MEDICAL POLICY – 7.01.572
Irreversible Electroporation (NanoKnife® System)

Effective Date: Jan. 3, 2020
Last Revised: Sept. 10, 2019
Replaces: N/A

RELATED MEDICAL POLICIES:
7.01.95 Radiofrequency Ablation of Miscellaneous Solid Tumors Excluding Liver Tumors
7.01.133 Microwave Tumor Ablation
7.01.526 Cryosurgical Ablation of Miscellaneous Solid Tumors Other than Liver, Prostate, or Dermatologic Tumors
8.01.61 Focal Treatments for Prostate Cancer
8.01.521 Radioembolization for Primary and Metastatic Tumors of the Liver

Select a hyperlink below to be directed to that section.

POLICY CRITERIA | CODING | RELATED INFORMATION
EVIDENCE REVIEW | REFERENCES | HISTORY

∞ Clicking this icon returns you to the hyperlinks menu above.

Introduction

Irreversible electroporation is a surgical method used to destroy soft tissue (ablation). It is considered a non-thermal type of ablation since it does not produce heat to destroy tissue but uses direct-current electrical fields applied to soft tissue. These direct-current electrical fields create very small holes in the cell membranes of the tissue where it is applied causing the cell to become more porous, which results in the death of the cell. When these electrical fields are delivered for a long enough time and at a high enough energy level, they will permanently damage the tissue. This method of treatment is unproven. More studies are needed to show that it is safe and effective.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria
Drug

**Irreversible electroporation (NanoKnife® System)**

Investigational

The use of irreversible electroporation (IRE) (ie, NanoKnife® System) is considered investigational for all indications, including but not limited to, ablation of soft tissue or of solid organs, such as the liver or pancreas.

Coding

<table>
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<td>CPT</td>
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<td>48999</td>
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<td>Unlisted procedure, urinary system</td>
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Related Information

N/A

Evidence Review

Description

“The NanoKnife® System delivers a series of high voltage direct current electrical pulses between two electrodes placed within a target area of tissue.”¹ These electrical pulses create nanopore or micropore defects in the cell membrane, increasing the cell’s permeability which
results in cell death. Once enough high voltage electrical pulses have been delivered, the cells become irreversibly damaged. This non-thermal ablation technique is called irreversible electroporation.\textsuperscript{2,3}

**Background**

“The NanoKnife® System delivers a series of high voltage direct current electrical pulses between two electrodes placed within a target area of tissue.”\textsuperscript{1} These electrical pulses create nanopore or micropore defects in the cell membrane, increasing the cell’s permeability which results in cell death. Once enough high voltage electrical pulses have been delivered, the cells become irreversibly damaged. This non-thermal ablation technique is called irreversible electroporation.\textsuperscript{2,3}

It is proposed that this technique causes less damage to tissue compared with thermal or radiation procedures. The reported benefit of this type of minimally invasive ablation procedure is that it can be used in areas where precision and preservation of the surrounding tissue, blood vessels, and nerves is paramount. This conservation of critical structures is thought to lead to fewer adverse effects.\textsuperscript{4} It does require the use of general anesthesia and complete neuromuscular blockade (paralysis) due to the muscle contractions brought about by the strong electric fields created by IRE and the direct stimulation of the neuromuscular junction. It is performed by an interventional radiologist along with an anesthesiologist.\textsuperscript{5}

The procedure involves percutaneously placing several electrodes in the form of long needles around the targeted area of soft tissue. It can also be used in open or laparoscopic intraoperative procedures. Imaging such as ultrasound, magnetic resonance or tomography is used to guide the placement of the needles. The needles are then connected to the IRE generator.\textsuperscript{6} The NanoKnife® System consists of a console with a screen, generator, foot pedal, electrode probe spacer and single-use, disposable electrode probes. The system uses a proprietary algorithm to generate a treatment plan. Depending on the size of the treatment field and the number of electrodes used, the ablation procedure takes place between one and 10 minutes. The electrodes may be repositioned under imaging guidance to extend the targeted treatment area until an entire tumor and appropriate treatment margins have been ablated.\textsuperscript{7}

“The NanoKnife® System has been cleared by the FDA for the surgical ablation of soft tissue. It has not received clearance for the therapy or treatment of any specific disease or condition.”\textsuperscript{8} Some of the areas where IRE has been studied is in the ablation of renal masses, liver lesions, pancreatic adenocarcinoma, lung cancer, prostate cancer, uveal melanoma, and thyroid cancer, among others.
The following are considered contraindications by the manufacturer for using the NanoKnife® System: ablation of lesions in the presence of any implanted electronic devices such as cardiac pacemakers or defibrillators, ablation of lesions near any implanted metal or electronic device, ablation of lesions of the eye, or use in a patient with a history of epilepsy, cardiac arrhythmia, or myocardial infarction. The manufacturer also notes that some of the adverse effects that have been associated with the use of the NanoKnife® system include: arrhythmias, muscle contractions, hemorrhage, mechanical perforation, pneumothorax, infection, and damage to vital anatomical structures such as nerves, blood vessels, ducts or glands.1

Summary of Evidence

For individuals with primary or metastatic liver tumors or locally advanced pancreatic adenocarcinoma, the evidence includes several non-randomized, retrospective cohort studies, comparative registry studies, retrospective single-arm studies, and prospective single-arm studies, all of which had limitations (Narayanan et al. [2017], Cannon et al. [2013], Dollinger et al. [2015], Niessen et al. [2016], and Martin et al. [2015, 2013, 2012]). All sample sizes were small, none of the studies were randomized prospective comparative studies, and follow-up has been limited to short-term intervals. These studies suggest the irreversible electroporation ablation procedure using the NanoKnife® System may be safe, somewhat low-risk, and may enhance survival for small tumors <3 cm, especially for tumors that are located near critical structures that have proven difficult to treat with other ablative methods.

