# Prior Authorization Review Panel
## MCO Policy Submission

A separate copy of this form must accompany each policy submitted for review. Policies submitted without this form will not be considered for review.

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Type of Submission – Check all that apply:

- [ ] New Policy
- [x] Revised Policy*
- [ ] Annual Review – No Revisions
- [ ] Statewide PDL

*All revisions to the policy must be highlighted using track changes throughout the document.

Please provide any clarifying information for the policy below:

**CPB 0828 Irreversible Electroporation (NanoKnife)**

This CPB has been revised to state that the use of irreversible electroporation (IRE) (NanoKnife) is considered experimental and investigational for cancer pelvic pain, cervical cancer, gastrointestinal stromal tumors, lymphoma, musculoskeletal system tumors, osteosarcoma, and pre-sacral cancer.

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<th>Name of Authorized Individual (Please type or print):</th>
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<td>Dr. Bernard Lewin, M.D.</td>
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Irreversible Electroporation (NanoKnife)

Policy

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.

Aetna considers the use of irreversible electroporation (IRE) including use of the NanoKnife for tissue ablation experimental and investigational for all indications (including the following; not an all-inclusive list) due to insufficient evidence in the peer-reviewed literature:

- Abdominal tumor
- Breast cancer
- Cancer pelvic pain
- Catheter-based cardiac ablation (e.g., atrial fibrillation, and ventricular arrhythmias)
- Cervical cancer
- Colorectal liver metastases
- Fibrous sarcoma
- Gastric cancer
- Gastro-intestinal stromal tumors
- Glioma
- Head and neck cancers (e.g., thyroid cancer)
- Hepatocellular carcinoma
- Intracranial meningioma
- Lymphoma
- Musculoskeletal system tumors
- Osteosarcoma
- Pancreatic cancer
- Pediatric tumors (including bone, lung, and soft tissue cancers)
- Pelvic tumor
- Peri-biliary tumors (e.g., hilar cholangiocarcinoma (Klatskin tumor))
- Pre-sacral cancer
- Prostate cancer
- Renal cell carcinoma
- Renal masses
- Uveal melanoma.

Background
The field of irreversible electroporation (IRE) in medicine has been growing in recent years as a tool in tissue ablation (Rubinsky, 2007). The process of IRE occurs as a consequence of certain electrical fields being applied across a cell permeabilizing the cell membrane and leading to cell death, primarily when the electrical fields cause permanent permeabilization and consequent loss of cell homeostasis. In comparison with current physical ablation technologies, IRE does not result in any thermal effect (Breton and Mir, 2011).

The Nanoknife is a low-energy direct current (LEDC) thermal ablation system, which received Food and Drug Administration (FDA) 510K clearance on October 24, 2011 (FDA, 2011). The NanoKnife System has received FDA clearance for the surgical ablation of soft tissue. It has not received clearance for the therapy or treatment of any specific disease or condition (AngioDynamics, 2011). The NanoKnife System transmits LEDC energy from the generator to electrode probes placed in a target area for the surgical ablation of soft tissue.

Ball et al (2010) conducted a clinical trial of IRE for tumor ablation therapy. A pulsating direct current of 20 to 50 A and 500 to 3000 V was delivered into metastatic or primary tumors of the liver, kidney, or lung via needle electrodes inserted under computed tomography (CT) or ultrasound guidance with use of a relaxant general anesthetic. Twenty-one patients were included. The results showed that electrical discharge produced generalized upper body muscular contractions requiring neuromuscular blockade. Two patients developed positional neuropraxia because of the extended arm position requested for CT scanning. Some patients developed self-limiting ventricular tachycardias that are now minimized by using an electrocardiogram (ECG) synchronizer. Three patients developed pneumothoraces as a result of the needle electrode insertion. The authors concluded that relaxant general anesthesia is
Irreversible Electroporation (NanoKnife) required for IRE of the liver, lung, and kidney and that an ECG synchronizer should be used to minimize the risk of arrhythmias. The authors further noted that attention to the position of the arms is required to maximize CT scan quality but minimize brachial plexus strain and that simple post-operative analgesia is all that is required in most patients.

Thomson et al (2011) conducted a single-center prospective non-randomized cohort study to investigate the safety of IRE for tumor ablation in humans. Thirty-eight study subjects received IRE treatment under general anesthesia. The study population included patients with advanced malignancy of the liver, kidney, or lung (69 separate tumors) which were unresponsive to alternative treatment. Clinical examination, biochemistry, and CT scans of the treated organ were performed before, immediately after, and at 1 month and 3 post-procedure. The authors reported no mortalities occurring by 30 days post-procedure and that transient ventricular arrhythmia occurred in 4 patients and that ECG synchronized delivery was used subsequently in the remaining 30 patients, with 2 further arrhythmias (supraventricular tachycardia and atrial fibrillation). One patient developed obstruction of the upper ureter after IRE. One adrenal gland was unintentionally directly electroporated, which produced transient severe hypertension. There was no other evidence of adjacent organ damage related to the electroporation. Two patients developed temporary neurapapraxia as a result of arm extension during a prolonged period of anesthesia and biopsy in 3 patients showed coagulative necrosis in the regions treated by IRE. The authors further noted that complete target tumor ablation verified by CT was achieved in 46 of the 69 tumors treated with IRE (66 %), while most treatment failures occurred in renal and lung tumors. The authors concluded that IRE appears safe for human clinical use if ECG-synchronized delivery is utilized. They recommended comparative evaluation with alternative ablative technologies.

Charpentier (2012) explored IRE as a novel, non-thermal form of tissue ablation using high-voltage electrical current to induce pores in the lipid bilayer of cells, resulting in cell death. PubMed searches were performed using the keywords electroporation, IRE, and ablation. The abstracts for the 2012 meetings of both the American Hepato-Pancreato-Biliary Association and the Society for Interventional Radiology were also searched. All articles and abstracts with any reference to electroporation were identified and reviewed. All studies and abstracts pertaining to electroporation were reviewed. All data pertaining to the safety and effectiveness of IRE were extracted from pre-clinical and clinical studies. Pre-clinical data detailing the theory and design of IRE systems were also extracted. Pre-clinical studies have suggested that IRE may have advantages over conventional forms of thermal tumor ablation including no heat sink effect and preservation of the acellular elements of tissue, resulting in less unwanted collateral damage. The early clinical experience with IRE demonstrated safety for the ablation of human liver tumors. Short-term data regarding oncologic outcome is now emerging and appears encouraging. The author concluded that IRE is likely to fill a niche void for the ablation of small
liver tumors abutting a major vascular structure and for ablation of tumors abutting a major portal pedicle where heat sink and collateral damage must be avoided for maximum efficacy and safety. Moreover, they stated that studies are still needed to define the short-term and long-term oncologic effectiveness of IRE.

Olweny and Cadeddu (2012) provided an overview of the current research on renal tissue ablation, highlighting novel ablation techniques and technologies. Although nephron-sparing surgery is the gold standard treatment for small renal masses confirmed malignant, ablative therapies are an option in elderly patients, who may be poor surgical candidates. Radiofrequency ablation (RFA) and cryoablation have each been used for renal tissue ablation for over a decade, but their effectiveness in ablation of central lesions or lesions more than 3 cm in size is limited. Increasing ablation size and improving effectiveness of thermal energy delivery are the goals of research in RFA and cryoablation. The authors stated that novel ablation technologies including IRE, microwave ablation, and high-intensity focused ultrasound among others have undergone preliminary pre-clinical and clinical evaluation in select series, but require further development and assessment of outcomes prior to routine clinical use for renal tumor ablation.

Kingham et al (2012) evaluated the safety and short-term outcomes of IRE to ablate peri-vascular malignant liver tumors. A retrospective review of patients treated with IRE between January 1, 2011 and November 2, 2011 was performed. Patients were selected for IRE when resection or thermal ablation was not indicated due to tumor location. Treatment outcomes were classified by local, regional, and systemic recurrence and complications. Local failure was defined as abnormal enhancement at the periphery of an ablation defect on post-procedure contrast imaging. A total of 28 patients had 65 tumors treated; 22 patients (79 %) were treated via an open approach and 6 (21 %) were treated percutaneously. Median tumor size was 1 cm (range of 0.5 to 5 cm). Twenty-five tumors were less than 1 cm from a major hepatic vein; 16 were less than 1 cm from a major portal pedicle. Complications included 1 intra-operative arrhythmia and 1 post-operative portal vein thrombosis. Overall morbidity was 3 %. There were no treatment-associated mortalities. At median follow-up of 6 months, there was 1 tumor with persistent disease (1.9 %) and 3 tumors recurred locally (5.7 %). The authors concluded that this early analysis of IRE treatment of peri-vascular malignant hepatic tumors demonstrated safety for treating liver malignancies. They stated that larger studies and longer follow-up are needed to determine long-term effectiveness.

Cannon et al (2013) evaluated the safety and effectiveness of IRE for hepatic tumors in the clinical setting. An IRB approved prospective registry of patients undergoing IRE for hepatic tumors over a 2-year period. Factors analyzed included patient and tumor characteristics, treatment related complications, and local recurrence free survival (LRFS) for ablated lesions -- LRFS was calculated according to Kaplan-Meier, with secondary analyses stratified by
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procedural approach (laparotomy, laparoscopy, and percutaneous) and tumor histology. There were 44 patients undergoing 48 total IRE procedures, 20 colorectal metastases, 14 hepatocellular, and 10 other metastases. Initial success was achieved in 46 (100 %) treatments. Five patients had 9 adverse events, with all complications resolving within 30 days. Local recurrence free survival at 3, 6, and 12 months was 97.4 %, 94.6 %, and 59.5 %, respectively. There was a trend toward higher recurrence rates for tumors over 4 cm (HR 3.236, 95 % confidence interval [CI]: 0.585 to 17.891; p = 0.178). The authors concluded that IRE appears to be a safe treatment for hepatic tumors in proximity to vital structures. Moreover, they stated that further prospective evaluation is needed to determine the optimal effectiveness of IRE in relation to size and technique for IRE of the liver.

