to sensitive structures (e. g. bile ducts).
- IRE efficacy appears promising in the liver, pancreas and prostate with tolerable morbidity.
- In contrast, there are no evidential benefits of IRE in the lung parenchyma.

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- Die IRE sollte vorrangig bei Tumoren in unmittelbarer Umgebung sensibler Strukturen (z. B. Gallengängen) Anwendung finden.
- Insbesondere für Leber, Pankreas und Prostata zeigt die IRE eine gute onkologische Wirksamkeit bei geringer Komplikationsrate.
- Währenddessen konnten für die Anwendung bei Lungentumoren keine Vorteile der IRE gegenüber gängigen Verfahren gezeigt werden.

Introduction

Ablative therapies have become well accepted locoregional approaches in the treatment of solid tumors [1]. The latest addition to the family of ablative techniques is irreversible electroporation (IRE), which was first introduced as a novel minimally invasive ablative modality in 2005 [2]. IRE employs short electrical pulses to permanently permeabilize cell membranes resulting in homeostatic dysbalance and eventual cell death. This mechanism was extensively studied in preclinical settings where IRE has been proven to effectively ablate substantial amounts of tumor tissue. However, reported clinical experience remains sparse and mainly non-standardized.

This narrative review will provide a clinical synopsis of IRE ablation in the treatment of solid tumors. With a focus on IRE applications in the liver, pancreas, lung, kidney and prostate, achievements and limitations of non-thermal ablation in the field of image-guided therapies will be exemplified.

Technical principles of IRE

Given the term "electroporation", the mechanistic phenomenon behind IRE is based on an increase of cell membrane permeability through the application of high-voltage electrical currents. Therefore, IRE employs the positioning of adjustable needle electrodes (18G) in or around the targeted tumor under image guidance, preferably using ultrasound (US) or computed tomography (CT). Microsecond electrical fields are utilized to alter the transmembrane potential inducing irreversible instabilities in the cell membranes. As a result, nanoscale pores (80 – 490 nm) are formed and followed by a disruption in cell homeostasis. Eventually, cell death in IRE treatment zones occurs homogenously with a narrow transitional zone [2, 3]. „Irreversible" refers to definite cell ablation that prevents the resealing of membranes after treatment and achieves permanent permeabilization. From a clinical perspective, the implementation of irreversible ablation essentially depends on the proper setting of critical parameters such as the modifiable altitude, duration, shape, number and frequency of applied pulses [3 – 5].

IRE has been proven to effectively ablate tumor cells in vitro [3] as well as in vivo [6 – 9] with an acceptable toxicity profile. In this setting, two major methodic advantages were identified that spur on research in the field of IRE. Firstly, as opposed to the majority of ablative modalities, IRE has the remarkable characteristic of being nearly non-thermal [2, 6, 10]. Subsequently, the effect of blood flow on IRE is negligible and there will be no reduction of ablative efficacy contiguous to blood vessels through the "heat sink effect" [2, 10, 11]. This marks a momentous contrast to thermal regimes, which are substantially influenced by perfusion [12] and also limited in their application near heat-sensitive structures such as bile ducts, nerves or intestinal loops [13].

Secondly, it is of major importance for all locoregional therapies to achieve precise and well-controlled ablation of the tumor and a peritumoral safety margin while sparing healthy surrounding structures. Hence, IRE is a beneficial modality as targeted cell ablation occurs selectively with preservation of connective tissue, adjacent nerves and blood vessels within the sharply delineated ablation zone [14, 15]. Subsequently, treatment-related complications are minimized and intact vasculature accelerates resolution of the lesions [4, 16, 17].

Clinical Considerations

IRE is performed percutaneously or via open surgical or laparoscopic access. Usually, tumors assigned for IRE are declared unresectable and not suitable for thermal ablation due to the proximity to sensitive structures (e. g. nerves or bile ducts) [7]. Preprocedural imaging data are transferred to a pulse generator that calculates the position and number of probes based on a computer algorithm [18]. In the majority of trials, IRE was performed using NanoKnife (Angiodynamics) and configurations were set according to standard algorithms provided by the manufacturer. Usually, a series of 90 high-speed currents is administered with a duration of 20 – 100 microseconds and up to 3000 V [18, 19]. Consequently, a typical session takes less than 1 minute to treat a tumor 3 cm in diameter and approximately 3 to 5 min when additional ablations are performed [17].

Despite the short ablation time, general anesthesia is mandatory as complete neuromuscular blockade is required to avoid muscle contractions triggered by the applied currents [16]. Hence, apart from site-specific complications, IRE procedures include all risks related to anesthesia [16, 19]. In order to prevent current-related ventricular arrhythmia as a potentially severe complication, ablation pulses should be applied in an electrocardiogram (ECG)-gated fashion, except for prostate ablation [16, 19]. A recent prospective analysis of treatment-related adverse events included 28 patients who were treated with open (n = 13) or percutaneous (n = 15) IRE for different abdominal tumors. Despite ECG synchronization, cardiac arrhythmia occurred in two patients during laparotomy (n = 1, ventricular extrasystole) and percutaneous pancreatic IRE (n = 1, bigeminy) but appeared to be mild without hemodynamic relevance and was self-limiting within one day [20].

In terms of follow-up, standardized criteria have not yet been defined to predict successful ablation. However, in a number of clinical trials, tumor response to IRE was determined based on the Response Evaluation Criteria in Solid Tumors (RECIST) with well-demarcated hypoattenuating ablation zones indicating successful interventions [21, 23] and new or persistent enhancement indicating incomplete ablation or local recurrence (LR) [18, 19, 21].

Clinical Results

In order to provide a status quo overview of the clinical experience reported for IRE, the bibliographic database of Pubmed was screened for prospective and retrospective original articles using the search terms "IRREVERSIBLE ELECTROPORATION", "NON-THERMAL ABLATION" and "ABLATION" in combination with synonyms for each tumor entity described below.

Liver

Thomson et al. were the first to investigate the safety and efficacy of IRE in 38 patients, 25 of whom presented with primary or secondary liver tumors (range: 1 – 5 cm). After 63 IRE ablations, the complete response (CR) rate for hepatocellular carcinoma (HCC) was 83.3 % whereas CR in colorectal liver metastases (CRM) was observed in 50 % according to RECIST on 1- and 3-month follow-up imaging. Lesions ≥ 5 cm did not show significant tumor response [21]. Similarly, another prospective trial included 11 patients for percutaneous IRE in 18 HCC lesions with a diameter of 1.0 – 6.1 cm. Lesions ≤ 3 cm required 4 ablations with repositioned needles, while bigger lesions were treated with 16 ablations per session on average. Moreover, 6 patients had received repeated treatment due to LR and intrahepatic metastases. Except for transient postprocedural pain (64 %), no complications were observed in this study. At 6 mo, response evaluation revealed CR in a total of 72 % and 93 % of tumors ≤ 3 cm and the local progression-free survival (PFS) was 18 ± 4 mo and the distance PFS was 14 ± 6 mo [24]. The previous findings are also in line with the preliminary results of a prospective multicenter phase II trial conducted by Lencioni et al. using IRE for the treatment of early stage HCC. According to RECIST, 23 out of a total of 29 tumors showed CR (79 %). Within 1 mo of follow-up, complications were rare including one case of transient hepatic decompensation and one hematothorax [25].

Table 1 Key prospective investigations of IRE for liver malignancies.

Tab. 1 Prospektive Studien zur Anwendung von IRE bei malignen Lebertumoren.

author (year)	patients	target lesions	IRE	treatment-related adverse events	follow-up	results	ref.
Thomson et al. (2011)	n = 38	n = 25 liver malignancies including CRM (n = 6) and HCC (n = 11) diameter: 1 – 5 cm	percutaneous image-guided IRE	transient ventricular arrhythmia in 4 patients (11 %) (electrocardiographically synchronized delivery was used in the remaining 30 patients); cardiac arrhythmia, pneumothorax, brachial plexus injury, pain	1 and 3 mo	50 % CR rate for CRM (RECIST); 83.3 % CR rate for HCC; no significant tumor response in lesions ≥ 5 cm	21
Cheung et al. (2013)	n = 11	HCC (n = 18), 7/18 lesions were located adjacent to sensitive structures diameter: 1.0 – 6.1 cm	percutaneous image-guided IRE	no major complications; transient urinary retention in n = 4 (36 %), transient pain in n = 7 (64 %)	14 – 24 mo	complete ablation of 13 lesions (72 %); 93 % CR rate for tumors ≤ 3 cm; 18 ± 4 mo local PFS, 14 ± 6 distance PFS; n = 6 (55 %) with LR and intrahepatic mets required repeated treatment	24
Lencioni et al. (2012)	n = 26	29 early-stage HCC lesions ≤ 3 cm	percutaneous image-guided IRE	no 30-day mortality; transient hepatic decompensation (n = 1, 4 %) with spontaneous resolution and hemothorax related to electrode placement (n = 1, 4 %)	1 mo	CR in 23 (79 %), PR in 4 (13 %), SD in 1 (3 %) and PD in 1 (3 %) lesions (mRECIST)	25
Cannon et al. (2013)	n = 44	centrally located primary or secondary liver tumors: HCC (n = 14), CRM (n = 20), others (n = 10) diameter 2.1 – 2.7 cm	surgical and percutaneous image-guided IRE	adverse events in n = 5 (11 %) resolved within 30 days of treatment	3, 6 and 12 mo	technical success in 95 % of CRM and 100 % of HCC and others; local control at 3, 6, and 12 months was 97.4 %, 94.6 %, and 59.5 %; trend towards higher recurrence rates in tumor ≥ 4 cm lower recurrence rates after surgical probe placement	18
Eisele et al. (2014)	n = 14	HCC (n = 5), CRM (n = 6), ICC (n = 2) diameter: 1.5 ± 0.5 cm	surgical and percutaneous image-guided IRE	no major complications	3 – 12 mo	12 ablations (92 %) were technically successful; 3 ablations (21 %) turned out to be incomplete within 6 mo (all of them after percutaneous); LR in tumors > 2 cm and bifocal tumor sites	26

In two prospective studies, IRE was performed either via percutaneous or surgical access. In the first trial, 44 patients with centrally located HCCs (n = 14), CRMs (n = 20) and other secondary liver malignancies (n = 10) (range: 2.1 – 2.7 cm) were included. Technical success was achieved in 100 % of HCCs and 95 % of CRM lesions. CR was reported in 100 % of cases according to RECIST with a local PFS of 97.4 %, 94.6 % and 59.5 % at a 3-, 6- and 12-month follow-up, respectively. The authors observed a trend towards higher recurrence rates in tumors > 4 cm as well as for percutaneous probe placement [18]. The second series included 13 patients with HCC (n = 5), CRM (n = 6) and recurrent intrahepatic cholangiocarcinoma (n = 2) and an average tumor size of 1.5 ± 0.5 cm. Surgical access for IRE was combined with hepatic resection (n = 6). Except for one procedure, IRE was technically successful without treatment-related complications. Three ablations (23 %) turned out to be incomplete within 6 mo, all of which were after percutaneous approaches. Moreover, LR was observed in two other patients with tumors > 2 cm and in one site of a patient with bifocal ablation. Hence, the authors claim that percutaneous access, diameters exceeding 2 cm and CRM as an indication are associated with a higher risk of local failure [26] (**Table 1**).

A number of retrospective studies focused on the effect of IRE on central hepatic structures [27, 28]. In this setting, Kingham et al. analyzed imaging-based tumor response and adverse events in 28 patients after IRE. The lesions appeared to have a small median size of 1 cm (range: 0.5 – 5 cm) and were located < 1 cm from a major hepatic vein or portal pedicle. However, the overall morbidity was low with 3 % including a single event of arrhythmia and portal vein thrombosis (PVT). As for efficacy, one patient presented with stable disease (SD) (1.9 %) at 6 mo and LR was observed in three patients (5.7 %) [29].

Overall, research on IRE in hepatic malignancies has been successfully initiated and multifaceted clinical evidence is primarily available for HCC and CRM (**Fig. 1**). With regards to this, IRE demonstrated favorable toxicity even when performed in proximity to sensitive structures and current literature suggests technical practicability and beneficial clinical outcomes, particularly for surgical access. However, lesion size remains a limiting factor for the efficacy of IRE in this setting that could possibly be countered by optimizing the number and configuration of needles.

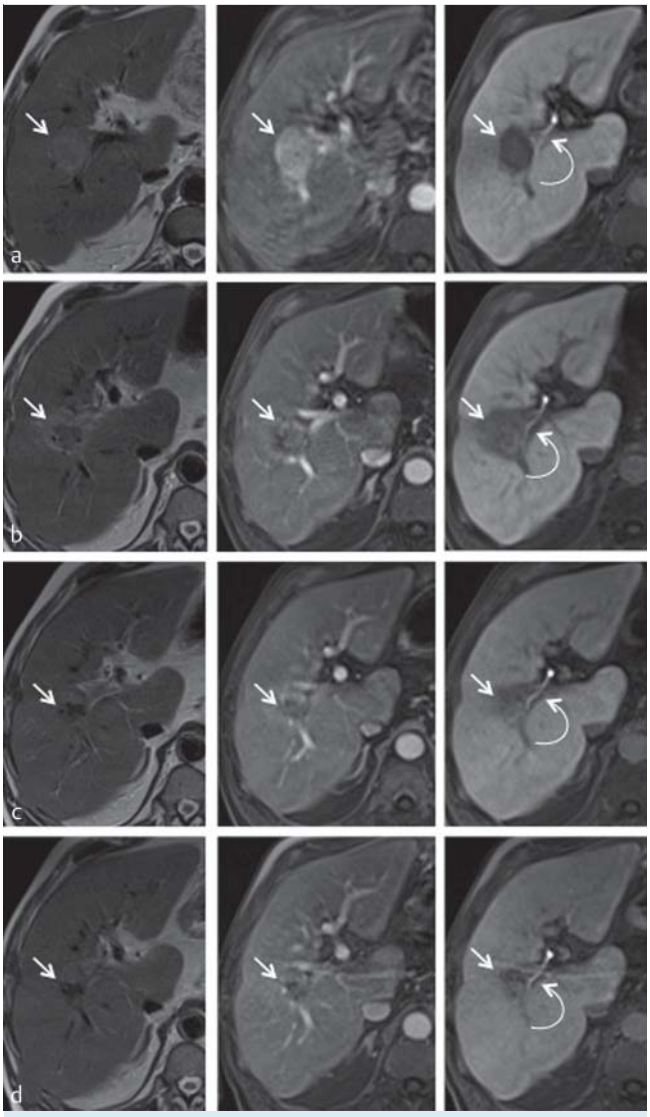

Fig. 1 Patient with unresectable hepatocellular carcinoma (HCC). Preprocedural pre- and post-contrast MRI scans **a** show a large HCC located close to the liver hilum. IRE was performed using five electrodes and follow-up MRI examinations at one **b**, three **c** and six **d** months demonstrate progressive shrinkage of the ablation zone (arrow) with good local tumor control. Furthermore, follow-up Gd-EOB-DTPA–enhanced MRI scans show the intact bile duct (bent arrow) located in the immediate vicinity of the ablation zone.

Abb. 1 Patient mit einem unresektablen großen hilusnahen hepatozellulären Karzinom (HCC). Dargestellt sind native MRT-Bilder sowie nach Kontrastmittelgabe vor **a** sowie einen Monat **b**, drei **c** und sechs **d** Monate nach Behandlung des HCC mittels IRE mit fünf Elektroden. Die Nachuntersuchungen zeigen eine kontinuierliche Größenabnahme des Tumors (Pfeil). Gd-EOB-DTPA-MRT-Bilder zeigen zusätzlich die intakten Gallenwege (gebogener Pfeil) in unmittelbarer Nähe zur Ablationszone.

Pancreas

Bagla et al. reported on the first case of IRE ablation in a single patient who was successfully treated for unresectable locally advanced pancreatic carcinoma (LAPC) [30]. Soon afterwards, the first prospective series was conducted to examine the safety and feasibility of IRE in 27 patients with LAPC and celiac plexus invasion who had all received previous therapies. Tumors with an average diameter of 3 cm were located in the pancreatic head (n = 15) and body (n = 12). Except for one case, IRE was performed via open approach. At the 90-day follow-up, imaging revealed 100 % technical success and as a result, 6 patients were eligible for resection subsequent to ablation. Postprocedural complications included moderate pain and PVT as well as bile leakage and wound infection in 9 patients (33 %). One patient was lost within follow-up period. However, the authors claimed IRE to be a challenging but feasible treatment option in LAPC with acceptable morbidity [31].

In a different setting, the authors performed open IRE with concurrent resection and combined chemoradiation of LAPC in 54 patients. Compared with a matched patient group receiving chemoradiation only, the results demonstrated significantly improved PFS (14 vs. 6 mo) and overall survival (OS) (20 vs. 13 mo) [32]. Similarly, in a recent large multicenter prospective trial, 200 patients were included to investigate the efficacy of multimodal treatment approaches including IRE for the therapy of stage III LAPC. All patients received induction chemotherapy or chemoradiation followed by IRE alone (n = 150) or with consecutive pancreatic resection (n = 50). The median OS was 24.9 mo (range: 4.9 – 85 mo) and 6 patients (3 %) developed LR within a median follow-up of 29 mo. Compared to historical reports, the authors

suggest a benefit for combined treatment regimens including IRE as compared to chemotherapy alone [33].

