Clinical Policy Bulletin: Irreversible Electroporation (NanoKnife)

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Policy

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:

- Breast cancer
- Colorectal liver metastases
- Hepatocellular carcinoma
- Pancreatic cancer
- Pediatric tumors (including bone, lung, and soft tissue cancers)
- Peri-biliary tumors
- Prostate cancer
- Renal cell carcinoma
- 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 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.

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.”

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 neurapraxia 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, high-lighting 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. Radio-frequency 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.

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 locally advanced pancreatic cancer (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 (LPFS); 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.

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 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 (2014) 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 aim of this trial is 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 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.

Fornage and Hwang (2014) described the various techniques used for percutaneous ablation of breast cancer, their preliminary results, and their limitations. The techniques include thermo-therapy (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. Tissue response 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, juxtapaglomerular 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.
Irreversible Electroporation (NanoKnife):

No specific code

The above policy is based on the following references: