BlueCross BlueShield of Alabama

Name of Blue Advantage Policy:

Focal Treatments for Prostate Cancer

Policy #: 596
Category: Surgery

Latest Review Date: September 2020
Policy Grade: C

BACKGROUND:

Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*

    - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
    - *Furnished in a setting appropriate to the patient's medical needs and condition;*
    - *Ordered and furnished by qualified personnel;*
    - *One that meets, but does not exceed, the patient's medical need; and*
    - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

POLICY:

Blue Advantage Blue will treat **the use of any focal or subtotal therapy modality to treat patients with localized prostate cancer** as a **noncovered benefit** and as **investigational**.

*****Refer also to Blue Advantage policy 178: *MRI-Guided Focused Ultrasound (MRgFUS)***
*****Refer also to Blue Advantage *NCD for Cryosurgery of Prostate (230.9)***
*****Refer also to Blue Advantage policy 119: *Radiofrequency Ablation of Solid Tumors Excluding Liver Tumors***
*****Refer also to Blue Advantage policy 337: *Oncologic Applications of Photodynamic Therapy, Including Barrett's Esophagitis***

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

DESCRIPTION OF PROCEDURE OR SERVICE:

Prostate cancer is the second most common cancer diagnosis men receive in the United States, and the behavior of localized prostate cancer can prove difficult to predict on a case-by-case basis. Most men with the cancer undergo whole-gland treatments, which can often lead to substantial adverse effects. In an effort to reduce tumor burden and minimize morbidity associated with radical treatment, investigators have developed a therapy known as focal treatment. Focal treatment seeks to ablate either an "index" lesion (defined as the largest cancerous lesion with the highest-grade tumor), or, alternatively, to ablate nonindex lesions and other areas where cancer has been known to occur. Addressed in this review are several ablative methods used to remove cancerous lesions in localized prostate cancer (e.g., focal laser ablation, high-intensity focused ultrasound, cryoablation, radiofrequency ablation, photodynamic therapy). All methods, except focal laser ablation, use ultrasound guidance to focus on the tumor (focal laser ablation uses magnetic resonance imaging to guide the probe).

Prostate Cancer

According to the National Cancer Institute (NCI), nearly 240,000 new cases were expected to be diagnosed in the United States in 2013 and would be associated with around 30,000 deaths. Autopsy studies in the pre prostate-specific antigen (PSA) screening era have identified incidental cancerous foci in 30% of men 50 years of age, with incidence reaching 75% at age 80 years. However, NCI Surveillance Epidemiology and End Results data show age-adjusted cancer-specific mortality rates for men with prostate cancer have declined from 40 per 100,000 in 1992 to 22 per 100,000 in 2010. This decline has been attributed to a combination of earlier detection via PSA screening and improved therapies.

Diagnosis
Localized prostate cancers may appear very similar clinically at diagnosis. However, they often exhibit diverse risk of progression that may not be captured by accepted clinical risk categories (e.g., D'Amico criteria) or prognostic tools based on clinical findings (e.g., PSA titers, Gleason grade, or tumor stage). In studies of conservative management, the risk of localized disease progression based on prostate cancer–specific survival rates at 10 years may range from 15% to 20% to perhaps 27% at 20-year follow-up. Among elderly men (>70 years) with this type of low-risk disease, comorbidities typically supervene as a cause of death; these men will die with prostate cancer present rather than from the cancer. Other very similar-appearing low-risk tumors may progress unexpectedly rapidly, quickly disseminating and becoming incurable.

Treatments
The divergent behavior of localized prostate cancers creates uncertainty whether to treat immediately. A patient may choose definitive treatment upfront. Surgery (radical prostatectomy) or external-beam radiotherapy (EBRT) are most commonly used to treat patients with localized prostate cancer. Complications most commonly reported with radical prostatectomy or EBRT and with the greatest variability are incontinence (0%-73%) and other genitourinary toxicities (irritative and obstructive symptoms); hematuria (typically ≤5%); gastrointestinal and bowel toxicity, including nausea and loose stools (25%-50%); proctopathy, including rectal pain and bleeding (10%-39%); and erectile dysfunction, including impotence (50%-90%).

American Urological Association guidelines suggest patients with low- and intermediate-risk disease have the option of entering an "active surveillance" protocol, which takes into account patient age, patient preferences, and health conditions related to urinary, sexual, and bowel function. With this approach, the patient will forgo immediate therapy, but continue regular monitoring until signs or symptoms of disease progression are evident, at which point curative treatment is instituted.

Focal Treatment of Localized Prostate Cancer
Given significant uncertainty in predicting behavior of individual localized prostate cancers, and the substantial adverse effects associated with definitive treatments, investigators have sought a therapeutic "middle ground." The latter seeks to minimize morbidity associated with radical treatment in those who may not actually require it while reducing tumor burden to an extent that reduces the chances for rapid progression to incurability. This approach is termed *focal treatment*, in that it seeks to remove - using any of several ablative methods described next - cancerous lesions at high risk of progression, leaving behind uninvolved glandular parenchyma. The overall goal of focal treatment is to minimize the risk of early tumor progression and preserve erectile, urinary and rectal functions by reducing damage to the neurovascular bundles, external sphincter, bladder neck, and rectum. Although focal treatment is offered as an alternative middle approach to management of localized prostate cancer, several key issues must be considered in choosing it. They include patient selection, lesion selection, therapy monitoring, and the modality used to ablate lesions.

Patient Selection
A proportion of men with localized prostate cancer have been reported to have, or develop, serious misgivings and psychosocial problems in accepting active surveillance, sometimes

leading to inappropriately discontinuing it. Thus, appropriate patient selection is imperative for physicians who must decide whether to recommend active surveillance or focal treatment for patients who refuse radical therapy or for whom it is not recommended due to the a risk-benefit balance.

Lesion Selection

Proper lesion selection is a second key consideration in choosing focal treatment of localized prostate cancer. Although prostate cancer has always been regarded as a multifocal disease, clinical evidence shows that between 10% and 40% of men who undergo radical prostatectomy for presumed multifocal disease actually have a unilaterally confined discrete lesion, which, when removed, would "cure" the patient. This view presumably has driven the use of region-targeted focal treatment variants, such as hemiablation of the half of the gland containing tumor, or subtotal prostate ablation via the "hockey stick" method. While these approaches can be curative, the more extensive the treatment, the more likely the functional adverse outcomes would approach those of radical treatments.

The concept that clinically indolent lesions comprise most of the tumor burden in a patient with organ-confined prostate cancer led to development of a lesion-targeted strategy, which is referred to as "focal therapy" in this evidence review. This involves treating only the largest and highest grade cancerous focus (referred to as the "index lesion"), which has been shown in pathologic studies to determine clinical progression of disease. This concept is supported by molecular genetics evidence that suggests a single index tumor focus is usually responsible for disease progression and metastasis. The index lesion approach leaves in place small foci less than 0.5 cm in volume, with Gleason score less than 7 that are considered unlikely to progress over a 10- to 20-year period. This also leaves available subsequent definitive therapies as needed should disease progress.

Identification of prostate cancer lesions-disease localization-particularly the index lesion, is critical to oncologic success of focal therapy; equally imperative to success is the ability to guide focal ablation energy to the tumor and assess treatment effectiveness are additionally important to treatment success. At present, no single modality meets the requirements for all 3 activities (disease localization, focal ablation energy to the tumor, assessment of treatment effectiveness). Systematic transrectal ultrasound (TRUS)–guided biopsy alone has been investigated, but is considered insufficient for patient selection or disease localization for focal therapy.

Multiparametric magnetic resonance imaging (mp-MRI), typically including T1-, T2-, diffusion-weighted imaging, and dynamic contrast-enhanced imaging, has been recognized as a promising modality to risk-stratify prostate cancer and select patients and lesions for focal therapy. Evidence shows mp-MRI can detect high-grade, large prostate cancer foci with performance similar to transperineal prostate mapping (TPM) using a brachytherapy template. For example, for the primary end point definition (lesion, ≥4 mm; Gleason score, ≥3+4), with TPM as the reference standard, sensitivity, negative predictive value, and negative likelihood ratios with mp-MRI were 58% to 73%, 84% to 89%, and 0.3 to 0.5, respectively. Specificity, positive predictive value, and positive likelihood ratios were 71% to 84%, 49% to 63%, and 2.0 to 3.44, respectively. The negative predictive value of mp-MRI appears sufficient to rule out clinically significant prostate cancer and may have clinical use in this setting. However, although mp-MRI

technology has capability to detect and risk-stratify prostate cancer, several issues constrain its widespread use for these purposes (e.g., mpMRI requires highly specialized MRI-compatible equipment; biopsy within the MRI scanner is challenging; interpretation of prostate MRI images requires experienced uroradiologists) and it is still necessary to histologically confirm suspicious lesions using TPM.

Therapy Monitoring

Controversy exists as to the proper end points for focal therapy of prostate cancer. The primary end point of focal ablation of clinically significant disease with negative biopsies evaluated at 12 months posttreatment is generally accepted according to a European consensus report. The clinical validity of MRI to analyze the presence of residual or recurrent cancer compared with histologic findings is offered as a secondary end point. However, MRI findings alone are not considered sufficient in follow-up. Finally, although investigators indicate PSA levels should be monitored, they are not considered valid end points because the utility of PSA kinetics in tissue preservation treatments has not been established.

Modalities Used to Ablate Lesions

Five ablative methods for which clinical evidence is available are considered herein: focal laser ablation (FLA); high-intensity focused ultrasound; cryoablation; radiofrequency ablation (RFA); and photodynamic therapy (PDT). Each method requires placement of a needle probe within a tumor volume followed by delivery of some type of energy that destroys the tissue in a controlled manner. All methods except FLA currently rely on ultrasound guidance to the tumor focus of interest; FLA uses MRI to guide the probe. This evidence review does not cover focal brachytherapy.

Focal Laser Ablation

FLA refers to the destruction of tissue using a focused beam of electromagnetic radiation emitted from a laser fiber introduced transperineal or transrectal into the cancer focus. Tissue is destroyed through thermal conversion of the focused electromagnetic energy into heat, causing coagulative necrosis. Other terms for FLA include photothermal therapy, laser interstitial therapy, and laser interstitial photocoagulation.

High Intensity Focused Ultrasound

High-intensity focused ultrasound works by focusing high-energy ultrasound waves on a single location, which increases the local tissue temperature to over 80°C. This causes a discrete locus of coagulative necrosis of approximately 3x3x10 mm. The surgeon uses a transrectal probe to plan, carry out, and monitor treatment in a real-time sequence to ablate the entire gland or small discrete lesions.

Cryoablation

Cryoablation induces cell death through direct cellular toxicity from disruption of the cell membrane caused by ice-ball crystals and vascular compromise from thrombosis and ischemia secondary to freezing below -30°C. It is performed by transperineal insertion under TRUS guidance of a varying number of cryoprobe needles into the tumor.

Radiofrequency Ablation
RFA uses energy produced by a 50-watt generator with a frequency of 460 kHz. The energy is transmitted to the tumor focus through 15 needle electrodes inserted transperineally under ultrasound guidance into the tissue. It produces an increase in tissue temperature causing coagulative necrosis.

Photodynamic Therapy
PDT uses an intravenous photosensitizing agent that distributes to prostate tissue, followed by delivery of light via transperineally inserted needles. The light induces a photochemical reaction that causes production of reactive oxygen species that are highly toxic and reactive with tissue causing functional and structural damage (i.e., cell death). A major concern with PDT is that real-time monitoring of tissue effects is not possible, and the variable optical properties of prostate tissue complicate assessment of necrosis and treatment progress.

KEY POINTS:
The most recent literature review was updated through August 5, 2020.

Summary
For individuals who have primary localized prostate cancer who receive focal therapy using laser ablation, high-intensity focused ultrasound, cryoablation, radiofrequency ablation, or photodynamic therapy, the evidence includes a high-quality systematic review, studies from a registry cohort, and numerous observational studies. Relevant outcomes are overall survival, disease-specific survival, symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. The evidence is highly heterogeneous and inconsistently reports clinical outcomes. No prospective, comparative evidence was found for focal ablation techniques vs current standard treatment of localized prostate cancer, including radical prostatectomy, external-beam radiotherapy, or active surveillance. Methods have not been standardized to determine which and how many identified cancerous lesions should be treated for best outcomes. No evidence supports which, if any, of the focal techniques leads to better functional outcomes. Although high disease-specific survival rates have been reported, the short follow-up periods and small sample sizes preclude conclusions on the effect of any of these techniques on overall survival rates. The adverse effect rates associated with focal therapies appear to be superior to those associated with radical treatments (e.g., radical prostatectomy, external-beam radiotherapy); however, the evidence is limited in its quality, reporting, and scope. The evidence is insufficient to determine the effects of the technology on health outcomes.

Practice Guidelines and Position Statements
National Comprehensive Cancer Network
The National Comprehensive Cancer Network guidelines for prostate cancer (v.2.2020) recommend cryosurgery or high-intensity focused ultrasound (HIFU) as options for radiotherapy recurrence for nonmetastatic disease; cryosurgery is not recommended for the initial treatment of localized prostate cancer.

National Institute for Health and Care Excellence
The National Institute for Health and Care Excellence (NICE; 2019) issued guidance on the use cryoablation for localized prostate cancer. Cryoablation and high-intensity ultrasound are not recommended for the treatment of localized prostate cancer because there was a lack of evidence on quality-of-life benefits and long-term survival.