Another large prospective multicenter investigation including 107 patients with locally advanced hepatic (n = 42) as well as pancreatic (n = 37) tumors with a small size of < 0.5 cm was published by the same group. Probes were placed percutaneously (n = 33) or surgically (n = 84) for a median number of two lesions. In terms of efficacy, a local PFS of 12.7 mo in total was reported. High grade adverse events occurred in 4.19 % of cases including biliary complications and bleeding [34].

The efficacy of IRE was recently investigated in an intraoperative setting with the use of a prospective database. 48 patients with LAPC < 3.5 cm and a history of previous treatments were scheduled for pancreatic resection. Of a total of 44 adverse events after ablation, 5 were possibly IRE device-related and included bile leakage and PVT. No LR was observed at the 90-day follow-up. However, at 24 mo, 28 patients (58 %) showed LR and metastatic disease. The median PFS and OS were reported as 11 and 22.4 mo, respectively [35]. A smaller prospective single-center study was conducted in 10 patients with LAPC (range: 2.5 – 3.9 cm) of the pancreatic head (n = 7) and body (n = 3) refractory to previous treatments. Regarding efficacy, tumor response according to RECIST demonstrated PR in 4 (40 %), PD in 3 (30 %) and SD in another 3 (30 %) patients at a median follow-up of 7.6 mo. Within 30 days, 1 patient demonstrated lung metastases and 2 patients developed liver metastases within 60 days. Complications occurred in 8 patients (80 %) with 1 intraoperative hypertensive episode. On day 23 after IRE, CT imaging of 1 patient (10 %) revealed a pancreatic abscess and pancreoduodenal fistula [36] (**Table 2**).

In contrast to previous trials, recently published prospective data on 50 pretreated patients with pancreatic cancer (3 neuroendocrine tumors, 47 LAPC) revealed comparatively devastating perioperative morbidity and mortality for IRE as the primary treatment (n = 29) or margin extension procedure after surgical resection (n = 27). Contrary to a median OS of 12.03 mo in the operative group, IRE for primary treatment revealed an OS of 7.71 mo. 6 patients (11 %) died within 90 days of follow-up and the overall recurrence rate was 58 % with distant metastases occurring at a median of 9.2 mo and local recurrence at 8.6 mo [37].

Narayanan et al. retrospectively reported on the safety and efficacy of percutaneous IRE in 14 patients with LAPC (range: 2.5 – 7 cm), 3 of them with metastatic disease. All patients had received previous treatments. As for clinical outcome, 1 patient was treated twice after initial remission and LR at 7 mo. 2 other patients had local progressive disease (PD) after 1 and 2 mo, respectively, and 2 developed new metastases and 1 had metastatic progression. 6 patients demonstrated SD and 2 subsequently underwent margin-negative resections and remained disease-free after 11 and 14 mo, respectively. 1 patient developed pneumothorax and another developed transient pancreatitis. The 3 patients with metastatic disease died as a result of PD [38].

The most recent review from 2014 was designed to outline morbidity and survival after IRE in 74 patients with pancreatic cancer. 70 patients had LAPC (range: 1 – 7 cm), and the remainder presented with metastatic disease. IRE was performed percutaneously (27 %) under US (30 %) or CT guidance (70 %) or surgically (70.3 % laparotomy, 2.7 % laparoscopy). Regarding procedure-related complications such as bleeding, morbidity was fairly low for IRE ablation alone but differed considerably from 0 % to 33 % due to varying access modalities. Depending on the study design, a 6-month survival of 40 % and 70 % and a PFS and OS of 14 and 20 mo, respectively, were reported. Compared to non-IRE groups

