Regence

Medical Policy Manual Surgery, Policy No. 242

Irreversible Electroporation

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Irreversible electroporation 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 CRITERIA

Irreversible electroporation is considered **investigational** for treatment of primary or metastatic solid tumors including, but not limited to, tumors of the liver, pancreas, kidney lung, or prostate.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

1. Radiofrequency Ablation (RFA) of Tumors Other than Liver, Surgery, Policy No. 92
2. Cryosurgical Ablation of Miscellaneous Solid Tumors Outside of the Liver, Surgery, Policy No. 132
3. Magnetic Resonance (MR) Guided Focused Ultrasound (MRgFUS) and High Intensity Focused Ultrasound (HIFU) Ablation, Surgery, Policy No. 139
4. Microwave Tumor Ablation, Surgery, Policy No. 189

5. Ablation of Primary and Metastatic Liver Tumors, Surgery, Policy No. 204
6. Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy for Tumors Outside of Intracranial, Skull Base, or Orbital Sites, Surgery, Policy No. 214
7. Focal Laser Ablation of Prostate Cancer, Surgery, Policy No. 222

BACKGROUND

IRREVERSIBLE ELECTROPORATION

Electroporation generates high-frequent 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. Electroporation can be temporary (reversible electroporation) or permanent (irreversible electroporation [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.[1-3]

Irreversible electroporation (IRE) has been proposed as a treatment for people with inoperable cancer due to comorbidities and/or tumor involvement in nearby critical structures. IRE is being investigated in the treatment of many types of cancer, including liver tumors (hepatocellular carcinoma and cholangiocarcinoma), pancreatic cancer, kidney tumors, lung tumors, and prostate cancer.

REGULATORY STATUS

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. The NanoKnife System™ (Angiodynamics) was originally cleared through the 510(k) process (K102329) in 2011 for the surgical ablation of soft tissue.[4] In 2024, the indication for NanoKnife was expanded to surgical ablation of soft tissue, including prostate tissue.[5]

EVIDENCE SUMMARY

LIVER TUMORS

Hepatocellular Carcinoma (HCC)

Systematic Reviews

Wade (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.[6] 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 one non-randomized, comparative study (Sugimoto, 2019) of IRE; the study compared IRE with radiofrequency ablation (RFA) (n = 21 patients).[7] 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.[8-16]

Two comparative studies were identified. Sugimoto (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.[7]

Blaise (2021) reported results of a retrospective comparative study including patients with HCC and tumor portal invasion treated by percutaneous ablation (n=44) from one center compared to a control group drawn from an external RCT including patients treated with sorafenib or trans-arterial radioembolization (TARE).[17] The percutaneous ablation group included 26 patients treated by multi-bipolar radiofrequency ablation (MBP-RFA) alone, 15 by IRE alone, and three by both MBP-RFA and IRE. Forty-one patients treated by percutaneous ablation (MBP-RFA or IRE) were matched using propensity-score matching with 41 patients either from TARE or sorafenib groups from an external RCT. Median overall survival was 16 months (95% confidence interval [CI], 13 to 24) in the ablation group versus 14 months (95% 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.

Studies Including Metastatic Liver Tumors

Cannon (2013) reported results of the largest single-arm study (n=44) which was from a prospective registry of patients undergoing IRE for hepatic tumors.[9] The patients had colorectal metastasis (n=20), HCC (n=14), and other metastases (n=10). Five patients (11%) had nine 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.

