
Medical Policy



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***Current Policy Effective Date: 5/1/26**
(See policy history boxes for previous effective dates)

Title: Irreversible Electroporation of Tumors (e.g. Nanoknife) Located in the Liver, Pancreas, Kidney, Lung or Prostate

Description

Irreversible electroporation is a minimally invasive cancer treatment that produces high-frequency electric pulses to create an electric current that permanently damages cell membranes causing cell death due to the inability to maintain homeostasis. Irreversible electroporation produces no thermal effect and appears to preserve vessels, nerves and the extracellular matrix.

Medical Policy Statement

Irreversible electroporation for treatment of primary or metastatic solid tumors of the liver, pancreas, kidney, lung and prostate is **experimental and investigational**. There is insufficient evidence to determine that the technology results in an improvement in net health outcomes.

Inclusionary and Exclusionary Guidelines (Clinically based guidelines that may support individual consideration and pre-authorization decisions)

N/A

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

NA

Other codes (investigational, not medically necessary, etc.):

47384

0600T

0601T

Note: Code(s) may not be covered by all contracts or certificates. Please consult customer or provider inquiry resources at BCBSM or BCN to verify coverage.

Background

Electroporation generates high-frequency electric pulses between two or more electrodes which produces an electric current that damages the cell membrane and allows molecules to pass into the cell passively causing destruction of cancer cells. Electroporation can be temporary (reversible electroporation) or permanent (irreversible electroporation or IRE). In IRE, the cell membrane is permanently damaged causing cell death due to the inability to maintain homeostasis. IRE achieves its action with no thermal effect. IRE appears to preserve vessels, nerves and the extracellular matrix.

Irreversible electroporation (IRE) has been proposed to be tissue-selective with potential advantages compared with current thermal-ablation technologies or radiotherapy. It is a consideration for those individuals who are non-surgical candidates, for example in hepatocellular cancer (HCC).

Liver Tumors

The National Cancer Institute estimates that there will be over 42,240 new cases of liver and intrahepatic bile duct cancer in 2025.⁴ Liver and intrahepatic-bile duct cancer death is the fifth most common cancer related death in males and the seventh most common in females.⁵ Approximately 75% of primary liver tumors are hepatocellular carcinoma (HCC) and the remaining cases are mostly cholangiocarcinoma (CCA). HCC is a primary liver malignant tumor that typically develops in the setting of chronic liver disease.⁶ The prognosis following diagnosis depends on several factors including tumor mass and hepatic reserve.

Pancreatic Cancer

Pancreatic ductal adenocarcinoma has a poor prognosis. The National Cancer Institute estimates that in 2025, there will be over 67,440 new cases of pancreatic cancer in the U.S. and over 51,000 pancreatic cancer deaths.⁴ Pancreatic cancer is the third-leading cause of cancer death in men and women.

Risk factors for developing pancreatic cancer include: cigarette smoking, obesity, alcohol use, diabetes, pancreatitis and hereditary factors.⁸

Surgical resection is considered the only curative therapy although the majority of cases of pancreatic cancer are unresectable. Locally advanced pancreatic cancer accounts for 30% of newly diagnosed cases of pancreatic cancer and is usually unresectable due to local involvement of adjacent vessels. The 5-year overall survival rate is < 5% for locally advanced, unresectable disease.⁹

Kidney Tumors

The National Cancer Institute estimates that there will be over 80,980 new cases of kidney cancer and over 14,000 kidney cancer related deaths in 2025.⁴ At diagnosis, approximately 65% of disease is localized disease.⁴

Lung Tumors

The National Cancer Institute estimates that there will be over 226,650 new cases of lung cancer and over 124,000 lung cancer deaths in 2025.⁴ Lung cancer is the second most commonly diagnosed cancer and the leading cause of cancer death in both men and women.

Prostate Cancer

The National Cancer Institute estimates that there will be over 313,780 new cases of prostate cancer and over 35,000 prostate cancer deaths in 2025.⁴ The 5-year relative survival rate for prostate cancer is 97.9%. The most common risk factor for developing prostate cancer is increasing age.²⁴ Device categories, including IRE, are noted as not currently FDA approved or cleared for the treatment of prostate cancer as focal or whole gland therapy and should only be used in the context of a clinical trial.²⁵

Summary of Evidence

For individuals being treated with locoregional therapy for tumors in the liver who receive irreversible electroporation (IRE), the evidence includes primarily single-arm studies. Relevant outcomes are overall survival, disease-specific survival, symptoms, morbid events, functional outcomes, and quality of life. Irreversible electroporation may be an option for locoregional therapy that is less damaging to nearby blood vessels, bile ducts, and nerves than thermal ablation therapies. Most studies of IRE for liver tumors lack a comparator arm. One comparative study was identified reporting health outcomes but the study is retrospective and included 18 patients treated with IRE. Therefore, there are insufficient data to determine how survival or adverse events compare to other methods for locoregional therapy. There is a lack of standardization on appropriate use. Larger studies are still needed to determine the safety and effectiveness of IRE for HCC local treatment. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with locally advanced pancreatic cancer who receive IRE, the evidence includes single-arm studies. Relevant outcomes are overall survival, disease-specific survival, symptoms, morbid events, functional outcomes, and quality of life. Thermal ablation therapies are not commonly used to treat pancreatic cancer due to the increased risk of trauma to the adjacent major anatomical structures. Irreversible electroporation may be an alternative that does not cause thermal injury to nearby sensitive structures. However, there is a lack of consensus on the optimal IRE treatment protocol. Studies of IRE for pancreatic tumors are single-arm. There are insufficient data to determine whether survival is improved with chemotherapy followed by IRE compared to chemotherapy alone. Two randomized controlled

trials are underway. Prospective, single arm studies suggest a high complication rate. There are no studies reporting functional or quality of life outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals being treated with locoregional therapy for tumors in the kidneys who receive IRE, the evidence includes single-arm studies. Relevant outcomes are overall survival, disease-specific survival, symptoms, morbid events, functional outcomes, and quality of life. Only one study has included more than 10 participants. No comparative data are available. Therefore, there are no data to determine how survival or adverse events compare to other methods for locoregional therapy. There are no studies reporting functional or quality of life outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals being treated with locoregional therapy for tumors in the lungs who receive IRE, the evidence includes single-arm studies. Relevant outcomes are overall survival, disease-specific survival, symptoms, morbid events, functional outcomes, and quality of life. Irreversible electroporation may be an option for locoregional therapy that is less damaging to nearby bronchovascular structures. The ALICE study was a prospective, single-arm study conducted at 2 centers that was stopped early (n=23) due to failing to meet expected efficacy at an interim analysis based on high recurrence rates of 61% at a median follow-up of 1 year. No comparative data are available. Therefore, there are no data to determine how survival or adverse events compare to other methods for locoregional therapy. There are no studies reporting functional or quality of life outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals being treated with locoregional therapy for tumors in the prostate who receive IRE, the evidence includes systematic reviews of observational studies and one prospective nonrandomized trial. Relevant outcomes are overall survival, disease-specific survival, symptoms, morbid events, functional outcomes, and quality of life. Irreversible electroporation is suggested as an option in clinical guidelines for secondary treatment of biopsy-proven recurrence of prostate cancer after radiation. Studies included in systematic reviews for IRE as initial therapy were too heterogeneous to conduct any pooled analyses. Across those studies, reports of biopsy-proven recurrence post-IRE ranged from 0% to 38.9%. Similarly, studies included in the systematic review for IRE as salvage therapy were also too dissimilar to conduct meta-analyses. Rates of local oncological control post-IRE varied from 67% to 77%, although the definition of control also varied across studies. In the PRESERVE study, 71% of patients had negative in-field biopsies at 12 months, which aligned with results from observational studies across systematic review. The small sample sizes, heterogeneity across studies and study populations, and observational study designs all preclude conclusions of efficacy compared to other standard treatments. No subgroup analyses have been conducted across various severities of prostate cancer. Additionally, the short follow-up times are insufficient to establish long-term oncological effects. No comparative data with guideline-recommended standard of care are available. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Rationale

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms. The following is a summary of the key literature to date.

Liver Tumors

Clinical Context and Therapy Purpose

The purpose of irreversible electroporation (IRE) in individuals being treated with locoregional therapy for tumors in the liver is to provide a treatment option that is an alternative to or an improvement on existing therapies.

Populations

The relevant population(s) of interest are individuals being treated with locoregional therapy for hepatocellular carcinoma (HCC) or intrahepatic cholangiocarcinoma (CCA).

These individuals are generally nonsurgical candidates with one or a few small localized HCC or intrahepatic CCA or those for whom local ablation is being used to downstage in preparation for other treatments. Ablative strategies may be used as a curative treatment for small lesions (≤ 3 cm).

IRE has also been used in patients with hepatic metastases.