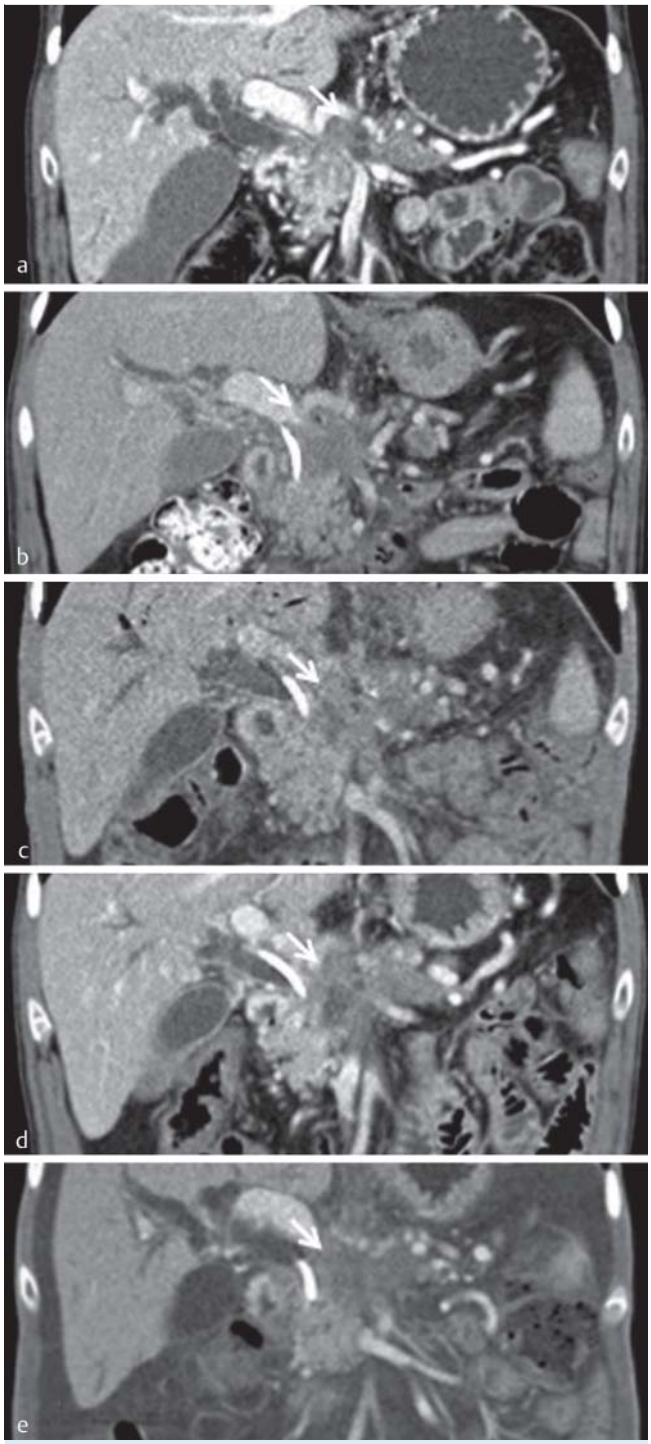

Fig. 2 Patient with locally advanced pancreatic adenocarcinoma (LAPC) (arrow) rated as unresectable by visceral surgeons. The preprocedural CT scan **a** shows the LAPC in the head and body of the pancreas and consecutive intrahepatic cholestasis. Follow-up CT examinations one day **b** as well as one **c**, three **d** and five months **e** after IRE ablation using four electrodes show progressive shrinkage of the tumor with good local tumor control. The integrity of the nearby vessels is also confirmed by contrast-enhanced CT images.

Abb. 2 Patient mit einem als unresektabel eingestuften lokal fortgeschrittenen Pankreasadenokarzinom (LFPC) (Pfeil). Die CT-Voraufnahme **a** zeigt die Lokalisation des LFPC in Pankreaskopf und -korpus und eine intrahepatische Cholestase. CT-Bilder, die einen Tag **b** sowie einen Monat **c**, drei **d** und fünf Monate **e** nach IRE mit vier Elektroden angefertigt wurden, demonstrieren eine kontinuierliche Größenabnahme des Tumors nach der Ablation bei gleichzeitig erhaltener Integrität der umliegenden Gefäße.

Table 2 Key prospective investigations of IRE for pancreatic cancer.

Tab. 2 Prospektive Studien zur Anwendung von IRE bei Pankreaskarzinom.

Author (year)	patients	target lesions	IRE	treatment-related adverse events	follow-up	results	ref.
Martin et al. (2012)	n = 27	LAPC of pancreatic head (n = 15) and body (n = 12) diameter: 1 – 5.5 cm	surgical (n = 26) and percutaneous (n = 1) IRE	9 patients (33 %) presented with 18 complications including pain, PVT, bile leaks, wound infection; n = 4 device-related adverse events; 90-day mortality: n = 1 (4 %)	3-mo intervals	no evidence of residual tumors at 3 mo; 6 patients (22 %) were eligible for resection after IRE	31
Martin et al. (2013)	n = 139	LAPC of pancreatic head (n = 35) and body (n = 19) diameter: 1 – 5.5 cm (for combined treatment)	IRE (n = 54) combined with chemotherapy or radiation (47/54) vs. chemothera-py/radiation only (n = 85)	32/54 patients (59 %) presented with 67 different complications within 90 days; e. g. bild leaks (n = 2), duodenal leaks (n = 2)	3-mo intervals	improved local PFS (14 vs. 6 mo; p = 0.01) and OS (20 vs. 13 mo, p = 0.03) compared to chemotherapy/-radiation only; 15/54 patients (28 %) had LR after a median follow-up of 15 months	32
Martin et al. (2015)	n = 200	radiographic stage III LAPC (all patients received induction chemotherapy or chemoradiation)	IRE alone (n = 150) or combined with pancreatic resection (n = 50)	37 % of patients reported complications	median: 29 mo	n = 6 (3 %) had LR; median OS was 24.9 mo (4.9 – 85 mo) prolonged survival compared to chemotherapy/-radiation only (historical reports)	33
Martin et al. (2014)	n = 107	advanced hepatic malignancies (n = 42) and LAPC (n = 37) diameter: < 0.5 cm	surgical (n = 84) and percutaneous (n = 33) IRE	43 patients (40 %) with 84 complications; high-grade adverse events in 21 patients (19 %) with n = 19 attributable to IRE; increased complication rate after surgical IRE; 90-day mortality: n = 2 (2 %)	3-mo intervals (median: 29 mo)	n = 12 (4.7 %) incomplete ablations; inverse association of LR-free survival and lesion size (p = 0.02); n = 7 (5.9 %) with persistent disease at 3-mo follow-up received re-ablation; local PFS was 12.7 mo; median time to LR was 12 mo (liver) and 16 mo (LAPC)	34
Kwon et al. (2014)	n = 48	LAPC diameter: < 3.5 cm	intraoperative IRE	n = 5 treatment-related complications including bile leakage and PVT	24 mo	no recurrence within 90 days; LR and metastases in n = 52 (58 %) after 24 mo; median PFS was 11 mo and OS was 22.4 mo	35
Paiella et al. (2015)	n = 10	LAPC of pancreatic head (n = 7) and body (n = 3) refractory to previous treatments diameter: 2.5 – 3.9 cm	surgical IRE	pancreatic abscess with pancreoduodenal fistula in 1 patient (10 %) on post-treatment day 23; n = 1 (10 %) hypertensive episode intraoperative; 13 complications in 8 patients (80 %)	median 7.6 mo (weekly for 90 days, then quarterly)	lung metastases within 30 days (n = 1, 10 %), liver metastases within 60 days (n = 2, 20 %); OS was 7.5 mo (range, 2.5 – 15.9 mo); n = 9 died from disease, n = 1 died of septic shock 2 weeks after IRE; PR in n = 4 (40 %), PD in n = 3 (30 %) and SD in n = 3 (30 %) (RECIST)	36
Kluger et al. (2015)	n = 50	LAPC (n = 47) and neuroendocrine pancreatic tumors (n = 3) diameter: ≤ 3 cm	IRE for primary treatment and for margin extension combined with surgery	n = 13 (26 %) grade 1 and 2 complications within 30 days; e. g. bleeding, gastric ulcer perforation, bile duct strictures and necrosis; no correlation between complications (grade 3 – 5) and adjustable parameters of IRE	median 8.69 mo	OS was 12.03 mo after surgery and 7.71 mo after primary IRE treatment; overall recurrence rate was 58 %: 47 % distant (median 9.2 mo) and 11 % local recurrence (median 8.6 mo)	37

(PFS of 6 and OS of 11 mo), a prognostic benefit for IRE became apparent [39].