Mandel et al (2013) noted that uveal melanoma (UM) is the most common primary intra-ocular tumor in adults and is characterized by high rates of metastatic disease. Although brachytherapy is the most common globe-sparing treatment option for small- and medium-sized tumors, the treatment is associated with severe adverse reactions and does not lead to increased survival rates as compared to enucleation. The use of IRE for tumor ablation has potential advantages in the treatment of tumors in complex organs such as the eye. Following previous theoretical work, these researchers evaluated the use of IRE for uveal tumor ablation in human ex-vivo eye model. Enucleated eyes of patients with UM were treated with short electric pulses (50 to 100 µs, 1,000 to 2,000 V/cm) using a customized electrode design. Tumor bio-impedance was measured before and after treatment and was followed by histopathological evaluation. These investigators found that IRE caused tumor ablation characterized by cell membrane disruption while sparing the non-cellular sclera. Membrane disruption and loss of cellular capacitance were also associated with significant reduction in total tumor impedance and loss of impedance frequency dependence. The effect was more pronounced near the pulsing electrodes and was dependent on time from treatment to fixation. The authors concluded that future studies should further evaluate the potential of IRE as an alternative method of UM treatment.

Yeung et al (2014) examined the safety and effectiveness of IRE for ablation of liver tumor. The PubMed and MEDLINE databases were systematically searched. Clinical research published in English in the last 10 years until October 2013 that address clinical issues related to IRE of human liver tumors were selected. "Liver tumor", "local ablative therapy", and "irreversible electroporation" were used as the search terms. The data extracted for this review was analyzed by the authors, with a focus on the safety and effectiveness of IRE. The complete response (CR) rates look promising, ranging from 72 % to 100 %, except in 1 study in a subgroup of liver tumors in which the CR rate was only 50 % that was likely due to the inclusion of larger-size tumors. In 1 study, the local recurrence rate at 12 months was approximately 40 %. As for the safety of IRE, there were only a few reported complications (cardiac arrhythmia, pneumothorax, and electrolyte disturbance) that were mostly transient and not serious. There was no reported
mortality related to the use of IRE. The authors concluded that IRE is a potentially effective liver tumor ablative therapy that gives rise to only mild and transient side-effects. They stated that further studies with better patient selection criteria and longer follow-up are needed to clarify its role as a first-line liver tumor treatment modality.

Scheffer et al (2014a) provided an overview of current clinical results of IRE, a novel, non-thermal tumor ablation technique that uses electric pulses to induce cell death, while preserving structural integrity of bile ducts and vessels. All in-human literature on IRE reporting safety or efficacy or both was included. All adverse events were recorded. Tumor response on follow-up imaging from 3 months onward was evaluated. In 16 studies, 221 patients had 325 tumors treated in liver (n = 129), pancreas (n = 69), kidney (n = 14), lung (n = 6), lesser pelvis (n = 1), and lymph node (n = 2). No major adverse events during IRE were reported. Irreversible electroporation caused only minor complications in the liver; however, 3 major complications were reported in the pancreas (bile leak [n = 2], portal vein thrombosis [n = 1]). Complete response at 3 months was 67 % to 100 % for hepatic tumors (93 % to 100 % for tumors o 3 cm). Pancreatic IRE combined with surgery led to prolonged survival compared with control patients (20 months versus 13 months) and significant pain reduction. The authors concluded that in cases where other techniques are unsuitable, IRE is a promising modality for the ablation of tumors near bile ducts and blood vessels. They gave an extensive overview of the available evidence, which is limited in terms of quality and quantity. With the limitations of the evidence in mind, IRE of central liver tumors seems relatively safe without major complications, whereas complications after pancreatic IRE appear more severe. The available limited results for tumor control are generally good. These researchers stated that the future of IRE for difficult-to-reach tumors appears promising.

Silk et al (2014) evaluated biliary complications after IRE ablation of hepatic tumors located less than 1 cm from major bile ducts. A retrospective review was conducted of all percutaneous IRE ablations of hepatic tumors within 1 cm of the common, left, or right hepatic ducts at a single institution from January 2011 to September 2012. Computed tomography imaging performed before and after treatment was examined for evidence of bile duct dilatation, stricture, or leakage. Serum bilirubin and alkaline phosphatase levels were analyzed for evidence of biliary injury. There were 22 hepatic metastases in 11 patients with at least 1 tumor within 1 cm of the common, left, or right hepatic duct that were treated with IRE ablations in 15 sessions. Median tumor size treated was 3.0 cm (mean of 2.8 cm ± 1.2, range of 1.0 to 4.7 cm). Laboratory values obtained after IRE were considered abnormal after 4 treatment sessions in 3 patients (bilirubin, 2.6 to 17.6 mg/dL; alkaline phosphatase, 130 to 1,035 U/L); these abnormal values were transient in 2 sessions. Two patients had prolonged elevation of values, and 1 required stent placement; both of these conditions appeared to be secondary to tumor progression rather than bile duct injury. The authors concluded that this clinical experience suggested that IRE may be a
treatment option for centrally located liver tumors with margins adjacent to major bile ducts where thermal ablation techniques are contraindicated. They stated that further studies with extended follow-up periods are needed to establish the safety profile of IRE in this setting.

Valerio et al (2014a) stated that IRE has been proposed to be tissue selective and so might have favorable characteristics compared to the currently used prostate ablative technologies. The authors described the design of a trial to determine the adverse events, genito-urinary side effects and early histological outcomes of focal IRE in men with localized prostate cancer. This is a single-center, prospective development (stage 2a) study following the IDEAL recommendations for evaluating new surgical procedures. A total of 20 men who have magnetic-resonance imaging (MRI)-visible disease localized in the anterior part of the prostate will be recruited. The sample size permits a precision estimate around key functional outcomes. Inclusion criteria include prostate-specific antigen (PSA) of less than or equal to 15ng/ml, Gleason score less than or equal to 4+3, stage T2N0M0 and absence of clinically significant disease outside the treatment area. Treatment delivery will be changed in an adaptive iterative manner so as to allow optimization of the IRE protocol. After focal IRE, men will be followed during 12 months using validated patient reported outcome measures (IPSS, IIEF-15, UCLA-EPIC, EQ-5D, FACT-P, MAX-PC). Early disease control will be evaluated by mpMRI and targeted transperineal biopsy of the treated area at 6 months. The authors concluded that the NEAT trial will assess the early functional and disease control outcome of focal IRE using an adaptive design. This protocol can provide guidance for designing an adaptive trial to assess new surgical technologies in the challenging landscape of health technology assessment in prostate cancer treatment.

Valerio et al (2014b) evaluated the safety and clinical feasibility of focal IRE of the prostate. These investigators assessed the toxicity profile and functional outcomes of consecutive patients undergoing focal IRE for localized prostate cancer in 2 centers. Eligibility was assessed by mpMRI and targeted and/or template biopsy. Irreversible electroporation was delivered under trans-rectal ultrasound guidance with 2 to 6 electrodes positioned trans-perineally within the cancer lesion. Complications were recorded and scored accordingly to the NCI Common Terminology Criteria for Adverse Events; the functional outcome was physician reported in all patients with at least 6 months follow-up. A contrast-enhanced MRI 1 week after the procedure was carried out to assess treatment effect with a further mpMRI at 6 months to rule out evidence of residual visible cancer. Overall, 34 patients with a mean age of 65 years (S.D. = ±6) and a median PSA of 6.1 ng/ml (interquartile range (IQR)= 4.3 to 7.7) were included. Nine (26 %), 24 (71 %) and 1 (3 %) men had low, intermediate and high risk disease, respectively (D'Amico criteria). After a median follow-up of 6 months (range of 1 to 24), 12 grade-1 and 10 grade-2 complications occurred. No patient had grade greater than or equal to 3 complication. From a functional point of view, 100 % (24/24) patients were continent and potency was preserved in 95 % (19/20) men potent before treatment. The volume of ablation was a median of 12 ml (IQR =
5.6 to 14.5 ml) with the median PSA after 6 months of 3.4 ng/ml (IQR = 1.9 to 4.8 ng/ml). Multi-parametric MRI showed suspicious residual disease in 6 patients, of whom 4 (17%) underwent another form of local treatment. The authors concluded that focal IRE has a low toxicity profile with encouraging genito-urinary functional outcomes. Moreover, they stated that further prospective development studies are needed to confirm the functional outcomes and to explore the oncological potential.

Fornage and Hwang (2014) described the various techniques used for percutaneous ablation of breast cancer, their preliminary results, and their limitations. The techniques include thermotherapy (radiofrequency ablation, laser irradiation, microwave irradiation, and insonation with high-intensity focused ultrasound waves), cryotherapy, and IRE. The authors concluded that the techniques used for percutaneous ablation of breast cancer raise many questions and issues that must be addressed before percutaneous ablation can be adopted for the treatment of early breast cancer.