Interventions

The therapy being considered is IRE. The NanoKnife System is an IRE system cleared in the US for the surgical ablation of soft tissue. The NanoKnife System is a software-controlled low-energy direct-current generator that includes single electrode probes and an optional probe spacer. Voltage is applied between pairs of probes in a series of pulses with adjustable waveform.¹⁶

The IRE procedure is performed under computed tomography guidance and electrocardiography synchronization due to the possibility of muscular spasms caused by high-voltage pulses.¹⁷ IRE is performed under general anesthesia, either percutaneously or open. The physician places 2 to 6 electrodes to bracket the targeted tissue and then applies the series of electrical pulses.¹⁸

Comparators

The following therapies are currently being used to make decisions about locoregional therapy in HCC and intrahepatic CCA: radiofrequency ablation (RFA), microwave ablation (MWA), surgical ablation, percutaneous ethanol injection, cryoablation, arterially directed therapies (i.e., arterial embolization), and radiation therapy (including stereotactic body radiation therapy [SBRT]).

Outcomes

Overall survival, disease-free survival and recurrence, quality of life, complications and adverse events are outcomes of interest. IRE can cause cardiac arrhythmias and uncontrolled muscle contractions.

Median survival for HCC depends on etiology but is generally less than 1 year.¹⁹ Median survival for intrahepatic CCA is generally less than 2 years.²⁰ Therefore trials with outcomes of 1 to 2 years of follow-up are preferred.

There is no consensus as to the optimal approach for or length of post-treatment surveillance in patients undergoing locoregional therapy for HCC.

Review of Evidence

Systematic Reviews

Wade et al (2023) reported results of a systematic review and meta-analysis of ablative and non-surgical therapies for early and very early HCC commissioned by the National Institute for Health Care Research in the UK.²¹ The objective was to review and compare the effectiveness of all current ablative and non-surgical therapies for patients with small HCC (≤ 3 cm). The authors included 37 RCTs ($n > 3700$) comparing ablative and non-surgical therapies to any comparator in the network meta-analysis. The authors identified only 1 non-randomized, comparative study (Sugimoto et al) of IRE; the study compared IRE with RFA ($n = 21$ patients). The Sugimoto study was rated as having a high risk of bias using the Cochrane tool and is reviewed in the following section.

Randomized Controlled Trials

No RCTs were identified.

Nonrandomized Studies

The majority of studies of IRE for liver cancer have not included a comparator and have included samples sizes smaller than 50.^{22,23,24,25,26,27,28,29,30}

Cannon et al (2013) reported results of the largest single-arm study ($n=44$) which was from a prospective registry of patients undergoing IRE for hepatic tumors.²³ The patients had colorectal metastasis ($n=20$), HCC ($n=14$), and other metastasis ($n=10$). 5 patients (11%) had

9 adverse events but all complications resolved within 30 days. Local recurrence free survival at 3, 6, and 12 months was 97%, 95%, and 60%, respectively.

Two comparative studies were identified. Sugimoto et al (2019) reported results of a prospective study in 21 patients with HCC comparing RFA (n = 11) to IRE (n = 10). However, they reported only physiological outcomes; no health outcomes were reported.³¹

Blaise et al (2021) reported results of a retrospective comparative study including patients with HCC and tumor portal invasion treated by percutaneous ablation (n = 44) from 1 center compared to a control group drawn from an external RCT including patients treated with sorafenib or trans-arterial radioembolization (TARE).³² The percutaneous ablation group included 26 patients treated by multi-bipolar radiofrequency ablation (MBP-RFA) alone, 15 by IRE alone and 3 by both MBP-RFA and IRE. 41 patients treated by percutaneous ablation (MBP-RFA or IRE) were matched using propensity-score matching with Forty-one patients either from TARE or sorafenib groups from an external RCT. Median overall survival was 16 months (95% CI, 13 to 24) in the ablation group versus 14 months (95% confidence interval [CI], 9 to 24) in the control group. Median progression-free survival was 7 months (95% CI, 3 to 10) in the ablation group versus 4 months (95% CI, 3 to 6) in the control group.³²

Section Summary: Liver Tumors

Studies of IRE for liver tumors were primarily single-arm studies. One comparative study was identified reporting health outcomes but the study is retrospective and included 18 patients treated with IRE. There was insufficient data to determine how survival or adverse events compare to other methods for locoregional therapy. There were no studies reporting functional or quality of life outcomes. There was a lack of standardization on appropriate use. A protocol for patient selection, procedural parameters, perioperative care, and follow-up of IRE for the treatment of liver tumors have been proposed³³ but the protocol has not yet been tested.