To sum up, IRE has repeatedly proven to prevent recurrence and hold back local progression with a prognostic benefit in patients with LAPC (**Fig. 2**). It is particularly encouraging that some studies report cases of patients who could be transferred to resection after IRE. Major complications included PVT and bile leaks but the overall morbidity was tolerable.

Lung

Besides the liver and kidney, IRE was also performed in the lung in 3 patients (CRM, breast cancer metastasis, non-small cell lung cancer (NSCLC)) in a prospective setting. This early case series by Thomson et al. examined the efficacy and safety of the procedure as described earlier in this review. However, as opposed to liver tumors, all patients presented with PD at a 1- and 3-month follow-up according to RECIST. As revealed by biopsy, treatment failure occurred as a result of incomplete ablation. 2 patients developed pneumothoraces related to central lung ablation that resolved spontaneously. 1 patient was lost within the follow-up period [21].

Another case series reported on the IRE treatment of 2 patients with lung malignancies. The first patient presented with a hilar sarcoma metastasis (2.3x2.4x1.7 cm) and the second patient had suprahilar non-small cell lung cancer (NSCLC; 2.1x1.9x2.1 cm) and comorbid radiogenic pulmonary fibrosis. At a 6- and 2-month follow-up, CT and PET/CT imaging revealed LR and even PD similar to the previously described study. Subsequently, the authors postulated the failure of IRE in lung parenchyma due to limited feasibility [40].

The first controlled prospective study was a recent multicenter phase II trial (ALICE) to investigate the safety and efficacy of IRE in primary and secondary lung malignancies, mainly CRM (n = 13). Initially, 36 patients with previous treatments but normal lung function were included but the study was terminated early after the treatment of 23 patients. Treated target lesions measured a median diameter of 1.6 cm (range: 0.8 – 2.7 cm). As for major complications, 11 patients developed pneumothoraces, 8 of which required chest tubes. Regarding efficacy, 7 patients showed CR (39 %), 1 had partial remission (4 %), 1 had SD (4 %) and 14 developed PD (61 %) at a 3-month follow-up using CT and PET/CT. As precise parallel probe alignment was limited by the thoracic cavity, effective ablation could not be guaranteed and IRE eventually failed to demonstrate efficacy in this setting. Moreover, needle tract seeding was observed in 3 cases (13 %) [41].

Mainly due to fundamental feasibility limitations, IRE has so far failed to prove efficacy in lung parenchyma. Common complications included pneumothoraces in numerous patients.

Kidney

Pech et al. reported the first-in-man phase I clinical trial to examine the feasibility and safety of intraoperative IRE in 6 patients with local renal cell carcinoma (RCC) who were scheduled for curative tumor resection. IRE was performed approximately 15 minutes prior to surgery. Except for one minor arrhythmia, no adverse effects were recorded within the short-term follow-up period of 12 weeks. However, immediate biopsy could not demonstrate cell death in the specimens [42].

A recent pilot study ("IRENE trial") to investigate the histopathological effects of IRE included 3 patients with localized RCC (T1a; range: 1.5 – 1.7 cm) in a central (n = 1) or peripheral (n = 2) location. Focal IRE was performed in a percutaneous fashion 4 weeks prior to renal resection. Contrary to an expected homogenous ablation zone, ex vivo analyses revealed structuring of the treated area with central necrosis surrounded by tissue that was secondarily damaged by nutritive deprivation. Additionally, 2 resected tissues demonstrated residual tumor satellites within the ablation zone [43].

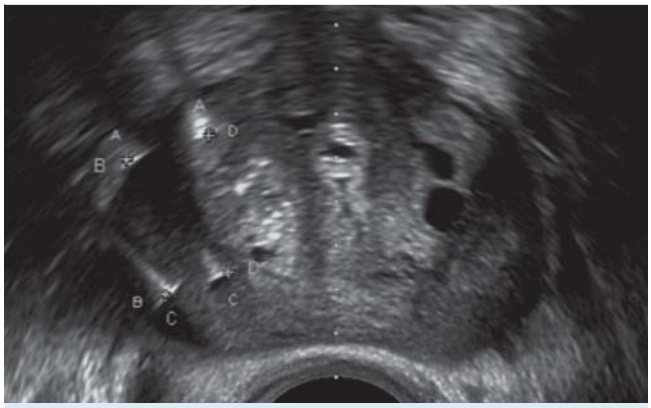

Fig. 3 Unenhanced transrectal ultrasound (TRUS) imaging during IRE ablation of a small prostate cancer lesion (Gleason score: 3 + 3 = 6) of the right lobe shows four electrode tips that are placed in parallel alignment and encompass the tumor.

Abb. 3 Dargestellt sind transrektale Ultraschallbilder eines kleinen Prostatakarzinoms (Gleason Score: 3 + 3 = 6) im rechten Prostatalappen während einer IRE-Ablation mit vier parallelen Elektroden.

Thomson et al. performed IRE of 11 renal tumors (RCC, n = 11; other tumors, n = 4) with a median tumor size of 2.7 (range: 1.6 – 5.3 cm). The primary efficacy was 45 % and CR was achieved in RCC lesions. The authors reported on 1 case of accidental adrenal ablation followed by severe hypotension for 2 mo and hematuria in 2 patients after central IRE [21].

However, IRE for the treatment of RCC proved feasible and safe in the presented trial but prospective efficacy studies on IRE are warranted.

Prostate

Onik et al. reported the first case series including 16 patients with unifocal prostate cancer of varying Gleason scores. Based on preprocedural biopsies, the cancer loci were targeted under transrectal US (TRUS) guidance (**Fig. 3**). IRE was well tolerated in all patients. Immediate postprocedural Doppler US revealed the preservation of the neurovascular bundle and continence and potency remained unaffected in all patients. At a 3-week follow-up, biopsies of the ablation zone showed necrotic and fibrotic tissue with no evidence of cancer in 15 patients and one micro-focus of Gleason 6 cancer outside the treated area [44].

Brausi et al. presented the results of a prospective IRE pilot study in 11 patients with low-risk prostate cancer. They reported no major intraprocedural complications. However, during the follow-up, 1 patient had acute urinary retention and 3 presented with transient incontinence. After 1 mo, histopathological reports were negative in 8 patients (73 %) showing coagulative necrosis and fibrosis. 3 patients had residual disease and 2 of them underwent second IRE ablation [45].

With special regard to the technical success of ablation procedures, a multicenter prospective trial reporting on 16 men who were treated with IRE for localized prostate cancer 4 weeks prior

Table 3 Key investigations of IRE for prostate cancer.

Tab. 3 Studien zur Anwendung von IRE bei Prostatakarzinom.

author (year)	patients	target lesions	IRE	treatment-related adverse events	follow-up	results	ref.
Onik et al. (2010)	n = 16	unifocal prostate cancer; varying Gleason scores	TRUS-guided IRE	no complications	3 weeks	biopsies (n = 15) revealed uniform destruction of glandular cellular elements and reactive fibrosis within ablation zone; microfocus of Gleason 6 lesion outside ablation area (n = 1, 6 %); preservation or recurrence of continence and potency (100 %) (Doppler-US)	44
Brausi et al. (2011)	n = 11	low-risk prostate cancer; varying Gleason scores		transient incontinence (n = 3, 27 %), acute urinary retention (n = 1, 9 %)	1 mo	histopathological analysis revealed coagulative necrosis and fibrosis in n = 8 (73 %) and residual disease in n = 3 (27 %) with 2 patients being repeatedly treated	45
Van den Bos et al. (2015)	n = 16	localized prostate cancer (scheduled for radical prostatectomy)	TRUS-guided focal (n = 6) or extended (n = 10; ≥ 4 electrodes) IRE	no serious adverse events	4 weeks (prior to surgery)	100 % complete ablation with histopathologically confirmed necrosis and fibrosis within sharply demarcated ablation zone, no skip lesions; correlation of needle configuration with ablation zone	47
Ting et al. (2015)	n = 25	low-intermediate risk prostate cancer		no alterations of urinary, sexual or bowel function according to clinical examinations and questionnaires	8 mo	no suspicious findings within ablation zone on mp-MRI (n = 24) or biopsy (n = 21) in all patients; n = 5 (21 %) had suspicious findings adjacent to treatment zone on mp-MRI with n = 4 (19 %) confirmed by biopsy; n = 2 (8 %) with suspicious findings outside of ablation zone on mp-MRI and n = 1 (5 %) approved by biopsy	49
Valerio et al. (2014)	n = 34 *(retrospective analysis)*	localized prostate cancer low (26 %), intermediate (71 %), high (3 %) risk	TRUS-guided	n = 12 (35 %) grade 1, n = 10 (29 %) grade 2 adverse events	1 – 24 mo, median 6 mo	preservation of continence (100 %) and potency (95 %); ablation volume: 5.6 – 14.5 ml; suspicious residual disease in n = 6 (18 %) after 6 mo with 3 patients being repeatedly treated	51

to radical prostatectomy was recently published. Within the short follow-up period, no serious adverse events occurred. The histopathological examination of the harvested tissue revealed complete necrosis and fibrosis of the ablation zone which corresponded well with the configuration of needle placement for focal (n = 6) or extended (n = 10; ≥ 4 electrodes) IRE [46, 47]. Additionally, CEUS and T2-weighted MRI were found to be adequate imaging modalities to visualize the effects of IRE as they correlated well with the results of the histopathological analysis [48].

Another single-center prospective trial included 25 patients with low-intermediate-risk prostate cancer, who were followed up for 8 mo with various clinical examinations as well as mpMRI and biopsies. Analysis of the ablation zone did not reveal suspicious findings for residual disease, whereas 4 patients (19 %) demonstrated pathologically confirmed residual tumor adjacent to the treatment zone and 1 patient (5 %) had suspicious findings outside the ablation area [49].

A recent two-center retrospective analysis investigated the local safety of transperineal IRE and included 34 patients with localized prostate cancer. The maximum cancer length was 0.6 ± 0.3 cm. Electrodes were placed under TRUS guidance around the lesion. In terms of safety, a median standardized [50] clinical follow-up of 6 mo revealed 12 (35 %) grade 1, 10 (29 %) grade 2 and no severe grade 3 complications. From a functional point of view, continence was preserved in 100 % (24/24) and potency in 95 % (19/20) of patients. Multiparametric (mp) MRI after 6 mo demonstrated suspicious residual disease in 6 patients, 3 of whom underwent another form of local treatment [51] (**Table 3**).