Section Summary: Liver Tumors

Studies of IRE for liver tumors are primarily single-arm. One comparative study was identified reporting health outcomes but the study is retrospective and included 18 patients treated with IRE. Therefore, there is insufficient 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. There is 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 has been proposed but has not been tested.[18]

PANCREATIC CANCER

American Society of Clinical Oncology published recommendations from a meeting of a working group on outcomes in clinical trials of treatments for pancreatic cancer. The group concluded that a 3- to 4-month improvement in overall survival in gemcitabine-eligible and gemcitabine/albumin-bound paclitaxel-eligible individuals and a 4- to 5-month improvement in overall survival for fluorouracil + leucovorin + irinotecan + oxaliplatin (FOLFIRINOX)-eligible individuals was clinically meaningful.[19]

REVIEW OF EVIDENCE

Systematic Reviews

Charallambous (2020) reported results of a systematic review of nine studies of IRE in 460 patients with locally advanced pancreatic cancer published between 2000 and 2019.[20] Four of the studies were prospective and five 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 five patients.

Randomized Controlled Trials

No published RCTs were identified.

Nonrandomized Studies

The published studies for IRE in pancreatic cancer are single-arm.[21-31]

Holland (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.[32] 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.

Raurus (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).[25] 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 four 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).[25]

The DIRECT registry study 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. Initial results from the multicenter, observational, non-randomized study have been published by Martin (2024).[33] One hundred fourteen individuals were enrolled in the registry

over four 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 one [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 one 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.

Section Summary: Pancreatic Cancer

There is a lack of consensus on the optimal IRE treatment protocol.[34] Studies of IRE for pancreatic tumors are single-arm. There is insufficient data to determine whether survival is improved with chemotherapy followed by IRE compared to chemotherapy alone; RCTs are underway. Prospective, single arm studies suggest a high complication rate. There are no studies reporting functional or quality of life outcomes.

KIDNEY TUMORS

Systematic Reviews

Hilton (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.[35] 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 seven 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.[36-45]

Canvasser (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.[37] 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. Two-year local recurrence-free survival was 92%.

Section Summary: Kidney Tumors

Studies of IRE for kidney tumors are single-arm. Only one study has included more than 10 participants. No comparative data are available. Therefore, there is 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.

LUNG TUMORS

The IRE procedure is performed under computed tomography guidance and electrocardiography synchronization due to the possibility of muscular spasms caused by high-voltage pulses.[46] IRE is performed under general anesthesia, either percutaneously or open. The physician places two to six electrodes to bracket the targeted tissue and then applies the series of electrical pulses.[47]

REVIEW OF EVIDENCE

Randomized Controlled Trials

No published RCTs were identified.

Nonrandomized Studies

Two nonrandomized, prospective, single-arm studies have been published.[39, 48] Thomson (2011) includes a mix of tumor types in 38 participants including lung.[39]

Ricke (2015) reported results of the ALICE single-arm, multicenter (two sites) trial.[48] 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, 4% (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 eight individuals.[48]

Section Summary: Lung Tumors

Studies of IRE for lung tumors are single-arm. The ALICE study was a prospective, single-arm study conducted at two 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 one year. No comparative data are available. Therefore, there is 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.

PROSTATE TUMORS

The IRE procedure is performed under computed tomography guidance and electrocardiography synchronization due to the possibility of muscular spasms caused by high-voltage pulses.[46] 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.[47]

Initial Treatment of Low- or Intermediate-Risk Prostate Cancer

<u>Systematic Reviews</u>

Zhang (2025) and Prabhakar (2024) published systematic reviews of IRE used for initial treatment of low- or intermediate-risk prostate cancer.[49, 50] Nineteen (N=1452) and 14 (N=899) observational studies were included in Zhang and Prabhakar, respectively. The heterogeneity across studies did not allow for meta-analyses or pooled results in either review.

Zhang reported that the in-field clinically significant prostate cancer rate was reported between 0% to 15.6% in the repeat biopsy after IRE.[49] The retreatment rate was reported from 8% to 36.6%. The three 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 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.[50] 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 (2025)[49]	Prabhakar (2024)[50]
Blazevski 2020	●	●
Blazevski 2021	●	●
Collettini 2019	●	●
de la Rosette 2023	●	
Gielchinsky and Lev-Cohain 2023	●	
Giganti 2019	●	●
Geboers 2022		●
Guenther 2019	●	
Güleryüz 2021	●	
Miñana López 2023	●	
Murray 2016	●	●
Scheltema 2018		●
Scheltema 2023	●	●
Shin 2023	●	
Ting 2016	●	●
Valerio 2014	●	●
Valerio 2017	●	●
van den Bos 2018	●	●
Wang 2022	●	●
Yaxley 2022	●	●
Zhang 2023	●	

IRE: irreversible electroporation.

