Focal Treatments for Prostate Cancer

Policy Number: 8.01.61  Last Review: 2/2022
Origination: 2/2021  Next Review: 2/2023

Blue KC has developed medical policies that serve as one of the sets of guidelines for coverage decisions. Benefit plans vary in coverage and some plans may not provide coverage for certain services discussed in the medical policies. Coverage decisions are subject to all terms and conditions of the applicable benefit plan, including specific exclusions and limitations, and to applicable state and/or federal law. Medical policy does not constitute plan authorization, nor is it an explanation of benefits.

When reviewing for a Medicare beneficiary, guidance from National Coverage Determinations (NCD) and Local Coverage Determinations (LCD) supersede the Medical Policies of Blue KC. Blue KC Medical Policies are used in the absence of guidance from an NCD or LCD.

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will not provide coverage for Focal Treatments for Prostate Cancer. This is considered investigational.

When Policy Topic is covered
n/a

When Policy Topic is not covered
Use of any focal therapy modality to treat patients with localized prostate cancer is investigational.

Considerations
There is no specific CPT code for these focal treatments. It is likely they are reported with CPT code 55899 unlisted procedure, male genital system.

Description of Procedure or Service

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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 [HIFU], cryoablation, radiofrequency ablation [RFA], 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, HIFU, cryoablation, RFA, or photodynamic therapy, the evidence includes systematic reviews, studies from a registry cohort, and numerous observational studies. Relevant outcomes are overall survival (OS), disease-specific survival, symptoms, change in disease status, functional outcomes, quality of life (QoL), and treatment-related morbidity. The evidence is highly heterogeneous and inconsistently reports clinical outcomes. No prospective, comparative evidence was found for the majority of focal ablation techniques versus 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 OS 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 that the technology results in an improvement in the net health outcome.

**Background**

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Prostate Cancer

Prostate cancer is the second most common cancer diagnosed among men in the U.S. According to the National Cancer Institute, nearly 248,530 new cases are estimated to be diagnosed in the U.S. in 2021, associated with around 34,130 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 that age-adjusted cancer-specific mortality rates for men with prostate cancer declined from 40 per 100,000 in 1992 to 19 per 100,000 in 2018. This decline has been attributed to a combination of earlier detection via PSA screening and improved therapies.

Diagnosis

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 of prostate cancer 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. 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% to 73%) and other genitourinary toxicities (irritative and obstructive symptoms); hematuria (typically ≤5%); gastrointestinal and bowel toxicity, including nausea and loose stools (25% to 50%); proctopathy, including rectal pain and bleeding (10% to 39%); and erectile dysfunction, including impotence (50% to 90%).

American Urological Association guidelines have suggested that 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 forego 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-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.\(^{19,20,21,22,23}\) Although focal treatments are offered as an alternative middle approach to manage localized prostate cancer, several key issues must be considered in choosing it. These 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.\(^ {24}\) 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.\(^ {25} \)

**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.\(^ {26,27,28} \) 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.\(^ {29} \) 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.\(^ {30} \) 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.\(^ {31,32} \) This concept is supported by molecular genetics evidence that suggests that a single index tumor focus is usually responsible for disease progression and metastasis.\(^ {33,34} \) The index lesion approach leaves in place small foci less than 0.5 cm\(^3\) in volume, with a Gleason score less...
than 7, that are considered unlikely to progress over a 10- to 20-year period.\textsuperscript{35,36,37} 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 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).\textsuperscript{25,30} Systematic transrectal ultrasound-guided biopsy alone has been investigated; however, it has been considered insufficient for patient selection or disease localization for focal therapy.\textsuperscript{38,39,40,41,42} See separate policy on saturation biopsy for prostate cancer for additional information.

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.\textsuperscript{24,30,38} Evidence has shown mpMRI can detect high-grade, large prostate cancer foci with performance similar to transperineal prostate mapping using a brachytherapy template.\textsuperscript{43} For example, for the primary endpoint definition (lesion, $\geq$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 uroradiologists) and it is still necessary to histologically confirm suspicious lesions using transperineal prostate mapping.\textsuperscript{44}

**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 posttreatment is generally accepted according to a European consensus report.\textsuperscript{38} 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.\textsuperscript{38} Finally, although investigators have indicated that 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.\textsuperscript{35}
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 transperineally or transrectally 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 3x3x10 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 prostate mapping template, cryoablation is performed by transperineal insertion under transrectal ultrasound guidance of a varying number of cryoprobe needles into the tumor.