Wagstaff et al (2014) provided an overview of recent developments in the field of thermal ablation for renal cell carcinoma and focused on current standard techniques, new technologies, imaging for ablation guidance and evaluation, and future perspectives. Emerging long-term data on cryoablation and radiofrequency ablation (RFA) showed marginally lower oncologic outcomes compared to surgical treatment, balanced by better functional and peri-operative outcomes.

Reports on residual disease vary widely, influenced by different definitions and strategies in determining ablation failure. Stratifying disease-free survival (DFS) after RFA according to tumor size suggested 3 cm to be a reasonable cut-off for RFA tumor selection. Microwave ablation and high-intensity focal ultrasound are modalities with the potential of creating localized high temperatures. However, difficulties in renal implementation are impairing sufficient ablation results. These researchers noted that IRE, although not strictly thermal, is a new technology showing promising results in animal and early human research. The authors concluded that although high-level randomized controlled trials (RCTs) comparing thermal ablation techniques are lacking, evidence showed that thermal ablation for small renal masses is a safe procedure for both long-term oncologic and functional outcomes. They stated that thermal ablation continues to be associated with a low risk of residual disease, for which candidates should be properly informed; cryotherapy and RFA remain the standard techniques whereas alternative techniques require further studies.

Scheffer (2014b) evaluated the pathological response of colorectal liver metastases (CRLM) treated with IRE and the clinical safety and feasibility. A total of 10 patients with resectable CRLM were included in this study. During laparotomy, the metastases were treated with IRE and resected 60 mins later. Safety and feasibility were assessed based on adverse events, laboratory values, technical success and intra-operative ultrasound findings.
Irreversible Electroporation (NanoKnife) was assessed using triphenyl tetrazolium chloride (TTC) vitality staining and (immuno)histochemical stainings (HE, complement-3d and caspase-3). Ten lesions with a mean diameter of 2.4 cm were successfully electroporated and resected, on average, 84 mins later (range of 51 to 153 mins). One minor transient cardiac arrhythmia occurred during IRE. Ultrasound showed a sharply demarcated hypo-echoic ablation zone around the tumor. Triphenyl tetrazolium chloride showed avitality of all lesions, covering the complete tumor in 8/10 lesions. Although immunohistochemistry proved heterogeneous and difficult to interpret within the tumors, it confirmed irreversible cell damage in the tumor-free margin of all specimens. The authors concluded that this ablate-and-resect study demonstrated avitality caused by IRE of CRLM in humans. Moreover, they stated that further characterization of tissue- and tumor-specific electrical properties is needed to improve ablation protocols for maximized tissue ablation.

Gomez et al (2014) reviewed the existing evidence on the techniques and results of ablation for pediatric solid malignant or aggressive benign tumors. These investigators searched MEDLINE for papers published between 1995 and 2012 that reported outcomes of radiofrequency, microwave and cryoablation, interstitial laser therapy, IRE and percutaneous ethanol injection for patients younger than 18 years old. Data collection included factors related to the patient, tumor biology, ablation technique and cancer-specific end-points. Additional series of predominantly adults including data on patients younger than 18 years old were also identified. These researchers identified 28 patients treated by ablation in 29 regions: 5 patients undergoing ablation for liver lesions, 9 patients for lung metastases, 11 patients for bone and/or soft tissue and 4 patients for kidney or pancreas. The ablation was performed to treat primary tumors, local recurrences and metastases. The histology of the tumors was osteosarcoma in 6 patients, Wilms tumor in 3, rhabdomyosarcoma in 3, hepatoblastoma in 3, desmoid tumor in 3, adrenocortical carcinoma in 2 and a single case each of leiomyosarcoma, Ewing sarcoma, paraganglioma, solid-pseudopapillary neoplasm, sacrococcygeal teratoma, hepatic adenoma, juxtaglomerular cell tumor and plantar fibromatosis. Eighteen of the patients (64 %) experienced a complication, but only 6 (21 %) of these needed treatment other than supportive care. The authors concluded that although ablative techniques are feasible and promising treatments for certain pediatric tumors, large multi-center prospective trials will be needed to establish efficacy.

Rombouts et al (2015) stated that locally advanced pancreatic cancer (LAPC) is associated with a very poor prognosis. Current palliative radio-chemotherapy provides only a marginal survival benefit of 2 to 3 months. Several innovative local ablative therapies have been explored as new treatment options. These researchers provided an overview of the clinical outcomes of these ablative therapies. A systematic search in PubMed, Embase and the Cochrane Library was performed to identify clinical studies, published before June 1, 2014, involving ablative therapies in LAPC. Outcomes of interest were safety, survival, quality of life and pain. After screening
1,037 articles, 38 clinical studies involving 1,164 patients with LAPC, treated with ablative therapies, were included. These studies concerned RFA (7 studies), IRE (4 studies), stereotactic body radiation therapy (SBRT) (16 studies), high-intensity focused ultrasound (HIFU) (5 studies), iodine-125 (2 studies), iodine-125-cryosurgery (2 studies), photodynamic therapy (1 study) and microwave ablation (1 study). All strategies appeared to be feasible and safe. Outcomes for post-operative, procedure-related morbidity and mortality were reported only for RFA (4 to 22 % and 0 to 11 %, respectively), IRE (9 to 15 % and 0 to 4 %) and SBRT (0 to 25 % and 0 %). Median survival of up to 25.6, 20.2, 24.0 and 12.6 months was reported for RFA, IRE, SBRT and HIFU, respectively. Pain relief was demonstrated for RFA, IRE, SBRT and HIFU. Quality-of-life outcomes were reported only for SBRT, and showed promising results. The authors concluded that ablative therapies in patients with LAPC appeared to be feasible and safe. This review provided safety and feasibility data, but no evidence on clinical effectiveness.

Wendler et al (2015a) stated that IRE a new tissue ablation procedure available since 2007, could meet the requirements for ideal focal therapy (FT) with its postulated features, especially the absence of a thermal ablative effect. Thus far, there is no adequate tumor-entity-specific proof of its effectiveness, and its clinical application has been confined to very small patient cohorts. This also holds true for prostate cancer (PCa). Nevertheless, it is now being increasingly applied outside clinical trials-to a certain extent due to active advertising in the lay press. In this study, these researchers described current discrepancies between the clinical application and study situation and the approval and market implementation of the procedure. The media portrayal of IRE was discussed from different perspectives, particularly with reference to the FT of PCa. This was followed by a final clinical assessment of IRE using the NanoKnife system. According to the German Drug Act (AMG), evidence of additional benefit over existing therapy must be provided through comparative clinical trials. For medico-technical treatment procedures, on the other hand, such trial-based proof is not required according to the Medical Devices Act (MPG). The use of IRE even outside clinical trials has been actively promoted since the NanoKnife system was put on the market. This has led to an increase in the number of uncontrolled IRE treatments of PCa in the last 2 years. The patients have to cover the high treatment costs themselves in these cases. If articles in the lay press advertised the procedure with promising but unverified contents, false hopes are raised in those concerned. This is disastrous if it delays the use of truly effective treatment options. The authors concluded that IRE basically still has high potential for the treatment of malignancies; however, whether it can really be used for FT remains unclear due to the lack of data. This also holds true for the treatment of PCa. These investigators stated that only carefully conducted scientific research studies can clarify the unresolved issues regarding IRE of PCa. They stated that the urgently needed development of universally valid treatment standards for IRE is unnecessarily hampered by the flow commercially driven patients.
Head and Neck Cancers (e.g., Thyroid Cancer)

Meijerink and colleagues (2015) reported on the case of a 74-year old man who presented with a small loco-regional, histopathologically proven, fluorodeoxyglucose positron emission tomography (PET)/computed tomography (CT)-avid recurrence of follicular thyroid carcinoma in the left subglottic space after extensive surgical resection, adjuvant radioactive iodine therapy, and external beam radiation therapy (EBRT). Because all established focal therapies were contraindicated, percutaneous IRE was performed without complications. Follow-up imaging at 7 months showed a small ablation scar without signs for residual vital tumor tissue. The authors concluded that IRE may be a viable treatment option for selected cases of recurring head and neck tumors that are unsuitable for other local treatments.

Lung Cancer

In a prospective, single-arm, multi-center, phase II clinical trial, Ricke et al (2015) evaluated the safety and effectiveness of IRE on lung cancers. Patients with primary and secondary lung malignancies and preserved lung function were included in this trial. Primary and secondary end-points were safety and effectiveness. Recruitment goal was 36 subjects in 2 centers. Patients underwent IRE under general anesthesia with probe placement performed in fluoroscopy-CT. The IRE system employed was NanoKnife (Angiodynamics). System settings for the ablation procedure followed the manufacturer's recommendations. The Mann-Whitney U test was used to evaluate the correlation of 9 technical parameters with local tumor control; median follow-up was 12 months. The expected effectiveness was not met at interim analysis and the trial was stopped prematurely after inclusion of 23 patients (13/10 between both centers). The dominant tumor entity was colorectal (n = 13). The median tumor diameter was 16 mm (8 to 27 mm). Pneumothoraces were observed in 11 of 23 patients with chest tubes required in 8 (35 %). Frequently observed alveolar hemorrhage never led to significant hemoptysis; 14/23 showed progressive disease (61 %). Stable disease was found in 1 (4 %), partial remission in 1 (4 %) and complete remission in 7 (30 %) patients. The relative increase of the current during ablation was significantly higher in the group treated successfully as compared to the group presenting local recurrence (p < 0.05). Needle tract seeding was found in 3 cases (13 %). The authors concluded that IRE is not effective for the treatment of lung malignancies.

Renal Masses

Wagstaff et al (2015) stated that electroporation is a novel treatment technique utilizing electric pulses, traveling between 2 or more electrodes, to ablate targeted tissue. The first in human studies have proven the safety of IRE for the ablation of renal masses. However the effectiveness of IRE through histopathological examination of an ablated renal tumor has not yet
been studied. Before progressing to a long-term IRE follow-up study it is vital to have pathological confirmation of the effectiveness of the technique. Furthermore, follow-up after IRE ablation requires a validated imaging modality. The primary objectives of this study are the safety and the effectiveness of IRE ablation of renal masses. The secondary objectives are the effectiveness of MRI and contrast-enhanced ultrasound (CEUS) in the imaging of ablation result. A total of 10 patients, aged greater than or equal to 18 years, presenting with a solid enhancing mass, who are candidates for radical nephrectomy will undergo IRE ablation 4 weeks prior to radical nephrectomy. Magnetic resonance imaging and CEUS imaging will be performed at baseline, 1 week and 4 weeks post-IRE. After radical nephrectomy, pathological examination will be performed to evaluate IRE ablation success. The authors stated that the only way to truly assess short-term (4 weeks) ablation success is by histopathology of a resection specimen. In the authors’ opinion, this trial will provide essential knowledge on the safety and effectiveness of IRE for the ablation of renal masses, guiding future research of this promising ablative technique.

Kriegmair and associates (2018) stated that RCC is nowadays predominantly diagnosed in early stages due to the widespread use of sectional imaging for unrelated symptoms. Small renal masses (less than 4 cm) feature a largely indolent biology with a very low risk for metastasis or even a benign biology in up to 30 % of the cases. Consequently, there is a need for less invasive therapeutic alternatives to nephron-sparing surgery. Meanwhile, there is a broad portfolio of local ablation techniques to treat small renal tumors. These include the extensively studied RFA and cryoablation techniques as well as newer modalities like microwave ablation and IRE as more experimental techniques. Tumor ablation can be performed percutaneously under image guidance or laparoscopically. In particular, the percutaneous approach is a less invasive alternative to nephron-sparing surgery with lower risk for complications. Comparative studies and meta-analyses reported a higher risk for local recurrence after renal tumor ablation compared to surgery. However, long-term oncological results after treatment of small renal masses are promising and do not seem to differ from partial nephrectomy. The possibility for salvage therapy in case of recurrence also accounts for this finding. Especially old patients with an increased risk of surgical and anesthesiological complications as well as patients with recurrent and multiple hereditary RCC may benefit from tumor ablation. Tumor biopsy prior to intervention is associated with very low morbidity rates and is oncologically safe. It could help to assess the biology of the renal mass and prevent therapy of benign lesions.

Liu and colleagues (2019) stated that IRE is a novel technology used in the minimally invasive treatment of small solid organ tumors. Currently, there is a paucity of literature studying treatment of small renal masses (SRMs) with IRE. This pilot study was the 1st case series in Canada to use IRE in the treatment of SRMs. This retrospective, cohort pilot study included 5 patients (3 females and 2 males) who presented with a SRM that was deemed not amendable to any other treatment than a radical nephrectomy or IRE. The IRE procedures were carried out by
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an interventional radiologist in conjunction with a urologist using the Angiodynamics NanoKnife IRE device. Mean tumor size was 28 mm (range of 18 to 39), with a mean R.E.N.A.L. nephrometry score of 8.4 ± 0.55. Over a mean follow-up of 22.8 months (range of 14 to 31), 4 out of the 5 patients did not have a radiological recurrence. No AEs were reported after the 5 IRE procedures. Renal function was stable post-IRE, with no to negligible decreases in estimated glomerular filtration rate (eGFR) detected (range of +2 to -13 ml/min/1.73 m2). The authors concluded that this pilot study demonstrated that renal percutaneous IRE was safe to use in the context of challenging-to-treat SRMs. Early radiological and renal function outcomes were encouraging, but further study is needed to examine oncological success. The small sample size (n = 5), retrospective nature of the study, relatively short follow-up (mean of 22.8 months), and the lack of routine renal biopsy to confirm malignancy were the major limitations of this pilot study.

Cancer Pelvic Pain

Cascella and associates (2017) noted that pain is a common and debilitating symptom in pelvic cancer diseases. Failure in controlling this pain through pharmacological approaches calls for employing multi-modal management and invasive techniques. Various strategies are commonly used for this purpose, including palliative radiotherapy, epidural medications and intrathecal administration of analgesic and local anesthetic drugs with pumps, and neural or plexus blockade. These investigators focused on the features of minimally invasive palliative procedures (MIPPs), such as RFA, laser-induced thermotherapy (LITT), cryoablation, IRE, electrochemotherapy, microwave ablation, and cementoplasty as well as their role in palliation of cancer pelvic pain. The authors concluded that despite the evidence of effectiveness and safety of these interventions, there are still many barriers to accessing MIPPs, including the availability of trained staff, the lack of precise criteria of indication, and the high costs.

Cervical Cancer

Qin and colleagues (2016) examined the effects of IRE on the proliferation, migration, invasion and adhesion of human cervical cancer cell lines HeLa and SiHa. HeLa and SiHa cells were divided into a treatment group and control group. The treatment group cells were exposed to electric pulses at 16 pulses, 1-Hz frequency for 100 µsec with 1,000 V/cm strength. Cellular proliferation was determined 24 hours after treatment using a Cell Counting Kit-8 (CCK-8) assay and carboxy-fluorescein di-acetate-succinimidyl ester (CFDA-SE) labeling assay. The different phases of the cell cycle were detected using flow cytometry. Wound healing, Transwell invasion and Matrigel adhesion assays were performed to evaluate the migration, invasion and adhesion abilities of HeLa and SiHa cells. The expression levels of metastasis-associated proteins were determined by Western blot analysis; CCK-8 and CFSE labeling assays indicated that the
inhibition of cellular proliferation occurs in cells treated with IRE. Additionally, cell cycle progression was arrested at the G1/S phase. A Western blot analysis indicated that the expression levels of p53 and p21 proteins were increased, while those of cyclin-dependent kinase 2 (CDK2) and proliferating cell nuclear antigen (PCNA) proteins were decreased. However, wound healing, invasion and adhesion assays indicated that cellular migration, invasion and adhesion abilities were not significantly altered following exposure to IRE. The authors concluded that IRE was not observed to promote the migration, invasion or adhesion capacity of HeLa and SiHa cells. However, IRE may inhibit the capacity of cells to proliferate and their progression through the cell cycle in-vitro. They stated that these preliminary evidence suggested that the underlying mechanism involves increased expression levels of p53 and p21 and decreased expression levels of CDK2 and PCNA.

Gastro-Intestinal Stromal Tumors

An UpToDate review on “Local treatment for gastrointestinal stromal tumors, leiomyomas, and leiomyosarcomas of the gastrointestinal tract” (Morgan and Raut, 2016) does not mention irreversible electroporation / NanoKnife as a therapeutic option.

Osteosarcoma

Harris and colleagues (2016) stated that IRE induces apoptosis in tumor cells with electric energy, allowing treatment of unresectable tumors. One potential application is metastatic osteosarcoma in the pediatric population. A 12-year old underwent thoracotomy with resection of metastatic osteosarcoma; IRE was applied to 1 resected tumor section. Using 2 probes, 100 pulses with width of 90 ms were delivered. Efficacy was measured by increase in current draw during treatment. The treated sample was analyzed with hematoxylin and eosin and transmission electron microscopy. Default voltage of 1,800 kV was ineffective. Voltage of 2,700 kV caused excessive current draw and was aborted to prevent thermal injury. At 2,200 kV, current draw rise was 9 amps, signifying successful treatment. Untreated specimen showed viable osteosarcoma, normal surrounding lung tissue. Treated tumor had edema within the tumor and in surrounding lung tissue, with intra-alveolar hemorrhage and cellular architecture destruction. There was also evidence for cellular destruction such as disruption of lipid bilayer and release of intracellular fluid. Optimal voltage for treatment was 2,200 kV, likely higher due to electrical conduction variation in the aerated lung. The authors concluded that IRE may be a therapeutic option for pediatric patients with unresectable metastatic osteosarcoma.

Other Malignancies
Song and colleagues (2015) stated that IRE is a novel ablation method that has been tested in humans with lung, prostate, kidney, liver, lymph node and pre-sacral cancers. As a new non-thermal treatment, the use of IRE to ablate tumors in the musculoskeletal system might reduce the incidence of fractures. These researchers determined the ablation threshold of cortical bone and evaluated the medium- and long-term healing process and mechanical properties of the femur in a rabbit model post-IRE ablation. The ablation threshold of cortical bone was between 1,090 V/cm and 1,310 V/cm (120 pulses); IRE-ablated femurs displayed no detectable fracture but exhibited signs of recovery, including osteoblast regeneration, angiogenesis and bone remodeling. In the ablation area, re-vascularization appeared at 4 weeks post-IRE. Osteogenic activity peaked 8 weeks post-IRE and remained high at 12 weeks. The mechanical strength decreased briefly 4 weeks post-IRE, but returned to normal levels within 8 weeks. The authors concluded that their experiment revealed that IRE ablation preserved the structural integrity of the bone cortex, and the ablated bone was able to regenerate rapidly. They stated that IRE may hold unique promise for in-situ bone tissue ablation because rapid re-vascularization and active osteogenesis in the IRE ablation area are possible.