Pancreatic Cancer

Clinical Context and Therapy Purpose

The purpose of IRE in individuals with locally advanced pancreatic cancer is to provide a treatment option that is an alternative to or an improvement on existing therapies.

Review of Evidence

Systematic Reviews

Charallambous et al (2020) reported results of a systematic review of 9 studies of IRE in 460 patients with locally advanced pancreatic cancer published between 2000 and 2019.³⁶ Four of the studies were prospective and 5 were retrospective. None of the studies were comparative. Sample sizes ranged from 10 to 152. Follow-up duration ranged from 3 to 29 months. Adverse events were reported with varying methods across the studies. Intraoperative adverse events were described but rates were not given; hypertensive episodes, hypotensive episodes, and transient supraventricular tachycardia were noted in the studies. The rate of complications ranged from 14% to 53% across the studies but with varying definitions; IRE-related mortality was reported in 5 patients.³⁶

Randomized Controlled Trials

No published RCTs were identified. The DIRECT RCT (NCT03899636; n=528) is registered on clinicaltrials.gov with a completion date of April 2025. The DIRECT trial is a multicenter trial in the US designed to compare chemotherapy alone to chemotherapy followed by IRE in patients with stage III pancreatic cancer. In the United Kingdom, the Treatment of unresectable Locally Advanced Pancreas cancer with Percutaneous Irreversible Electroporation following initial systemic chemotherapy (LAP-PIE; ISRCTN14986389) is also designed to compare chemotherapy alone to chemotherapy plus IRE and had a completion date of June 2025; results have not yet been published.

Nonrandomized Studies

The published studies for IRE in pancreatic cancer are single-arm.^{37,38,39,40,41,42,43,44,45,46,47,}

Holland et al (2019) reported results of the largest prospective, multicenter study including 152 patients with locally advanced pancreatic cancer treated with IRE from 2015 to 2017 from the American Hepato-Pancreato-Biliary Association (AHPBA) Pancreatic Registry.⁵⁸ The registry had a standardized protocol for settings and delivery of energy during the IRE procedure. The median follow-up was 19 months following diagnosis. The overall adverse event rate was 18% and mortality was 2%. Nineteen (13%) patients experienced severe adverse events. Nine (6%) patients experienced local recurrence. Median time to progression, progression free survival, and overall survival from diagnosis were 27 months, 23 months, and 31 months, respectively.⁴⁶

Raurus et al (2020) reported results of the phase 2, prospective, single-arm study conducted in the Netherlands between 2012 and 2017 called the Percutaneous Irreversible Electroporation in Locally Advanced and Recurrent Pancreatic Cancer (PANFIRE-2; NCT01939665).⁴¹ PANFIRE-2 consecutively enrolled 50 study participants: 40 with locally advanced pancreatic cancer and 10 with isolated local recurrence after pancreatic tumor resection. Participants were adults with a maximum tumor diameter of 5 cm. Individuals with ventricular cardiac arrhythmias, an implanted stimulation device, or compromised liver function were excluded. The median hospital stay was 4 days (range, 2 to 21 days). The median largest tumor diameter was 4.0 cm (interquartile range [IQR], 3.7 to 4.6 cm). Fourteen minor and 21 major adverse events occurred in 29 participants (58% overall complication rate). Most minor adverse events involved gastrointestinal symptoms. Serious adverse events included biliary obstruction (n=4; 11%), cholangitis and/or pancreatitis (n=5; 14%) or pancreatic fistula (n=1; 3%), severe hematemesis due to bleeding from a duodenal ulcer (n=1; 3%), duodenal perforation (n=1; 3%), high-grade stenosis of the superior mesenteric artery (n=2; 6%), gastroparesis (n=3; 9%), and chyle leakage (n=1; 3%). Two participants died less than 90 days after IRE. The median overall survival for participants with locally advanced pancreatic cancer was 17 months from the time of diagnosis (95% CI, 15 to 19) and 10 months from IRE (95% CI, 8 to 11). Median local tumor progression-free survival was 10 months (95% CI, 8 to 11).⁵¹