Radiofrequency Ablation
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. Radiofrequency ablation produces an increase in tissue temperature causing coagulative necrosis.

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.

**Regulatory Status**

**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. Food and Drug Administration (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. In 2021, the FDA granted a breakthrough device designation to a novel artificial intelligence (AI)-enabled focal therapy system for the treatment of localized prostate cancer. The Avenda® Health Focal Therapy System combines an AI-based margin prediction software algorithm with focal laser ablation to deliver treatment directly to the prostate tumor. 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. In June 2018, EDAP received 510(k) clearance for its Focal-One® HIFU device designed for prostate tissue ablation procedures. This device fuses magnetic resonance and 3D biopsy data with real-time ultrasound imaging, allowing urologists to view detailed images of the prostate on a large monitor and direct high-intensity ultrasound waves to ablate the targeted area.

**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.

**Radiofrequency Ablation**
Radiofrequency ablation 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.
In 2020, an FDA advisory committee voted against recommending approval of padeliporfin di-potassium (Tookad®; Steba Biotech), a minimally invasive photodynamic therapy for localized prostate cancer, citing concerns that men with very low-risk disease would potentially choose this therapy instead of active surveillance, despite the unproven long-term benefits and harms of treatment.

**Rationale**
This evidence review was created in April 2015 and has been updated regularly with searches of the PubMed database. The most recent literature update was performed through July 28, 2021.

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

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

This review only assesses evidence on focal therapy for primary localized prostate cancer; it does not consider the recurrent or salvage setting.

**Focal Therapy Overview**

**Clinical Context and Therapy Purpose**
The purpose of focal therapy using either laser ablation, high-intensity focused ultrasound, cryoablation, radiofrequency ablation (RFA), or photodynamic therapy in men who have primary localized prostate cancer is to provide a treatment option that is an alternative to or an improvement on existing therapies.
The question addressed in this evidence review is: Does the use of focal therapy improve the net health outcome in men with primary localized prostate cancer?

The following PICO was used to select literature to inform this review.

**Populations**
The relevant population of interest is men with primary localized prostate cancer.

**Interventions**
The therapy being considered is focal therapy using either laser ablation, high-intensity focused ultrasound, cryoablation, RFA, or photodynamic therapy.

**Comparators**
The following therapies and practices are currently being used to make decisions about managing men with primary localized prostate cancer: surgery (radical prostatectomy), external-beam radiotherapy, and active surveillance.

**Outcomes**
The general outcomes of interest are overall survival (OS), tumor progression and recurrence, incontinence, and sexual dysfunction.

As a therapy situated between active surveillance and definitive therapy, focal therapy is a tissue-sparing procedure intended to maximize QoL (eg, incontinence, sexual dysfunction) by treating the index lesion. Thereafter, follow-up is conducted over at least 10 years to monitor for tumor(s) progression and possible definitive therapy.

**Study Selection Criteria**
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought;
- Studies with duplicative or overlapping populations were excluded.

**Review of Evidence**
No prospective, comparative studies were identified for the majority of the ablative technologies. The evidence primarily comprises systematic reviews of noncomparative studies, case series, and other observational studies. Of note, an RCT of padeliporfin (a photodynamic therapy) versus active surveillance in men with low-risk prostate cancer was published by Azzouzi et al (2017)\textsuperscript{48}; however, an FDA Advisory Committee voted against the approval of this agent in 2020 (see the Regulatory Status section).
Systematic Reviews

A high-quality systematic review published by Valerio et al (2014) compiled the bulk of the evidence available in the literature on the technologies included herein through 2012. This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Only studies that reported actual focal therapy procedures were included. Specific categories of data to be collected were prespecified. Study selection criteria were prespecified, with dual review and data extraction, and senior author arbitration as needed. The quality of included studies was assessed using the Oxford Centre for Evidence-based Medicine level of evidence for therapy. This review and its summarized statistics serve as the initial evidence source for this evidence review. Additional prospective studies of a comparative nature are reviewed in subsequent sections below.