Hepatocellular Cancer

Lyu and colleagues (2017) stated that liver cancer makes up a huge percentage of cancer mortality worldwide. Irreversible electroporation is a relatively new minimally invasive non-thermal ablation technique for tumors that applies short pulses of high frequency electrical energy to irreversibly destabilize cell membrane to induce tumor cell apoptosis. These researchers evaluated studies regarding the use of IRE treatment in liver tumors and metastases to liver. They searched PubMed for all of IRE relevant English language articles published up to September 2016. They included clinical trials, experimental studies, observational studies, and reviews. In recent years, increasingly more studies in both pre-clinical and clinical settings have been conducted to examine the safety and effectiveness of this new technique, shedding light on the crucial advantages and disadvantages that IRE possesses. Unlike the current leading thermal ablation techniques, such as radiofrequency ablation (RFA), microwave ablation (MWA), and cryoablation, IRE requires shorter ablation time without damaging adjacent important vital structures. The authors concluded that although IRE has been introduced in the clinical arena within the past decade, more studies are needed to establish its safety and effectiveness for clinical applications.

An assessment of irreversible electroporation by the Ludwig Boltzmann Institute for Health Technology Assessment (2019) concluded: “there is insufficient evidence that . . . IRE is more effective/safe or at least as effective/safe as the conventional standard of care (transarterial chemoembolisation [TACE], sorafenib or palliative care) in the treatment of primary or secondary inoperable liver cancer that is not suitable for thermal ablation.”
Pancreatic Cancer

Narayanan et al (2012) evaluated the safety of percutaneous IRE in patients with pancreatic adenocarcinoma. Irreversible electroporation was performed in patients with pancreatic cancer whose tumors remained unresectable after, or who were intolerant of, standard therapy. The procedures were all performed percutaneously under general anesthesia. Patients were then followed for adverse events, tumor response, and survival. A total of 15 IRE procedures were performed in 14 patients (1 was treated twice). Three patients had metastatic disease and 11 had LAPC. All patients had received chemotherapy previously, and 11 had received radiation. The median tumor size was 3.3 cm (range of 2.5 to 7 cm). Immediate and 24-hour post-procedural scans demonstrated patent vasculature in the treatment zone in all patients. Two patients underwent surgery 4 and 5 months after IRE, respectively. Both had margin-negative resections, and 1 had a pathologic complete response; both remain disease-free after 11 and 14 months, respectively. Complications included spontaneous pneumothorax during anesthesia (n = 1) and pancreatitis (n = 1), and both patients recovered completely. There were no deaths directly related to the procedure. All 3 patients with metastatic disease at IRE died from progression of their disease. The authors concluded that percutaneous IRE for pancreatic adenocarcinoma is feasible and safe; and they stated that a prospective trial is being planned.

Martin et al (2013) evaluated the overall survival (OS) in patients with LAPC treated with IRE. A prospective, multi-institutional evaluation of 54 patients who underwent IRE for unresectable pancreatic cancer from December 2009 to October 2010 was evaluated for OS and propensity matched to 85 matched stage III patients treated with standard therapy defined as chemotherapy and radiation therapy alone. A total of 54 LAPC patients have undergone IRE successfully, with 21 women, 23 men (median age of 61 (range of 45 to 80) years). Thirty-five patients had pancreatic head primary and 19 had body tumors; 19 patients underwent margin accentuation with IRE and 35 underwent in situ IRE. Forty-nine (90 %) patients had pre-IRE chemotherapy alone or chemo-radiation therapy for a median duration 5 months. Forty (73 %) patients underwent post-IRE chemotherapy or chemo-radiation. The 90-day mortality in the IRE patients was 1 (2 %). In a comparison of IRE patients to standard therapy, these researchers have seen an improvement in local progression-free survival ([PFS]; 14 versus 6 months, p = 0.01), distant PFS (15 versus 9 months, p = 0.02), and OS (20 versus 13 months, p = 0.03). The authors concluded that IRE ablation of locally advanced pancreatic tumors remains safe and in the appropriate patient who has undergone standard induction therapy for a minimum of 4 months can achieve greater local palliation and potential improved OS compared with standard chemo-radiation-chemotherapy treatments. Moreover, they stated that validation of these early results will need to be validated in the current multi-institutional phase 2 IDE study.
Moir et al (2014) performed a systematic review of IRE in the treatment of advanced pancreatic cancer. Multiple databases were searched to January 2014. Primary outcome measures were survival and associated morbidity. A total of 41 articles were initially identified; of these 4 studies met the inclusion criteria, yielding 74 patients. A total of 94.5% of patients had locally advanced tumors, the remainder had metastatic disease. Treated tumor size ranged from 1 to 7 cm; IRE approach included open (70.3 %), laparoscopic (2.7 %) and percutaneous (27 %; ultrasound-guided 30 %, CT-guided 70 %). Morbidity ranged from 0 to 33 %; due to the high number of simultaneous procedures performed (resection/bypass) it was difficult to ascertain IRE-related complications. However no significant bleeding occurred when IRE-alone was performed. Survival statistics suggested a prognostic benefit. Reported survival included: 6 month survival of 40 % (n = 5) and 70 % (n = 14); PFS and OS of 14 and 20 months, respectively (n = 54). Results of most interest showed a significant survival benefit in matched IRE versus non-IRE groups (PFS 14 versus 6 months; p = 0.01, OS 20 versus 11 months; p = 0.03). The authors concluded that initial evidence suggested IRE incurred a prognostic benefit with minimal morbidity. However, these researchers stated that more high quality research is needed to determine the role IRE may play in the multi-modal management of pancreatic cancers.

Martin and associates (2015) stated that ablative therapies have been increasingly utilized in the treatment of locally advanced pancreatic cancer (LAPC). Irreversible electroporation (IRE) is an energy delivery system, effective in ablating tumors by inducing irreversible membrane destruction of cells. These researchers examined the effectiveness efficacy of treatment with IRE as part of multi-modal treatment of LAPC. From July 2010 to October 2014, patients with radiographic stage III LAPC were treated with IRE and monitored under a multi-center, prospective institutional review board-approved registry. Perioperative 90-day outcomes, local failure, and overall survival (OS) were recorded. A total of 200 patients with LAPC underwent IRE alone (n = 150) or pancreatic resection plus IRE for margin enhancement (n = 50). All patients underwent induction chemotherapy, and 52 % received chemo-radiation therapy as well for a median of 6 months (range of 5 to 13 months) before IRE. Irreversible electroporation was successfully performed in all patients; 37 % of patients sustained complications, with a median grade of 2 (range of 1 to 5). Median length of stay was 6 days (range of 4 to 36 days). With a median follow-up of 29 months, 6 patients (3 %) have experienced local recurrence. Median OS was 24.9 months (range of 4.9 to 85 months). The authors concluded that for patients with LAPC (stage III), the addition of IRE to conventional chemotherapy and radiation therapy resulted in substantially prolonged survival compared with historical controls. These results suggested that ablative control of the primary tumor may prolong survival. The authors stated that these results need to be confirmed through a randomized trial of chemotherapy and radiation therapy compared with chemotherapy, IRE, and radiation therapy.
The drawbacks of this study included likely selection bias (patients who did not progress on systemic therapy, with good performance status, few co-morbidities, able to withstand a major surgical procedure, and often travel significant distances to tertiary care centers). If this selection bias of not treating patients with IRE at the time of diagnosis but after the biology of the tumor is better understood (i.e., through induction chemo for 4 to 6 months), then these 23- to 28-month median survival rates in these patients with LAPC can be possible. This was a registry and not a prospective study; there was some variability in the post-IRE imaging protocols between centers. Local recurrence or persistent disease based on RECIST criteria may be under-estimated, as conventional imaging has significant limitations in detecting viable tumor.

A 2016 assessment by the Canadian Agency for Drugs and Technologies in Health on “Irreversible electroporation for tumors of the pancreas or liver” concluded that IRE may be helpful in pancreatic tumors, but the results are based on data from small studies with no control group.

Tasu and colleagues (2017) noted that pancreatic adenocarcinoma has a very poor prognosis. Complete surgical resection remains the only current curative treatment. Locally advanced pancreatic cancers are considered as unresectable because of involvement of celiac and/or mesenteric vessels. Irreversible electroporation has recently been introduced to induce permanent cell death by apoptosis. Irreversible electroporation is a non-thermal cell-destruction technique that was claimed to allow destruction of cancerous cells with less damage to surrounding supporting connective tissues with collagenic structure (such as nearby blood vessels, biliary ducts, and nerves) than other types of treatment. The authors concluded that “To date, IRE is not a standard-of-care practice and must be reserved for research protocols. Nevertheless, the preliminary results in LAPC are highly encouraging”.