The DIRECT registry study (NCT03899649) is a Food and Drug Administration-approved Investigational Device Exemption study that aims to prospectively investigate the safety and efficacy of IRE treatment combined with chemotherapy compared to chemotherapy alone in patients with pancreatic cancer. It is conducted by the same group as the ongoing DIRECT RCT. Initial results from the multicenter, observational, non-randomized study have been published by Martin et al (2024).⁴⁷ One hundred fourteen individuals were enrolled in the registry over 4 years (n=87 in IRE arm and n=27 in chemotherapy only arm). All patients received standard chemotherapy, with the majority of patients (76.3%) receiving fluorouracil +

leucovorin + irinotecan + oxaliplatin (FOLFIRINOX)-based regimens. Initial results demonstrated equivalent morbidity and mortality rates with IRE + chemotherapy compared to chemotherapy alone. The 30-day all-cause mortality was similar in both groups (2 [2.3%] deaths with IRE vs 1 [3.7%] death in standard of care group). Ninety-day mortality was also similar (5 [6%] deaths and 2 [7.4%] deaths in the IRE and standard of care groups, respectively). Two patients in the IRE group died from treatment-related complications and 1 patient in the chemotherapy group died due to chemotherapy-related complications. Adverse event rates were similar between groups during the 90-day time period after enrollment.

Kidney Tumors

Clinical Context and Therapy Purpose

The purpose of IRE in individuals being treated with locoregional therapy for tumors in the kidney is to provide a treatment option that is an alternative to or an improvement on existing therapies.

Review of Evidence

Systematic Reviews

Hilton et al (2022) reported results of a systematic review of the safety and early oncological outcomes of 10 studies (n=83) of IRE for small renal masses.⁴⁹ The review included studies published through 2020. One cohort study (Canvasser 2017, described below) included 41 participants with renal cell carcinoma. The remaining studies were case series including 10 or fewer participants with renal masses. Follow-up was less than 12 months in 7 of the studies (range, 3 to 34 months). The most frequently reported adverse events were transient hematuria and asymptomatic perirenal hematomas.

Randomized Controlled Trials

No published RCTs were identified.

Nonrandomized Studies

The studies of IRE for renal cell cancer are single-arm and the majority have included 10 or fewer participants.^{50,51,52,53,54,,5556,57,58,59,}

Canvasser et al (2017) reported results of the largest study of IRE for renal masses, including 41 participants with cT1a renal masses treated with IRE in the US between 2013 and 2016.⁵¹ The study was prospective and single center. Mean follow-up was 22 months. No grade II or higher intraoperative or post-operative complications were reported. 2-year local recurrence-free survival was 92%.

Lung Tumors

Clinical Context and Therapy Purpose

The purpose of IRE in individuals being treated with locoregional therapy for tumors in the lung is to provide a treatment option that is an alternative to or an improvement on existing therapies.

Review of Evidence

Randomized Controlled Trials

No published RCTs were identified.

Nonrandomized Studies

Two nonrandomized, prospective, single-arm studies have been published.^{53,60} Thomson et al (2011) includes a mix of tumor types in 38 participants including lung.

Ricke et al (2015) reported results of the ALICE single-arm, multicenter (2 sites) trial.⁶⁰ The ALICE study was designed to enroll 36 participants with primary and secondary lung malignancies and preserved lung function. However, the study was stopped early (n=23) because the expected efficacy was not met at an interim analysis. Median follow-up was 12 months. Sixty-one percent (14/23) of participants developed progressive disease. Four percent (1/23) of participants had stable disease, Four percent (1/23) had partial remission, and 30% (7/23) had complete remission. Pneumothoraces occurred in 48% (11/23) of participants with chest tubes required in 8 individuals.⁶⁰

Prostate Tumors

Clinical Context and Therapy Purpose

The purpose of IRE in individuals being treated with locoregional therapy for tumors in the prostate is to provide a treatment option that is an alternative to or an improvement on existing therapies.

Review of Evidence

Initial Treatment of Low- or Intermediate-Risk Prostate Cancer

Systematic Reviews

Zhang et al (2025)⁶¹ and Prabhakar et al (2024)⁶² published systematic reviews of IRE used for initial treatment of low- or intermediate-risk prostate cancer. Nineteen (N=1452) and 14 (N=899) observational studies were included in Zhang et al and Prabhakar et al, respectively. The heterogeneity across studies did not allow for meta-analyses or pooled results in either review.

Zhang et al reported that the in-field clinically significant prostate cancer rate was reported between 0% to 15.6% in the repeat biopsy after IRE.⁶¹ The retreatment rate was reported from 8% to 36.6%. The 3 years failure-free survival was presented between 90% to 96.8%. The post-operative pad-free rate (an assessment of urinary function) ranged between 96.7% to 100%. The most common reported complications were urinary tract infection and hematuria, and major complications were rare.