Twenty-five series were included that evaluated a number of focal therapy methods used in the primary setting. The quality of evidence was low to medium, with no study yielding a level of evidence greater than 2b (individual cohort study). Twelve series used high-intensity focused ultrasound (n=226); 6 series (n=1400) used cryoablation (1 study included 1160 treated in the primary setting, 1400 total treated with cryoablation); 3 used focal laser ablation (n=16); 1 used RFA (n=14); and 1 used photodynamic therapy (n=6). In 2 series, focal treatments were mixed or included brachytherapy.

Patients in 12 series included had disease defined as low-risk (n=1109 [56%]), intermediate-risk (n=704 [36%]), and high-risk (n=164 [8%]); risk categories were not available in 13 series. The median age of patients ranged from 56 to 73 years. The prostate-specific antigen (PSA) level of patients ranged from 3.8 to 24 ng/mL. Individual Gleason scores were available in 20 series, with 1503 men having Gleason scores less than 6, 521 had Gleason scores of 7, and 82 had Gleason scores higher than 8. The median follow-up for the series ranged from 0 to 10.6 years. The disease was localized as follows: transrectal ultrasound biopsy in 2 series; transrectal ultrasound biopsy with Doppler ultrasound in 2 series; transrectal ultrasound biopsy plus magnetic resonance imaging (MRI) in 6 series; transperineal template-guided mapping biopsy and multiparametric magnetic resonance imaging (mpMRI) in 4 series. The preoperative assessment was not reported in 11 studies.

In all studies reporting such data in the Valerio et al (2014) systematic review, all known areas of cancer were treated. In no study was it explicitly stated that the index lesion was ablated and that other lesions were left untreated. Biochemical control based on PSA levels was reported in 5 series using the Radiation Therapy Oncology Group-ASTRO Phoenix Consensus Conference criteria. Other definitions used to define biochemical control were the American Society for Radiation Oncology (ASTRO; 5 series), Stuttgart (1 series), and Phoenix plus PSA velocity greater than 0.75 ng/mL annually (1 series). Biochemical control rates ranged from 86% at 8-year follow-up (n=318) to 60% at 5-year follow-up (n=56). Because follow-up was too short, progression to metastatic disease was not reported for most studies in the Valerio et al (2014) review. In those reporting
follow-up data, metastatic progression rates were very low (0% to 0.3%). Although a cancer-specific survival rate of 100% was reported in all series, such rates must be considered in the context of the small numbers of patients in individual studies and the short follow-up (only 3 studies had follow-up >5 years).

Across all studies, the median hospital length of stay was 1 day; other perioperative outcomes were poorly reported. Across studies, the most frequent complications associated with the treatment of prostate cancer, urinary retention, urinary stricture, and urinary tract infection, occurred in 0% to 17%, 0% to 5%, and 0% to 17%, respectively, of patients. Only 5 studies reported all 3 complications. Validated questionnaires were used in 9 series to report urinary functional outcomes; physician-reported rates were used in 5 studies. According to the questionnaires, the pad-free continence rate varied between 95% and 100%, whereas the range of leak-free rates was 80% to 100%. Validated questionnaire data showed erectile functional rates of 54% to 100%, while physician-reported data showed erectile functional rates of 58% to 85%. Other adverse outcomes were poorly reported, particularly the QoL data, with only 3 studies reporting this outcome.

Wolff et al (2015) reported on results of a systematic review of RCTs of radiotherapy versus other nonpharmacologic treatments, including high-intensity focused ultrasound and cryoablation for the treatment of localized prostate cancer. The review followed the Centre for Reviews and Dissemination and Cochrane guidelines for conduct and reporting. The selection criteria and outcomes of interest were prespecified. The search included publications up to February 2014. Reviewers found 2 RCTs of cryotherapy versus radiotherapy but both evaluated whole-gland instead of focal cryotherapy and found no RCTs of high-intensity focused ultrasound versus radiotherapy.