Scheffer and co-workers (2017) (i) examined the safety of percutaneous IRE for locally advanced pancreatic cancer and (ii) evaluated the quality of life (QOL), pain perception, and effectiveness in terms of time to local progression, event-free survival (EFS), and OS. All patients provided written informed consent for study participation, the ablation procedure, and data usage. Between January 2014 and June 2015, a total of 25 patients with histologically proved locally advanced pancreatic cancer 5 cm or smaller (13 women, 12 men; median age of 61 years; range of 41 to 78) were prospectively included to undergo percutaneous CT-guided IRE. Patients with a metallic biliary Wallstent, epilepsy, or ventricular arrhythmias were excluded. Kaplan-Meier estimates were used to investigate time to local progression, EFS, and OS. Safety was assessed on the basis of adverse events (AEs), which were graded according to the Common Terminology Criteria for Adverse Events. Pain perception and QOL were evaluated by using specific questionnaires. All patients underwent IRE. The median largest
tumor diameter was 4.0 cm (range of 3.3 to 5.0). After a median follow-up of 12 months (IQR: 7 to 16 months), median EFS after IRE was 8 months (95% CI: 4 to 12 months); the median time to local progression after IRE was 12 months (95% CI: 8 to 16 months). The median OS was 11 months from IRE (95% CI: 9 to 13 months) and 17 months from diagnosis (95% CI: 10 to 24 months). There were 12 minor complications (grade I or II) and 11 major complications (9 grade III, 2 grade IV) in 10 patients. There were no deaths within 90 days after IRE. The authors concluded that percutaneous IRE for locally advanced pancreatic cancer was generally well-tolerated, although major AEs can occur. They stated that these preliminary survival data are encouraging and support the setup of larger phase II and III clinical trials to evaluate the effectiveness of IRE plus chemotherapy in the neoadjuvant and adjuvant or 2nd-line setting compared with more widely adopted regimens such as chemotherapy and/or radiation therapy.

In a systematic review, Ansari and colleagues (2017) evaluated current experience of IRE for the ablation of pancreatic cancer. These investigators searched PubMed for all studies of IRE in human pancreatic cancer in English reporting at least 10 patients. The search yielded 10 studies, comprising a total of 446 patients. Percutaneous IRE was performed in 142 patients, while 304 patients were treated during laparotomy. Tumor sizes ranged from median 2.8 to 4.5 cm. Post-procedural complications occurred in 35% of patients, most of them were less severe; 9 patients (2.0%) died after the procedure. The technical success rate was 85 to 100%. The median recurrence-free survival was 2.7 to 12.4 months after IRE treatment. The median OS was 7 to 23 months post-operatively. The longest OS was noted when IRE was used in conjunction with pancreatic resection. The authors concluded that IRE appeared feasible and safe with a low post-procedural mortality. Moreover, they stated that further efforts are needed to address patient selection and efficacy of IRE, as well as the use of IRE for “margin accentuation” during surgical resection.

Leen et al (2018) reported on outcomes of 75 patients with unresectable pancreatic carcinoma who underwent percutaneous IRE after chemotherapy using computerised tomography guidance under general anaesthesia. Postoperative immediate and 30-day morbidity and mortality, progression-free (PFS) and overall survival (OS) were evaluated. Post-procedural immediate and 30-day mortality rates were both zero. All-grade adverse events were 25%. Median in-patient stay was 1 day (range, 1-5 days). Median OS and PFS post-IRE for LAPC were 27 and 15 months respectively. Four patients with LAPC down-staged post-IRE ablation to be surgically resectable, with R0 resections in 3 cases. The authors concluded that these results suggest that percutaneous IRE ablation of unresectable locally advanced pancreatic carcinoma is safe to integrate with standard-of-care chemotherapy and may improve survival, which provides a template for further evaluation in prospective randomized clinical trials.

In a follow-up retrospective study, Naranayan, et al. (2017) described the outcomes of 50
patients (23 women, 27 men; age range, 46-91 y; median age, 62.5 y) with biopsy-proven, unresectable locally-advanced pancreatic cancer (LAPC) who received percutaneous computed tomography (CT)-guided IRE. The primary objective was to assess the safety profile of the procedure; the secondary objective was to determine overall survival (OS). All patients had prior chemotherapy (1-5 lines, median 2), and 30 (60%) of 50 patients had prior radiation therapy. Follow-up included CT at 1 month and at 3-month intervals thereafter. The investigators reported that there were no treatment-related deaths and no 30-day mortality. Serious adverse events occurred in 10 (20%) of 50 patients (abdominal pain [n = 7], pancreatitis [n = 1], sepsis [n = 1], gastric leak [n = 1]). Median OS was 27.0 months (95% confidence interval [CI], 22.7-32.5 months) from time of diagnosis and 14.2 months (95% CI, 9.7-16.2 months) from time of IRE. Patients with tumors ≤ 3 cm (n = 24) had significantly longer median OS than patients with tumors > 3 cm (n = 26): 33.8 vs 22.7 months from time of diagnosis (P = .002) and 16.2 vs 9.9 months from time of IRE (P = .031). Tumor size was confirmed as the only independent predictor of OS at multivariate analysis. The investigators concluded that percutaneous image-guided IRE of unresectable LAPC is associated with an acceptable safety profile.

Papoulas and co-workers (2018) stated that achieving clear microscopic resection margins following pancreatico-duodenectomy (PD) is challenging particularly in borderline resectable pancreatic carcinoma (BRPC). Positive resection margins has been identified as a major independent prognostic factor; and IRE has emerged as a promising non-thermal ablative method that could be used in the treatment of pancreatic cancer as an adjunct to chemotherapy and surgery. This case report described the successful simultaneous intra-operative IRE and PD in a patient with BRPC, achieving clear microscopic resection margins. Technical aspects and histology showing the effect of IRE were presented. The authors stated that the role of IRE in the treatment of pancreatic adenocarcinoma should be further evaluated in prospective studies.

Guidance from the National Institute for Health and Care Excellence (2017) concluded that "Current evidence on the safety and efficacy of irreversible electroporation for treating pancreatic cancer is inadequate in quantity and quality. Therefore, this procedure should only be used in the context of research."

Furthermore, National Comprehensive Cancer Network's clinical practice guideline on "Pancreatic adenocarcinoma" (Version 2.2018) states that "Irreversible electroporation (IRE) is an ablative technique in which electric pulses are used to create nano-probes that induce cell death similar to apoptosis. This technique has been used in patients with locally advanced pancreatic cancer. IRE may be safe and feasible and may improve survival outcomes. However, due to concerns about complications and technical expertise, the panel does not currently recommend IRE for treatment of locally advanced pancreatic cancer".
Flak and colleagues (2019) reported on the initial experience with IRE of unresectable LAPC in their institution. From October 2013 to March 2018, patients with unresectable LAPC referred for IRE at the Department of Gastrointestinal Surgery, Aalborg University Hospital, were considered for inclusion in the study; 90-day morbidity, 30-day mortality, pain score, length of hospital stay (LOS) and OS were recorded. These researchers included 33 patients receiving 40 IRE ablations in total. The median visual analog scale (VAS) score was 4 (range of 0 to 10) 2 hours after IRE, and 1 (range of 0 to 8) 8 hours after IRE. The median LOS was 1 day (range of 1 to 13 days). Post-procedural complications occurred in 21 of 40 ablations (53 %), of which 8 (20 %) were major (Clavien-Dindo grade III or more). A proportion of the observed complications might be attributed to disease progression and not IRE per se. Although not statistically significant, these investigators observed increased severity of complications in tumors above 3.5 cm. The 30-day mortality was 5 % (2/40). The median OS was 10.7 months (range of 0.6 to 53.8 months) from the initial IRE procedure, and 18.5 months (range of 4.9 to 65.8 months) from time of diagnosis. The authors concluded that in their institution, IRE appeared to be a feasible consolidative treatment of unresectable LAPC with an acceptable safety profile. The oncological outcome of IRE in patients with unresectable LAPC is to be further evaluated in a planned phase-II clinical trial (CHEMOFIRE-2).

An assessment of irreversible electroporation by the Ludwig Boltzmann Institute (2019) concluded: "there is insufficient evidence that IRE is more effective/safe or at least as effective/safe as the conventional standard of care (chemotherapy, chemoradiotherapy or palliative care) in the treatment of inoperable locally advanced pancreatic cancer (LAPC) . . .".

Fibrous Sarcoma

In a single-case study, Qin and colleagues (2017) examined the safety and effectiveness of IRE ablation in unresectable fibrous sarcoma with 2 electrodes. A 74-year old woman with unresectable retroperitoneal malignant fibrous sarcoma was treated with percutaneous IRE; 4 ablations were performed on the mass, which measured 7.3 × 7.0 × 7.5 cm, with 2 electrodes. A contrast-enhanced CT scan 2 months post-operatively showed that the tumor had reduced to 5.1 × 4.0 × 5.2 cm, without obvious enhancement. Any adverse reactions were evaluated as level 1. The authors concluded that in the short-term, the IRE treatment with 2 electrodes for fibrous sarcoma appeared to be safe and effective. These preliminary findings need to be validated by well-designed studies.

Gastric Cancer
In a single-case study, Klein and colleagues (2017) stated that the combination of IRE and electrochemotherapy (IRECT) was safe, well-tolerated, and had anti-tumor activity in a patient with lymph node metastases from gastric cancer. The authors recommended the consideration of further clinical studies in a larger patient cohort to obtain detailed information on tolerability, efficacy and response rate of IRECT in the treatment of deep-seated tumors and cancerous tissue.

Glioma

Garcia and colleagues (2017) noted that IRE has been developed as a promising minimally invasive treatment to ablate spontaneous brain tumors with pulsed electric fields in a canine model. These researchers determined the Peleg-Fermi parameters needed to incorporate pulse number and pulse duration into the therapeutic planning of IRE. A total of 9 dogs were treated with IRE for spontaneous malignant glioma with MRI-based treatment planning. The treatment planning method consisted of building patient-specific finite element models and using them to compute electric fields used in the IRE treatment. They evaluated the predictive power of tumor coverage with electric field alone versus cell kill probability using radiographically confirmed clinical outcomes. Results of post-treatment diagnostic imaging, tumor biopsies, and neurological examinations indicated successful tumor ablation without significant direct neurotoxicity in 6 of the 7 dogs. Objective tumor responses were seen in 4 (80%) of 5 dogs with quantifiable target lesions according to RANO criteria; 2 dogs experienced survivals in excess of 1 year, including 1 dog that resulted in CR to IRE treatment for 5+ years to-date. Tumor fraction exposed to electric field over 600 V/cm was between 0.08 and 0.73, while tumor fraction exposed to electric field over 300 V/cm was between 0.17 and 0.95. Probability of cell kill of greater than or equal to 90% was found in tumor volume fractions between 0.21 and 0.99. The authors concluded that IRE is a safe and effective minimally invasive treatment for malignant glioma and can be predicted with the Peleg-Fermi cell kill probability function. A tumor coverage of greater than or equal to 0.9 at a cell kill probability of greater than or equal to 90% can be used to guide IRE treatments of spontaneous malignant glioma based on the radiographically confirmed clinical outcomes achieved. These preliminary findings need to be further investigated in well-designed human studies.

Pelvic Tumor

In a retrospective, single-center, case-series study, Vroomen and colleagues (2017) described the initial experience with IRE in the treatment of pelvic tumor recurrences; AEs were recorded using Common Terminology Criteria of Adverse Events (CTCAE) 4.0. Clinical outcome was determined using pain- and general-symptom assessment, including Seddon's peripheral nerve injury (PNI) types. Radiological outcome was evaluated by comparing baseline with 3-month
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18F-FDG PET-CT follow-up. A total of 8 patients (9 tumors [recurrences of primary rectal (n = 4), anal (n = 1), sigmoid (n = 1), cervical (n = 1), and renal cell carcinoma (n = 1)]) underwent percutaneous IRE as salvage therapy. Median longest tumor diameter was 3.7 cm (range of 1.2 to 7.0); 1 CTCAE grade III AE (hemorrhage) and 8 CTCAE grade II complications occurred in 6/8 patients: vagino-tumoral fistula (n = 1), lower limb motor loss (n = 3; PNI type II) with partial recovery in 1 patient, hypotonic bladder (n = 2; PNI types I and II) with complete recovery in 1 patient, and upper limb motor loss (n = 2; PNI type II) with partial recovery in both patients. No residual tumor tissue was observed at 3-month follow-up. After a median follow-up of 12 months, local progression was observed in 5/9 lesions (4/5 were greater than 3 cm pre-IRE); 1 lesion was successfully retreated. Debilitating pre-procedural pain (n = 3) remained unchanged (n = 1) or improved (n = 2). The authors concluded that IRE may represent a suitable technique to treat pelvic tumor recurrences, although permanent neural function loss can occur. Complete ablation appeared realistic for smaller lesions; for larger lesions symptom control should be the focus. These preliminary findings need to be validated by well-designed studies that include performances of general neurological examination and nerve conduction studies to objectify the neural function pre- and post-IRE.

This study had several drawbacks: (i) the study design was retrospective and the case number was limited (n = 8), (ii) the heterogeneity of tumor type and size, anatomical location, and treatment indication (symptom palliation or disease control) was high, and (iii) the inability to objectively quantify the level of nerve palsy after the ablation, especially given concomitant temporary muscle injury caused by IRE in some patients. An assessment of irreversible electroporation for prostate cancer by the Ludwig Boltzmann Institute for Health Technology Assessment (2018) concluded that "there is at present inadequate and insufficient evidence to show that IRE . . . have either a positive impact on survival and quality of life or the ability to prevent or delay prostatectomy."

Prostate Cancer

Dong and associates (2018) stated that IRE has been used in clinic for several years. The mechanism of IRE ablation is thermal independent; thus, the main structures (e.g., rectum, urethra, and neurovascular bundle) in prostate are spared during the treatment, which leads to the retention of prostate function. However, various clinical trials have shown that muscle contractions occur during this therapy, which warrants deep muscle anesthesia. Use of high-frequency bipolar pulses has been proposed to reduce muscle contractions during treatment, which has already triggered a multitude of studies at the cellular and animal scale. In this study, these investigators first examined the safety and efficacy of high-frequency bipolar pulses in human prostate cancer ablation. There were 40 men with prostate cancer aged between 51 and 85 years involved in this study. All patients received 250 high-frequency bipolar pulse bursts with
the repeat frequency of 1-Hz. Each burst comprised 20 individual pulses of 5 microseconds, so 1 burst total energized time was 100 microseconds. The number of the electrodes ranged 2 to 6, depending on tumor size. A small amount of muscle relaxant was still needed, so there were no visible muscle contractions during the pulse delivery process. Four weeks after treatment, it was found that the ablation margins were distinct in MRI scans, and the prostate capsule and urethra were retained; 8 patients underwent radical prostatectomy for pathological analysis after treatment, and the results of hematoxylin and eosin staining revealed that the urethra and major vasculature in prostate had been preserved. By overlaying the electric field contour on the ablation zone, the electric field lethality threshold was determined to be 522 ± 74 V/cm. The authors concluded that this study was the first to validate the feasibility of tumor ablation by high-frequency bipolar pulses and provided valuable experience of IRE in clinical applications.

Guidance from the National Institute for Health and Care Excellence (NICE) concluded: "Current evidence on the safety and efficacy of irreversible electroporation for treating prostate cancer is inadequate in quantity and quality. Therefore, this procedure should only be used in the context of research. Studies should include randomised controlled trials comparing the procedure with current standards."

Renal Cell Carcinoma

Pech et al (2011) studied 6 patients scheduled for curative resection of renal cell carcinoma (RCC) to assess the feasibility and safety of ablating RCC tissue by IRE. Irreversible electroporation was performed during anesthesia immediately before the resection with ECG synchronization. Analysis of hematological, serum biochemical, and ECG variables, including ST waveforms and axis deviations, showed no relevant changes during the study period. No changes in cardiac function after IRE therapy were found, but 1 case of supraventricular extrasystole was encountered. Initial histopathologic examination did not identify any immediate adverse effects of IRE. The authors concluded that "IRE seems to offer a feasible and safe technique by which to treat patients with kidney tumours and could offer some potential advantages over current thermal ablative techniques."

In a phase IIa, pilot study, Wendler et al (2015b) determined the effectiveness and feasibility of focal percutaneous IRE in patients with localized RCC as an uro-oncological tumor model. A total of 20 patients with kidney tumor (T1aN0M0) will be recruited. This sample permits an appropriate evaluation of the feasibility and effectiveness of image-guided percutaneous IRE ablation of locally confined kidney tumors as well as functional outcomes. Percutaneous biopsy for histopathology will be performed before IRE, with MRI 1 day before and 2, 7, 27 and 112 days after IRE; at 28 days after IRE the tumor region will be completely resected and analyzed by ultra-thin-layer histology. The authors stated that the IRENE study will investigate over a
short-term observation period (by MRI, post-resection histology and assessment of technical feasibility) whether focal IRE, as a new ablation procedure for soft tissue, is feasible as a percutaneous, tissue-sparing method for complete ablation and cure of localized kidney tumors. Results from the kidney-tumor model can provide guidance for designing an effectiveness and feasibility trial to assess this new ablative technology, particularly in uro-oncology.

Wendler and co-workers (2018) noted that the incidence of RCC has been rising for years. At the same time there is an increasing prevalence of chronic renal failure with subsequent higher morbidity and shorter life expectancy in those affected. In the last decades the gold standard has thus shifted from radical to partial nephrectomy or tumor enucleation. A treatment alternative can be advantageous for selected patients with high morbidity and an increased risk of complications in anesthesia or surgery. Active surveillance represents a controlled delay in the initiation of treatment with a curative intention. Percutaneous RFA and laparoscopic cryoablation are currently the most commonly used treatment alternatives. Newer ablation procedures, such as HIFU, IRE, microwave ablation, stereotactic ablative radiotherapy and high-dose brachytherapy have a high potential in some cases but are still considered experimental for the treatment of RCC.

Catheter-Based Cardiac Ablation

Sugrue and associates (2018) stated that cardiac ablation is an established treatment modality for the management of patients with cardiac arrhythmias. Current approaches to cardiac ablation employ thermal-based energy to achieve lesions within the heart. There are many shortcomings and limitations of thermal-based approaches. Electroporation is a non-thermal alternative approach to ablation that has shown significant promise in animal studies. These investigators performed an extensive review of the literature on the application of electroporation for ablation (both cardiac and collateral cardiac tissue). They examined IRE as a cardiac ablation modality; specifically focusing on the biophysics of electroporation, the limitations of current thermal-based approaches and examined the current data published on electroporation cardiac ablation. The authors concluded that IRE is a fast-growing novel ablation modality that has many advantages over current thermal-based approaches. These researchers stated that current research in animal models showed that IRE can be safely and efficaciously applied to the heart. They noted that although further research is needed, IRE represents an appealing option for the ablation cardiac arrhythmias (e.g., atrial fibrillation, and ventricular arrhythmia).

Sugrue and colleagues (2019) noted that IRE utilizing high voltage pulses is an emerging strategy for catheter-based cardiac ablation with considerable growth in the pre-clinical arena. These researchers carried out a systematic search for articles from 3 sources (PubMed, Embase, and Google Scholar). The primary outcome was the efficacy of tissue ablation with
characteristics of lesion formation evaluated by histologic analysis. The secondary outcome was focused on safety and damage to collateral structures. A total of 16 studies met inclusion criteria. IRE was most commonly applied to the ventricular myocardium (n = 7/16, 44 %) by a LifePak 9 Defibrillator (n = 9/16, 56 %), NanoKnife Generator (n = 2/16, 13 %), or other custom generators (n = 5/16, 31 %). There was significant heterogeneity regarding electroporation protocols. On histological analysis, IRE was successful in creating ablation lesions with variable transmurality depending on the electric pulse parameters and catheter used. The authors concluded that pre-clinical studies suggested that cardiac tissue ablation using IRE showed promise in delivering safe and effective lesions.