Of the studies included in Prabhakar et al that reported on recurrence within the zone of ablation, recurrence ranged from 0% to 38.9% for in-field and 3.6% to 28% for out-of-field recurrence.⁶² There was no standardized follow-up protocol that was followed across studies, but all the studies conducted serial prostate-specific antigen monitoring and a biopsy (6 to 12 months post-IRE). Across the studies, 58% reported that urinary continence returned to the

pretreatment levels and 25% reported a minor decrease in the continence from the baseline at 12-months of follow-up. Erections sufficient for intercourse varied from 44% to 75% at the baseline to 55% to 100% at 12-months of follow-up across all the studies.

The limited sample sizes, heterogeneity across studies, and observational study designs all preclude conclusions of efficacy compared to other standard treatments. Tables 1 and 2 summarize the trials included and the characteristics of included studies.

Table 1. Comparison of Trials Included in Systematic Reviews of IRE for Initial Treatment of Low- or Intermediate-Risk Prostate Cancer

Study	Zhang et al (2025) ⁶¹	Prabhakar et al (2024) ⁶²
Blazevski et al 2020	●	●
Blazevski et al 2021	●	●
Collettini et al 2019	●	●
de la Rosette et al 2023	●	
Gielchinsky and Lev-Cohain 2023	●	
Giganti et al 2019	●	●
Geboers et al 2022		●
Guenther et al 2019	●	
Güteryüz et al 2021	●	
Miñana López et al 2023	●	
Murray et al 2016	●	●
Scheltema et al 2018		●
Scheltema et al 2023	●	●
Shin et al 2023	●	
Ting et al 2016	●	●
Valerio et al 2014	●	●
Valerio et al 2017	●	●
van den Bos et al 2018	●	●
Wang et al 2022	●	●
Yaxley et al 2022	●	●
Zhang et al 2023	●	

IRE: irreversible electroporation.

Table 2. IRE as Initial Therapy Systematic Review Characteristics

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Zhang et al (2025) ⁶¹	Through August 2023	19	Patients with localized prostate cancer who received IRE as focal, initial treatment. ^a	1452 (10 to 429)	Single-arm or comparative observational studies (12 prospective, 7 retrospective)	NR to 60 months
Prabhakar et al (2024) ⁶²	Through May 2023	14	Men with localized prostate cancer treated with IRE as focal, initial treatment.	899 (19 to 217)	Single-arm or comparative observational studies (9 prospective, 5 retrospective)	6 to 44 months

IRE: irreversible electroporation; NR: not reported.

^aSome patients in 2 included trials were treated with IRE as salvage therapy.

Randomized Controlled Trials

No randomized comparative trials were identified that assessed the use of IRE as initial therapy for low- or intermediate-risk prostate cancer.

Nonrandomized Trials

George et al (2025) published the PRESERVE study, a prospective, nonrandomized, multicenter trial evaluating the outcomes of IRE with the NanoKnife System as prostate tissue ablation in patients with intermediate-risk prostate cancer.⁷⁶ Individuals were eligible for inclusion if they were men older than 50 years of age, with magnetic resonance imaging-visible, biopsy-proven, organ confined clinical stage $\leq$ T2c prostate cancer, with prostate-specific antigen (PSA) $\leq$ 15 ng/mL or a PSA density of <0.15 ng/mL² if PSA >15 ng/mL and Gleason grade group 2 or 3. All patients were treated under general anesthesia with IRE with the NanoKnife System, using a treatment margin of ≥ 10 mm. Duration of follow-up was 12 months post-IRE. The primary endpoint was the proportion of patients with an in-field biopsy negative for any amount of Gleason-gradable cancer at 12 months. Patients biopsied before 12 months with a positive in-field biopsy and those missing 12-month biopsy data were considered treatment failures. A total of 121 patients received IRE across 17 sites (median age, 67 years), with a median PSA at baseline of 5.8 ng/dL. The majority of patients included (83%) were White, 8.3% of patients were Black or African American, and 3.3% of patients were Hispanic or Latino. At 12 months, the primary efficacy endpoint showed that 71% of patients (86/121; 95% CI, 62% to 79%) had a negative in-field biopsy. At 12 months, the rate of any prostate cancer occurrence was 45% (49/110) and the rate of clinically significant prostate cancer anywhere was observed in 26% of patients (29/110). The secondary outcome of urinary function had a mean change from baseline to 12 months of 3 in the University of California Los Angeles Expanded Prostate Cancer Index Composite urinary domain total score and a mean change of -2 in the International Prostate Symptom Score total symptom score. Statistics were not reported on these secondary outcomes and no inferences can be made for statistical or clinical significance. At 12 months, 84% of patients with good baseline sexual function maintained erections sufficient for penetration. Fourteen (12%) patients experienced grade ≥ 3 adverse events and 3 patients experienced procedure-related grade 3 adverse events. The results of this trial led to the expanded indication for use of NanoKnife System in prostate tumor ablation.