For individuals with prostate cancer, the evidence includes 4 single arm prospective studies (Dong, et al. [2018], Valeriolo et al. [2017, 2014], Ting [2016]). These studies addressed safety and efficacy and adverse effects. Although IRE in the treatment of localized prostate cancer appears to be safe and has low urogenital toxicity, additional studies are needed to optimize patient selection and treatment parameters. The European Section of Urotechnology (ESUT) position statement (2018) stated that further prospective trials are required to assess medium to long term disease control of different ablative modalities for focal treatment of prostate cancer. There are no randomized trial comparisons to conventional radical prostatectomy or radiotherapy and there is limited oncologic follow-up. Wendler (2017) concluded, “…there is not enough evidence of its effectiveness or adverse effects to justify its use as a definitive treatment option for localized prostate cancer.”31

For individuals with renal cell carcinoma (RCC), the evidence includes one prospective single arm phase II study, a single arm prospective study, and a retrospective single arm study (Wendler [2018], Canvasser [2017], Trimmer [2015]). IRE appeared to be safe in the treatment of RCC but was found to require substantial procedural effort. There was also a high rate of microscopic
incomplete ablation found after IRE. Larger series, longer follow-up, and comparisons to conventional nephrectomy are needed.

For individuals with unresectable lung malignancies, the evidence includes a single arm prospective phase II trial and case series (Ricke [2015], Usman [2012]). Expected efficacy of the phase II trial was not met and the trial was stopped prematurely. The case series of 2 patients demonstrated the tumors both recurred at 6 months of follow-up.

Additional well-designed, randomized controlled studies are needed to firmly establish the safety and efficacy of IRE. Some of the current identified challenges are: the procedure itself has been found to be technically demanding, requiring technical skill and precision for the placement of multiple probes, histologic assessment and imaging of ablation zones following IRE need to be better defined due to the apoptotic cell death versus the coagulation necrosis seen with thermal ablation techniques in order to measure standardized response rates and to best determine local tumor recurrence. Currently, there is only one Investigational Device Exemption in place for the treatment of prostate cancer, so all other investigations into other tissue specific conditions are considered off-label.

**Ongoing and Unpublished Clinical Trials**

Some trials that might influence this policy are listed in Table 1.

**Table 1. Summary of Key Trials**

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trials Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<td>NCT02041936</td>
<td>Outcomes of Ablation of Unresectable Pancreatic Cancer Using the NanoKnife Irreversible Electroporation (IRE) System</td>
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<td>Dec 2019</td>
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<td>NCT03614910</td>
<td>Ablation of Unresectable Locally Advanced Pancreatic Cancer with NanoKnife® Irreversible Electroporation (IRE) System: Response and Tolerability</td>
<td>30</td>
<td>May 2023</td>
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<td>NCT03105921</td>
<td>Irreversible Electroporation (NanoKnife®) for the Treatment of Pancreatic Adenocarcinoma</td>
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<td>June 2020</td>
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</tbody>
</table>
NCT No. | Trials Name | Planned Enrollment | Completion Date |
--- | --- | --- | --- |
NCT03504995 | Efficacy and Safety Assessment of IRE of Localized Prostate Cancer | 10 | April 2020 |

NCT: national clinical trial.

Practice Guidelines and Position Statements

**National Institute for Health and Care Excellence (NICE)**

The National Institute for Health and Care Excellence (NICE) (2017) recommended that irreversible electroporation (IRE) for treating pancreatic cancer only be used in the context of research. The recommendation stated: “current evidence on the safety and efficacy of IRE for treating pancreatic cancer is inadequate in quantity and quality.” They noted that further research in the form of randomized controlled trials is needed.

**National Comprehensive Cancer Network**

National Comprehensive Cancer Network (NCCN) clinical practice guideline (Version 3.2019) on “Pancreatic Adenocarcinoma” states that IRE has been used in patients with locally advanced pancreatic cancer and may be considered safe and extend survival. “However, due to concerns about complications and technical expertise, the panel does not currently recommend IRE for treatment of locally advanced pancreatic cancer.”

**Medicare National Coverage**

There is no national coverage determination.

**Regulatory Status**

In 2011 NanoKnife® System (Angiodynamics, Inc.) was cleared through the 510(k) process (K102329) as a class II device. It is described as a low energy direct current non-thermal ablation device and substantially equivalent to its predecessors, the Oncobionic System with 6 Probe
Output (K080202) and the Oncobionic System (K080376). It is intended for the surgical ablation of soft tissue and classified as an electrosurgical cutting and coagulation device.

In May 2011, the FDA granted Investigational Device Exemption (IDE) approval for a clinical trial of the NanoKnife® for the ablation of low-risk, localized prostate cancer.

Product Code: OAB

References


**History**

<table>
<thead>
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<th>Date</th>
<th>Comments</th>
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<tbody>
<tr>
<td>10/01/19</td>
<td>New policy, approved September 10, 2019, effective January 3, 2020. Add to Surgery section. The use of irreversible electroporation (IRE) (ie, NanoKnife® System) is considered investigational for all indications.</td>
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U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

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