Atrial Fibrillation

Wojtaszczyk and colleagues (2018) noted that atrial fibrillation (AF) is one of the most important problems in modern cardiology. Thermal ablation therapies, especially RF, are currently "gold standard" to treat symptomatic AF by localized tissue necrosis. Despite the improvements in re-establishing sinus rhythm using available methods, both success rate and safety are limited by the thermal nature of procedures. Thus, while keeping the technique in clinical practice, safer and more versatile methods of removing abnormal tissue are being investigated. This review focused on IRE, a non-thermal ablation method, which is based on the unrecoverable permeabilization of cell membranes caused by short pulses of high voltage/current. While still in its pre-clinical steps for what concerns interventional cardiac electrophysiology, multiple studies have shown the efficacy of this method on animal models. The observed remodeling process showed this technique as tissue specific, triggering apoptosis rather than necrosis, and safer for the structures adjacent to the myocardium. So far, proposed IRE methodologies are heterogeneous. The number of devices (both generators and applicators), techniques, and therapeutic goals impair the comparability of performed studies. More questions regarding systemic safety and optimal processes for AF treatment remain to be answered. These investigators provided an overview of the electroporation process, and presented different results obtained by cardiology-oriented research groups that employed IRE ablation, with focus of AF-related targets.

Liu and co-workers (2018) stated that AF affects millions of individuals in the U.S; focal therapy is an attractive treatment for AF that avoids the debilitating effects of drugs for disease control. Perhaps the most widely used focal therapy for AF is heat-based RF (heating) ablation, although cryotherapy (cryo) is rapidly replacing it due to a reduction in side effects and positive clinical outcomes. A 3rd focal therapy, IRE, is also being considered. This study was designed to help guide treatment thresholds and compare mechanism of action across heating, cryo, and IRE. Testing was undertaken on HL-1 cells, a well-established cardiomyocyte cell line, to assess injury thresholds for each treatment method. Cell viability, as assessed by Hoechst and PI applications.
staining, was found to be minimal after exposure to temperatures = -40 °C (cryo), = 60 °C (heating), and when field strengths = 1,500 V/cm (IRE) were used. Viability was then correlated to protein denaturation fraction (PDF) as assessed by Fourier Transform Infrared (FTIR) spectroscopy, and protein loss fraction (PLF) as assessed by bicinchoninic acid (BCA) assay after the 3 treatments. These protein changes were assessed both in the supernatant and the pellet of cell suspensions post-treatment. These investigators found that dramatic viability loss (= 50 %) correlated strongly with = 12 % protein change (PLF, PDF or a combination of the 2) in every focal treatment. The authors concluded that these findings helped in defining both cellular thresholds and protein-based mechanisms of action that can be used to improve focal therapy application for AF.

Intracranial Meningioma

Latouche and colleagues (2018) noted that high-frequency IRE is a non-thermal method of tissue ablation that uses bursts of 0.5- to 2.0-microsecond bipolar electric pulses to permeabilize cell membranes and induce cell death. High-frequency IRE has potential advantages for use in neurosurgery, including the ability to deliver pulses without inducing muscle contraction, inherent selectivity against malignant cells, and the capability of simultaneously opening the blood-brain barrier (BBB) surrounding regions of ablation. In a feasibility study, these researchers examined if high-frequency IRE pulses capable of tumor ablation could be delivered to dogs with intracranial meningiomas; 3 dogs with intracranial meningiomas were treated. Subject-specific treatment plans were generated using MRI-based tissue segmentation, volumetric meshing, and finite element modeling. Following tumor biopsy, high-frequency IRE pulses were stereotactically delivered in-situ followed by tumor resection and morphologic and volumetric assessments of ablations. Clinical evaluations of treatment included pre- and post-treatment clinical, laboratory, and MRI examinations and AE monitoring for 2 weeks post-treatment. High-frequency IRE pulses were administered successfully in all subjects. No AEs directly attributable to high-frequency IRE were observed. Individual ablations resulted in volumes of tumor necrosis ranging from 0.25 to 1.29 cm3. In 1 dog, non-uniform ablations were observed, with viable tumor cells remaining around foci of intra-tumoral mineralization. The authors concluded that high-frequency IRE pulses could be delivered to brain tumors, including areas adjacent to critical vasculature, and were capable of producing clinically relevant volumes of tumor ablation; mineralization may complicate achievement of complete tumor ablation. These preliminary findings need to be further investigated.

Abdominal Tumor
Giorgio and colleagues (2019) reported their first results on patients affected by liver and abdominal malignant tumors, unfit for surgery or thermal ablation, treated with US-guided percutaneous IRE. From June 2014 to December 2016, all patients meeting the inclusion criteria (malignant hepatic or abdominal tumors not eligible for resection or thermal ablation) and not meeting the exclusion criteria (heart arrhythmia, pro-hemorrhagic hematological alterations, tumor size greater than 8 cm, presence of a biliary metallic stent) referred to the authors’ institutions were prospectively enrolled to undergo percutaneous US-guided IRE. A total of 16 patients (age range of 59 to 68 years, mean of 63; 7 women) with 18 tumors (diameter range of 1.3 to 7.5 cm) fulfilled the inclusion criteria and were included in the study. Data concerning efficacy (tested by a 1-week CEUS and a 4-week enhanced CT and/or enhanced MRI) and safety were recorded during a 18-month follow-up. All patients completed a 35- to 50-min procedure without complications; 1 patient with 6 cm Klatskin tumor also underwent a 2nd session for 1 month. A 1-week CEUS and a 4-week e-CT and/or e-MRI arterial phase contrast enhancement analysis showed an overall reduction of arterial flow with confirmation of un-enhanced lesions for 7 nodules. After 1 to 18 months of follow-up, no major complications were recorded and no tumor-related death occurred. The lesions of 2 patients disappeared 3 and 6 months following treatment, respectively. The authors concluded that IRE is a promising ablation modality in the treatment of malignant hepatic and abdominal tumors unsuitable for resection or thermal ablation.

CPT Codes / HCPCS Codes / ICD-10 Codes

*Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+".*

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>93650</td>
<td>Intracardiac catheter ablation of atrioventricular node function, atrioventricular conduction for creation of complete heart block, with or without temporary pacemaker placement</td>
</tr>
<tr>
<td>93655</td>
<td>Intracardiac catheter ablation of a discrete mechanism of arrhythmia which is distinct from the primary ablated mechanism, including repeat diagnostic maneuvers, to treat a spontaneous or induced arrhythmia (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
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<tr>
<td>93657</td>
<td>Additional linear or focal intracardiac catheter ablation of the left or right atrium for treatment of atrial fibrillation remaining after completion of pulmonary vein isolation (List separately in addition to code for primary procedure)</td>
</tr>
</tbody>
</table>

ICD-10 codes not covered if selection criteria are met (not all-inclusive):

- C00.0 - C14.8 Malignant neoplasm of lip, oral cavity, and pharynx
- C16.0 - C16.9 Malignant neoplasm of stomach
- C18.0 - C18.9, C20 Malignant neoplasm of colon and rectum
- C22.1 Intrahepatic bile duct carcinoma [peri-biliary]
- C22.8 Malignant neoplasm of liver, primary, unspecified as to type
- C25.0 - C25.9 Malignant neoplasm of pancreas
- C34.00 - C34.92 Malignant neoplasm of lung [pediatric]
- C41.0 - C41.9 Malignant neoplasm of bone [pediatric]
- C49.0 - C49.9 Malignant neoplasm of connective and other soft tissue [pediatric] [fibrous sarcoma]
- C50.001 - C50.929 Malignant neoplasm of breast
- C61 Malignant neoplasm of prostate
- C64.1 - C64.9 Malignant neoplasm of kidney, except renal pelvis
- C65.1 - C65.9 Malignant neoplasm of renal pelvis
- C69.00 - C72.9 Malignant neoplasm of eyes, brain and other part of central nervous system [includes glioma]
- C73 - C75.9 Malignant neoplasm of thyroid and other endocrine glands
- C76.0 Malignant neoplasm of head, face and neck
- C76.2 Malignant neoplasm of abdomen
- C78.00 - C78.2 Secondary malignant neoplasm of lung
- C78.5 Secondary malignant neoplasm of large intestine and rectum
- C78.7 Secondary malignant neoplasm of liver and intrahepatic bile duct
- C78.89 Secondary malignant neoplasm of other digestive organs [peri-biliary and pancreas]
- C79.00 - C79.02 Secondary malignant neoplasm of kidney
- C79.49 Secondary neoplasms of other parts of nervous system [uveal melanoma]
- C79.51 - C79.52 Secondary malignant neoplasm of bone and bone marrow
- C79.81 Secondary malignant neoplasm of breast
- C79.82 Secondary malignant neoplasm of genital organs [prostate]
The above policy is based on the following references:


37. Morgan J, Raut CP. Local treatment for gastrointestinal stromal tumors, leiomyomas, and leiomyosarcomas of the gastrointestinal tract. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed July 2016.


Amendment to
Aetna Clinical Policy Bulletin Number: 0828
Irreversible Electroporation (NanoKnife)

There are no amendments for Medicaid.