In conclusion, clinical experience with the use of IRE in prostate cancer is relatively limited but further results of prospective analyses in larger cohorts are forthcoming [52]. So far, safety reports on transperineal IRE state favorable safety, and clinical follow-ups demonstrate preserved continence and potency. However, prospective oncologic efficacy studies are sorely needed to finally

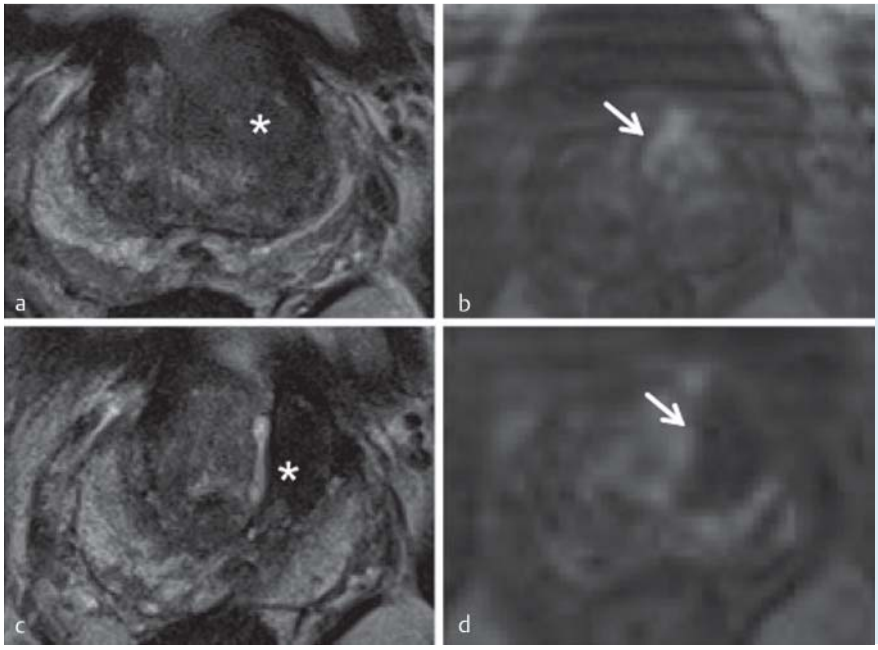

Fig. 4 Patient with prostatic cancer (*) (Gleason score: 3 + 3 = 6) in the transitional zone treated with ultrasound-guided IRE. The preprocedural precontrast **a** and postcontrast **b** MRI scans show the tumor in the ventral left prostatic lobe. Follow-up MRI examinations six months after IRE demonstrate a hypointense area in the ablation zone **c** and a sharply demarcated perfusion defect in the same area **d** (arrow) on T2-weighted images.

Abb. 4 Patient mit Prostatakarzinom (*) (Gleason Score: 3 + 3 = 6) in der Transitionalzone erhält eine Ultraschall-gestützte IRE-Behandlung. Native **a** und Kontrastmittel-MRT-Voraufnahmen **b** zeigen die Lokalisation des Tumors im ventralen Anteil des linken Prostatalappens. MRT-Bilder sechs Monate nach IRE weisen ein hypointenses Areal **c** und einen scharf abgrenzbaren Perfusionsdefekt **d** (Pfeil) in der Ablationszone auf den T2-gewichteten Sequenzen auf.

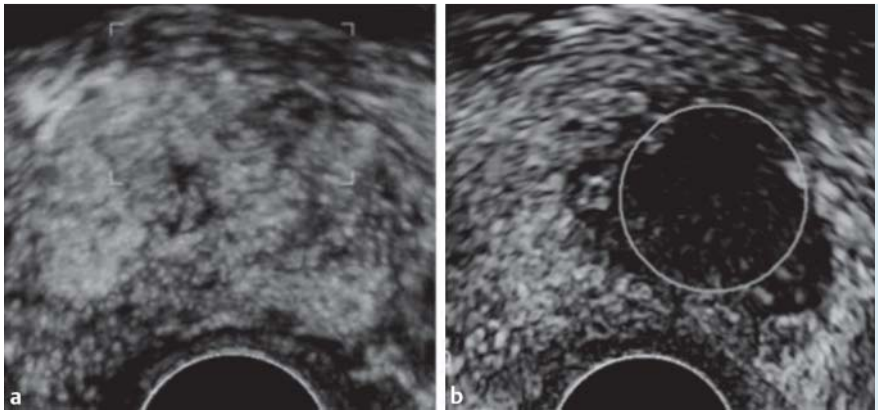

Fig. 5 Contrast-enhanced transrectal ultrasound (ceTRUS) of the prostate before **a** and 24 hours after **B** IRE ablation of a prostate cancer lesion located in the left prostate lobe. As early as 24 hours after the procedure, an extensive perfusion defect within the tumor can be seen on the ceTRUS image **b**.

Abb. 5 Dargestellt sind transrektale Ultraschallbilder der Prostata nach Kontrastmittelgabe vor **a** sowie 24 Stunden nach **b** IRE-Ablation eines kleinen Pankreaskarzinoms im linken Prostatalappen. Bereits 24 Stunden nach der Behandlung ist ein ausgeprägter Perfusionsdefekt im Tumorgewebe zu beobachten **b**.

establish IRE in the prostate as a new technique for locoregional tumor therapy (**Fig. 4, 5**).

Conclusion and Future Directions

Preclinical findings of IRE have been translated into clinical settings. At present, IRE appears to be filling a niche for the ablation of tumors in proximity to critical structures such as the hilus region or large vessels where either the heat sink effect or collateral damage constitute a concern for thermal ablation and resection. With respect to efficacy, the results of IRE found in this review appear promising in the liver, pancreas, and prostate where the overall morbidity is also tolerable. In terms of safety, no attributed mortality has been reported so far and mainly mild transient side effects such as postprocedural pain similar to radiofrequency ablation occur [53]. On the contrary, there is no evidential benefit of IRE in the lung parenchyma. In this setting, feasibility is limited and pneumothoraces occur as frequent potentially severe complications. Regarding renal IRE, no definite conclusion can be drawn here due to limited data. However, Pech et al. reported successful performance of IRE in the kidney with a favorable safety profile [41].

Overall, one of the shortcomings of IRE today remains the absence of clinically validated protocols to be used in different tumor entities. Current literature only provides a low level of evidence as the presented studies are mostly small case series or heterogeneously designed reports without control groups. IRE has so far been applied with palliative intent but may also be a feasible adjuvant procedure in resectable tumors. With regard to this, randomized controlled trials are required to determine IRE indication in a continuously growing armamentarium of locoregional therapies.

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