American Urological Association
The American Urological Association, along with the American Society for Radiation Oncology and the Society for Urologic Oncology, updated their joint guidelines on the management of clinically localized prostate cancer in 2017. The guidelines included the following recommendation on focal treatments:

> "Clinicians should inform low-risk prostate cancer patients who are considering focal therapy or high intensity focused ultrasound (HIFU) that these interventions are not standard care options because comparative outcome evidence is lacking. (Expert Opinion)"
>
> "Clinicians should inform intermediate-risk prostate cancer patients who are considering focal therapy or HIFU that these interventions are not standard care options because comparative outcome evidence is lacking. (Expert Opinion)"
>
> "Cryosurgery, focal therapy and HIFU treatments are not recommended for men with high-risk localized prostate cancer outside of a clinical trial. (Expert Opinion)"

National Cancer Institute
The National Cancer Institute (NCI) updated their information on prostate cancer treatments in 2018. NCI indicates cryotherapy and HIFU are new treatment options currently being studied in national trials. There is no recommendation for focal treatment of prostate cancer.

U.S. Preventive Services Task Force Recommendations
The U.S. Preventive Services Task Force published recommendations for prostate cancer screening. However, there are no recommendations for focal treatment of prostate cancer.

KEY WORDS:
Focal Laser Ablation, FLA, High-Intensity Focused Ultrasound, HIFU, Cryoablation, Radiofrequency Thermal Ablation, Radiofrequency ablation, RFA, Photodynamic Therapy, PDT, prostate cancer, localized prostate cancer, Visualase® Thermal Therapy System, Ablatherm®, Visual-ICE®, Ice Rod CX, CryoCare®, IceSphere, Photofrin®, psoralen, porfimer sodium, ultraviolet lamps, Tranberg Thermal Therapy System

APPROVED BY GOVERNING BODIES:
Focal Laser Ablation
In 2010, the Visualase® Thermal Therapy System (Medtronic) and in 2015 the TRANBERG Laser fiber (Clinical Laserthermia Systems) were cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process for use to necrotize or coagulate soft tissue through interstitial irradiation or thermal therapy under magnetic resonance imaging

guidance in cardiothoracic surgery, dermatology, otolaryngology, gastroenterology, general surgery, gynecology, head and neck surgery, neurosurgery, plastic surgery, orthopedics, pulmonology, radiology, and urology, for wavelengths 800 to 1064 nm. FDA product code: LLZ, GEX, FRN.

High-Intensity Focused US
In October 2015, the Sonablate® 450 (SonaCare Medical) was cleared for marketing through the 510(k) process after approval of a de novo request and classified the device as class II under the generic name "high intensity ultrasound system for prostate tissue ablation". This device was the first of its kind to be approved in the United States. In November 2015, Ablatherm®-HIFU (EDAP TMS) was cleared for marketing by FDA through the 510(k) process.

Cryotherapy
Some cryotherapy devices cleared for marketing by FDA through the 510(k) process for cryoablation of the prostate are: Visual-ICE® (Galil Medical), Ice Rod CX, CryoCare® (Galil Medical), and IceSphere (Galil Medical), and Cryocare® Systems (Endocare®). FDA product code: GEH.

Radiofrequency Ablation
Radiofrequency ablation devices have been cleared through the 510(k) process by FDA for the general use of soft tissue cutting and coagulation and ablation by thermal coagulation. Under this general indication, RFA may be used as a method to ablate tumors. FDA product code: GEI.

Photodynamic Therapy
FDA has granted approvals to several photosensitizing drugs and light applicators. Photofrin® (porfimer sodium) (Axcan Pharma) and psoralen are photosensitizers, ultraviolet lamps used in the treatment of cancer, were cleared from marketing by FDA through the 510(k) process. FDA product code: FTC.

BENEFIT APPLICATION:
Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

CURRENT CODING:
CPT Codes:
For Transperineal focal laser ablation:

0655T	Transperineal focal laser ablation of malignant prostate tissue, including transrectal imaging guidance, with MR-fused images or other enhanced ultrasound imaging **(Effective 7/1/21)**

53899	unlisted procedure, urinary system.

55880	Ablation of malignant prostate tissue **(Effective 1/1/2021)**
55899	unlisted procedure, male genital system

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POLICY HISTORY:

Adopted for Blue Advantage, April 2015
Available for comment May 2 through June 15, 2015
Medical Policy Group, September 2015
Medical Policy Group, June 2016
Medical Policy Group, September 2016
Medical Policy Group, September 2017
Medical Policy Group, October 2018 **(4):** Updates to Description, Key Points, Governing Bodies and References. No change to policy statement.
Medical Policy Group, September 2019
Medical Policy Group, September 2020
Medical Policy Group, November 2020: 2021 Annual Coding Update. Added CPT 55880 to the Current Coding section.
Medical Policy Group, June 2021: Quarterly coding update. Added code 0655T to Current Coding. Added key word: Tranberg Thermal Therapy System.