Table 2. IRE as Initial Therapy Systematic Review Characteristics

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Zhang 2023[49]	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

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Prabhakar (2024)[50]	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.
[a]Some 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.

Secondary Treatment for Biopsy-Proven Recurrence After Radiation

Systematic Reviews

Yilmaz (2025) published a systematic review investigating the use of IRE as salvage therapy in men with recurrent prostate cancer after radiation therapy.[51] 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 (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 five-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 two studies reporting a decline in the proportion of patients maintaining erections and two 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. Tables 3 and 4 summarize the trials included and the characteristics of included studies.

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

Studies	Yilmaz (2025)[51]
Blazevski 2022	●
Geboers 2023	●
Gielchinsky 2023	●
Scheltema 2017	●
Yaxley 2022	●

IRE: irreversible electroporation.

Table 4. IRE as Salvage Therapy Systematic Review Characteristics

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Yilmaz (2025)[51]	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.

Section Summary: Prostate Tumors

Studies of IRE for prostate tumors include systematic reviews of observational studies investigating IRE as initial treatment or as salvage therapy post-recurrence. 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. The small sample sizes, heterogeneity across studies, and observational study designs all preclude conclusions of efficacy compared to other standard treatments. No comparative data with guideline-recommended standard of care are available, meaning there is no data to determine how survival or adverse events compare to other methods for locoregional therapy.

PRACTICE GUIDELINE SUMMARY

NATIONAL COMPREHENSIVE CANCER NETWORK

The National Comprehensive Cancer Network (NCCN) guidelines for hepatocellular carcinoma (HCC) (v2.2025) states that “Irreversible electroporation (IRE) is an emerging modality for tumor ablation' and that 'Larger studies are needed to determine the effectiveness of IRE for local HCC treatment.”[52]

NCCN guidelines for biliary tract cancers (v2.2025) states that ablation is a reasonable alternative to surgical resection for intrahepatic cholangiocarcinoma (CCA), particularly in patients with high-risk disease.[53] Further, “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) states, “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.”[54]

NCCN guidelines for kidney cancer (v1.2026) do not refer to irreversible electroporation.[55] The guidelines state that 'Percutaneous ablation (eg, 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) (v1.2026) do not refer to irreversible electroporation. With respect to ablation therapies, the guidelines state:[56]

- Image-guided thermal ablation (IGTA) therapy (eg, 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.3.2026) 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.[57] Local therapy options for patients with recurrence in the prostate include cryotherapy, IRE (category 2B), high-intensity focused ultrasound, reirradation (ie, brachytherapy, stereotactic body radiotherapy), and radical prostatectomy plus pelvic lymph node dissection.

SUMMARY

There is not enough research to show that irreversible electroporation improves health outcomes for individuals with solid tumors, including but not limited to the liver, lung, pancreas, prostate and kidney. More research is needed that compares IRE to other available treatments to know whether IRE leads to longer survival and/or less toxicity for individuals with solid tumors. Therefore, the use of IRE to treat solid tumors is considered investigational.

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CODES

Codes	Number	Description
CPT	0600T	Ablation, irreversible electroporation; 1 or more tumors per organ, other than liver or prostate, including imaging guidance, when performed, percutaneous
	0601T	Ablation, irreversible electroporation; 1 or more tumors per organ, including fluoroscopic and ultrasound guidance, when performed, open
	47384	Ablation, irreversible electroporation, liver, 1 or more tumors, including imaging guidance, percutaneous
	55877	Ablation, irreversible electroporation, prostate, 1 or more tumors, including imaging guidance, percutaneous
HCPCS	None	

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