



Louisiana

Focal Treatments for Prostate Cancer

Policy # 00484

Original Effective Date: 12/16/2015

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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Whole Gland Cryoablation of Prostate Cancer is addressed separately in medical policy 00022.

Note: Magnetic Resonance-Guided Focused Ultrasound is addressed separately in medical policy 00180.

Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers use of any focal therapy modality to treat patients with localized prostate cancer to be **investigational**.*

Background/Overview

Prostate Cancer

Prostate cancer is the second most common cancer diagnosed among men in the U. S. According to the National Cancer Institute, nearly 240000 new cases were diagnosed in the U. S. in 2013 and would be associated with around 30000 deaths. Autopsy studies in the pre-prostate-specific antigen (PSA) screening era identified incidental cancerous foci in 30% of men 50 years of age, with incidence reaching 75% at age 80 years. However, the National Cancer Institute Surveillance Epidemiology and End Results Program data have shown age-adjusted cancer-specific mortality rates for men with prostate cancer declined from 40 per 100000 in 1992 to 22 per 100000 in 2010. This decline has been attributed to a combination of earlier detection via PSA screening and improved therapies.

Diagnosis

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From a clinical standpoint, different types of localized prostate cancers may appear similar during initial diagnosis. However, prostate cancer often exhibits varying degrees of risk progression that may not be captured by accepted clinical risk categories (eg, D'Amico criteria) or prognostic tools based on clinical findings (eg, 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 from the comorbidities with prostate cancer present rather than from cancer itself. Other very similar-appearing low-risk tumors may progress unexpectedly and 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 are frequently used to treat patients with localized prostate cancer. Complications most commonly reported with radical prostatectomy or external-beam radiotherapy and with the greatest variability are incontinence (0%-73%) and other genitourinary toxicities (irritative and obstructive symptoms); hematuria (typically $\leq 5\%$); 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 have suggested 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, patients forgo immediate therapy but continue regular monitoring until signs or symptoms of disease progression are evident—at which point curative treatment is instituted.

Focal Treatments for Localized Prostate Cancer

Given significant uncertainty in predicting the behavior of individual localized prostate cancers, and the substantial adverse events 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 surgery 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-

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risk of progression, leaving behind uninvolved glandular parenchyma. The overall goal of any 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 treatments are offered as an alternative middle approach to manage localized prostate cancer, several key issues must be considered in choosing it. They include patient selection, lesion selection, therapy monitoring, and modalities 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, the 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 risk/benefit balance.

Lesion Selection

Proper lesion selection is a second key consideration in choosing a focal treatment for localized prostate cancer. Although prostate cancer is a multifocal disease, clinical evidence has shown that between 10% and 40% of men who undergo radical prostatectomy for a 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 regionally targeted focal treatment variants, such as hemiablation of half the gland containing the 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 organ-confined prostate cancer led to the 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 the clinical progression of the 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 cm³ in volume, with a 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.

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Louisiana

Focal Treatments for Prostate Cancer

Policy # 00484

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

Multiparametric magnetic resonance imaging (mpMRI), 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 has shown mpMRI can detect high-grade, large prostate cancer foci with performance similar to transperineal prostate mapping using a brachytherapy template. For example, for the primary endpoint definition (lesion, ≥ 4 mm; Gleason score, $\geq 3+4$), with transperineal prostate mapping as the reference standard, sensitivity, negative predictive value, and negative likelihood ratios with mpMRI 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 mpMRI appears sufficient to rule out clinically significant prostate cancer and may have clinical use in this setting. However, although mpMRI technology has the capability to detect and risk-stratify prostate cancer, several issues constrain its widespread use for these purposes (eg, mpMRI requires highly specialized MRI-compatible equipment; biopsy within the MRI scanner is challenging; interpretation of prostate MRI images requires experienced urologists) and it is still necessary to histologically confirm suspicious lesions using transperineal prostate mapping.

Therapy Monitoring

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

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Louisiana

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Modalities Used to Ablate Lesions

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

Focal Laser Ablation

Focal laser ablation 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. The tissue is destroyed through the thermal conversion of the focused electromagnetic energy into heat, causing coagulative necrosis. Other terms for focal laser ablation include photothermal therapy, laser interstitial therapy, and laser interstitial photocoagulation.

High-Intensity Focused Ultrasound

High-intensity focused ultrasound focuses 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 3×3×10 mm. The surgeon uses a transrectal probe to plan, perform, 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. Using a transperineal prostatemapping template, cryoablation is performed by transperineal insertion under transrectal ultrasound guidance of a varying number of cryoprobe needles into the tumor.

Radiofrequency Ablation

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

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Louisiana

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Photodynamic Therapy

Photodynamic therapy uses an intravenous photosensitizing agent, which distributes through prostate tissue, followed by light delivered transperineally by inserted needles. The light induces a photochemical reaction that produces reactive oxygen species that are highly toxic and causes functional and structural tissue damage (ie, cell death). A major concern with photodynamic therapy is that real-time monitoring of tissue effects is not possible, and the variable optical properties of prostate tissue complicate the assessment of necrosis and treatment progress.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Focal Laser Ablation

In 2010, the Visualase[®] Thermal Therapy System (Medtronic) and, in 2015, the TRANBERG^{CLS} Laser fiber (Clinical Laserthermia Systems) were cleared for marketing by the U.S. FDA through the 510(k) process to necrotize or coagulate soft tissue through interstitial irradiation or thermal therapy under MRI guidance for multiple indications including urology, at wavelengths from 800 to 1064 nm. FDA product code: LLZ, GEX, FRN.

High-Intensity Focused Ultrasound

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 classification 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 U. S. In November 2015, Ablatherm[®]-HIFU (EDAP TMS) was cleared for marketing by the FDA through the 510(k) process.

Cryoablation

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

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Louisiana

Focal Treatments for Prostate Cancer

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Current Effective Date: 01/11/2021

Radiofrequency Ablation

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

Photodynamic Therapy

The FDA has granted approval to several photosensitizing drugs and light applicators. porfimer sodium (Photofrin[®]†; Axcan Pharma) and psoralen are photosensitizer ultraviolet lamps used to treat cancer; they were cleared for marketing by the FDA through the 510(k) process. FDA product code: FTC.

Rationale/Source

Description

Prostate cancer is the second most common cancer diagnosis men receive in the U. S., and the behavior of localized prostate cancer can prove difficult to predict on a case-by-case basis. Most men with prostate cancer undergo whole-gland treatments, which can often lead to substantial adverse events. 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 (eg, 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).

Description

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,

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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 event rates associated with focal therapies appear to be superior to those associated with radical treatments (eg, 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.

Supplemental Information

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 (2019) issued guidance on the use of 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 et al

The American Urological Association, along with the American Society for Radiation Oncology and the Society for Urologic Oncology (2017) updated their joint guidelines on the management of

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clinically localized prostate cancer. 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 NCI (2018) updated its information on prostate cancer treatments. The NCI indicated that cryoablation and HIFU were new treatment options currently being studied in national trials. The NCI offered no recommendation for or against these treatments.

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.

Medicare National Coverage

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 policy are listed in Table 1.

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
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<i>Ongoing</i>			
	Imperial Prostate 4: Comparative Health Research Outcomes of NOvel Surgery in Prostate Cancer	2450	May 2027
NCT03531099	Phase 3, Multicenter, Randomized Study, Evaluating the Efficacy and Tolerability of Focused HIFU Therapy Compared to Active Surveillance in Patients With Significant Low Risk Prostate Cancer	146	Oct 2024

NCT: national clinical trial.

^a Denotes industry-sponsored or cosponsored trial.

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Louisiana

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Policy # 00484

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Current Effective Date: 01/11/2021

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Louisiana

Focal Treatments for Prostate Cancer

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Current Effective Date: 01/11/2021

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Louisiana

Focal Treatments for Prostate Cancer

Policy # 00484

Original Effective Date: 12/16/2015

Current Effective Date: 01/11/2021

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Louisiana

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Policy # 00484

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Policy History

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- 12/03/2015 Medical Policy Committee review
- 12/16/2015 Medical Policy Implementation Committee approval. New Policy.
- 12/01/2016 Medical Policy Committee review
- 12/21/2016 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
- 01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
- 12/07/2017 Medical Policy Committee review
- 12/20/2017 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
- 12/06/2018 Medical Policy Committee review
- 12/19/2018 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
- 01/01/2019 Coding update
- 12/05/2019 Medical Policy Committee review

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Louisiana

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12/11/2019 Medical Policy Implementation Committee approval. Coverage eligibility unchanged. Coding update.

12/03/2020 Medical Policy Committee review

12/09/2020 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

06/21/2021 Coding update

Next Scheduled Review Date: 12/2021

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2019 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
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Louisiana

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Policy # 00484

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CPT	0582T, 53852, 53854, 53899, 55873, 55899, 96570, 96571 Code added eff 1/1/21: 55880 Code added eff 7/1/21: 0655T
HCPCS	C2618, J9600 Code deleted eff 1/1/21: C9747
ICD-10 Diagnosis	C61

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
 1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 3. Reference to federal regulations.

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NOTICE: If the Patient’s health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

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Louisiana

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