Secondary Treatment for Biopsy-Proven Recurrence After Radiation

Systematic Reviews

Yilmaz et al (2025) published a systematic review investigating the use of IRE as salvage therapy in men with recurrent prostate cancer after radiation therapy.⁷⁷ Five studies were included and all studies were observational. The heterogeneity across studies did not allow for meta-analyses or pooled results. Following IRE, oncological outcomes varied across studies. Geboers et al (N=74) noted that only 56% of patients underwent biopsy after IRE. Of these patients, 77% of them achieved local oncological control, with a 5-year progression-free survival rate of 60% and overall metastasis-free survival rate of 91%. The lowest rate of local oncological control after IRE across other included studies was 67%. No other studies reported 5-year progression-free survival rates or metastasis-free survival rates. Other functional outcomes included continence status post-IRE, which ranged from 73% to 100% across studies, and erection, with 2 studies reporting a decline in the proportion of patients maintaining erections and 2 studies reporting 50% preservation of erection. The small sample sizes, heterogeneity across studies, and observational study designs all preclude conclusions of efficacy compared to other standard treatments.

Table 3. Comparison of Trials Included in IRE as Salvage Therapy Systematic Review

Studies	Yilmaz et al (2025) ⁶⁴
Blazevski et al 2022	●
Geboers et al 2023	●
Gielchinsky et al 2023	●
Scheltema et al 2017	●
Yaxley et al 2022	●

IRE: irreversible electroporation.

Table 4. IRE as Salvage Therapy Systematic Review Characteristic.

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Yilmaz et al (2025) ⁶⁴	Through June 2024	5	Included men with recurrent prostate cancer after definitive RT treated with salvage IRE.	142 (6 to 74)	Observational single-arm or comparative studies (retrospective or prospective)	12 to 48 months

IRE: irreversible electroporation; RT: radiation therapy.

Randomized Controlled Trials

No RCTs were identified that assessed the use of IRE as salvage therapy for prostate cancer with recurrence after first-line therapy.

Supplemental Information

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN) guidelines for Hepatocellular Carcinoma (v.2.2025) states that 'Irreversible electroporation (IRE) is an emerging modality for tumor ablation'. Larger studies are needed to determine the effectiveness of IRE for local HCC treatment.⁶

NCCN guidelines for biliary tract cancers (v2.2025)⁷, states that ablation is a reasonable alternative to surgical resection for intrahepatic cholangiocarcinoma (CCA), particularly in patients with high-risk disease and 'Options for ablation include radiofrequency ablation, microwave ablation, and irreversible electroporation' for treatment of small, single intrahepatic CCA tumors (<3cm) amenable to complete ablation, whether recurrent or primary.

NCCN guidelines for pancreatic adenocarcinoma (v2.2025)¹⁰ states that 'IRE is an ablative technique in which electric pulses are used to create nanopores to induce cell death. This technique has been used in patients with locally advanced pancreatic cancer and may be safe and feasible and improve survival. However, due to concerns about complications and technical expertise, the Panel does not currently recommend IRE for treatment of locally advanced pancreatic cancer.'

NCCN guidelines for kidney cancer (v1.2026)¹¹ do not refer to irreversible electroporation. The guidelines state that 'Percutaneous ablation (e.g., cryosurgery, radiofrequency ablation, microwave ablation) is an option for the management of clinical stage T1 renal lesions. Percutaneous ablation is suitable for renal masses ≤3 cm. Percutaneous ablation is an option for clinical T1b masses in select patients not eligible for surgery.'

NCCN guidelines for non-small cell lung cancer (NSCLC) (v3.2026)¹³, do not refer to irreversible electroporation. With respect to ablation therapies, the guidelines state that:

- 'Image-guided thermal ablation (IGTA) therapy (e.g., cryotherapy, microwave, radiofrequency) may be an option for select patients' for initial treatment for stage 1A disease.
- 'IGTA may be considered for those patients who are deemed "high risk"—those with tumors that are for the most part surgically resectable but rendered medically inoperable due to comorbidities. In cases where IGTA is considered for high-risk or borderline operable patients, a multidisciplinary evaluation is recommended.'
- 'IGTA is an option for the management of NSCLC lesions <3 cm. Ablation for NSCLC lesions >3 cm may be associated with higher rates of local recurrence and complications.'

- 'There is evidence on the use of IGTA for selected patients with stage 1A NSCLC, those who present with multiple lung cancers, or those who present with locoregional recurrence of symptomatic local thoracic disease.'
- 'In the setting of progression at a limited number of sites on a given line of systemic therapy (oligoprogression), local ablative therapy to the
- oligoprogressive sites may extend the duration of benefit of the current line of systemic therapy.'

NCCN guidelines for prostate cancer (v.5.2026) recommend the use of local therapy as secondary treatment in the case of biopsy-proven recurrence in the prostate after radiation therapy without distant metastatic disease. Local therapy options for patients with recurrence in the prostate include cryotherapy, IRE (status 2B), high-intensity focused ultrasound, reirradiation (i.e., brachytherapy, stereotactic body radiotherapy), and prostatectomy plus pelvic lymph node dissection.¹⁵

National Institute for Health and Care Excellence

The NICE published an interventional procedures guidance in 2017 on IRE electroporation for treating pancreatic cancer.⁶⁵ The guidance stated 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.'

The NICE published an interventional procedure guidance in 2023 on IRE for treating prostate cancer.⁶⁶ The guidance states that "Irreversible electroporation for treating prostate cancer should only be used with special arrangements for clinical governance, consent, and audit or research...Further research should ideally be randomised controlled trials with an appropriate comparator. Further research could also include analysis of registry data or research databases. It should include details of patient selection, details of the procedure (including imaging) and short- and long-term outcomes."

Regulatory Status

The NanoKnife System™ (Angiodynamics) was originally cleared through the 510(k) process (K102329) in 2011 for the surgical ablation of soft tissue. In 2024, the indication for NanoKnife was expanded to surgical ablation of soft tissue, including prostate tissue. FDA product code: OAB.

Government Regulations

National:

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 5

Table 5. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT03899636 ^a	A Randomized, Multicenter, Controlled, Unblinded Study to Assess the Safety and Efficacy of the NanoKnife® System for the Ablation of Unresectable Stage 3 Pancreatic Adenocarcinoma	528	Apr 2025
NCT03899649 ^a	Registry to Evaluate Effectiveness and Safety of the NanoKnife System for the Ablation of Stage 3 Pancreatic Adenocarcinoma	532	Apr 2025
NCT05170802	AHPBA Registry Database (Collection of Clinical Data Related to Pancreatic Cancer & Treatment - Irreversible Electroporation (IRE))	30	Dec 2024
ISRCTN14986389 ^b	Investigating the feasibility of a clinical trial to test using irreversible electroporation to treat locally advanced pancreatic cancer following initial chemotherapy (LAP-PIE)	50	Nov 2024
NCT06886321	Evaluation of the Effectiveness of Irreversible Electroporation for the Treatment of Prostate Cancer	10	Jun 2027
NCT06270043	A Prospective Registry and Longitudinal Study of Patients Undergoing Focal Therapy for Localized Prostate Cancer	500	Feb 2034
NCT05513443	Prostate Cancer IRE Study (PRIS) - A Randomized Controlled Trial Comparing Focal to Radical Treatment in Localized Prostate Cancer	184	Sep 2026
NCT05345444	Radiation Therapy and IRreversible Electroporation for Intermediate Risk Prostate Cancer (RTIRE)	48	Apr 2027
NCT02255890	Registry of Irreversible Electroporation for the Ablation of Prostate Cancer With Use of Nanoknife Device; A Multi-Center, International Registry to Evaluate the Treatment of Prostate Cancer in Terms of Recurrence, Functional Outcomes and Safety.	361	Apr 2025

NCT: national clinical trial.

^a Denotes industry-sponsored or cosponsored trial.

^b ISRCTN registry

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Focal Treatments for Prostate Cancer
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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through January 2026, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
5/1/26	2/17/26		Joint policy established (jf) Vendor Managed: NA

Next Review Date: 1 Qtr, 2027

Pre-Consolidation Medical Policy History

Original Policy Date	Comments
BCN:	Revised:
BCBSM:	Revised:

BLUE CARE NETWORK BENEFIT COVERAGE

POLICY: Irreversible Electroporation of Tumors (e.g. Nanoknife) Located in the Liver, Pancreas, Kidney, Lung or Prostate

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Not covered
BCNA (Medicare Advantage)	See government section
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.