Bates et al (2021) undertook a PRISMA-adhering systematic review that evaluated the evidence base (from January 2000 to June 2020) for focal therapy as a treatment strategy for men with histologically proven, clinically localized prostate cancer as compared to standard management options. Focal therapy interventions included high-intensity focused ultrasound (HIFU), vascular targeted photodynamic therapy, laser ablation, thermal ablation, focal brachytherapy, radiofrequency waves, microwave ablation, focal external-beam radiotherapy, and irreversible electroporation. The comparator intervention included any standard management option such as radical prostatectomy, external beam radiotherapy, whole gland brachytherapy, and active surveillance/monitoring. Overall, 5 articles reporting on 4 primary comparative studies (1 RCT and 3 retrospective nonrandomized comparative studies; N=3961) and 10 eligible systematic reviews were identified. The RCT compared a vascular targeted photodynamic therapy (padeliporfin) versus active surveillance among patients with low-risk prostate cancer and concluded that patients who underwent photodynamic therapy had less progression (28% vs. 58%; adjusted hazard ratio [HR] 0.34; 95% confidence interval [CI], 0.24 to 0.46; p<.0001) and needed less radical therapy (6% vs. 29%; p<.0001) at 24 months. Despite these "positive" results, an FDA staff analysis cited issues with the trial design, endpoints, missing data, and adverse
events of padeliporfin therapy, resulting in the decline to recommend for approval by the FDA advisory committee. One retrospective study comparing focal HIFU with robotic radical prostatectomy found no significant difference in treatment failure at 3 years, with better continence and erectile function recovery with HIFU. The other 2 retrospective cohort studies compared focal laser ablation with radical prostatectomy and external beam radiotherapy and reported significantly worse oncologic outcomes with the focal treatment. Regarding the included systematic reviews, virtually all concluded that there was insufficient high certainty evidence to make definitive conclusions regarding the clinical effectiveness of focal therapy. The authors concluded that the "certainty of the evidence regarding the comparative effectiveness of focal therapy as a primary treatment for localized prostate cancer was low, with significant uncertainties" and that "until higher certainty evidence emerges...focal therapy should ideally be performed within clinical trials or well-designed prospective cohort studies."

**Laser Ablation**

Additional case series and nonrandomized studies have assessed focal laser ablation\(^54,55,56,\) since the Valerio et al (2014) review. In general, studies were small (range, 8 to 25 men), single-arm, lacked long-term follow-up (range, 3 to 6 months) and did not report clinical outcomes (eg, progression-free survival, OS). A recent 5-year follow-up of 30 men who had undergone focal laser ablation for localized prostate cancer\(^54,\) revealed that 25 (83%) remained free from failure over a median of 71 months.\(^57,\) Among these patients, 10 (40%) developed in-field recurrence, with 9 undergoing salvage partial gland ablation with various focal treatments.

**High-Intensity Focused Ultrasound**

Nahar et al (2020) prospectively reported on the short-term outcomes of focal HIFU as a primary treatment of localized prostate cancer in 52 patients at a single center, with a minimum follow-up of 12 months.\(^58,\) Of the 30 patients who underwent biopsy post-ablation, 25 (83.3%) had negative and 5 (16.7%) had positive in-field results. Four (13.3%) patients had a de novo positive out-of-field biopsy and negative in-field biopsy. Prostate-specific antigen was significantly reduced (p<.001) below 2 ng/dL at the 3, 6, 9, and 12 month follow-up in 35 (76.1%), 27 (73%), 21 (72.4%), and 13 (56.5%) patients, respectively. Only 5 major complications were noted in 4 patients; all 4 required transurethral resection of necrotic tissue blocking the bladder outlet after HIFU and 1 had concurrent epididymoorchitis complicated with scrotal abscess requiring incision and drainage. Additionally, urinary symptoms returned to near baseline within 3 to 6 months and sexual function returned to baseline at 12 months.

**Cryoaablation**

Lian et al (2016) reported on long-term results of a case series of 40 low- to intermediate-risk patients treated with primary focal cryoablation between 2006 and 2013 by a single urologist in China.\(^59,\) Biochemical recurrence was defined using the Phoenix definition, and treatment failure was defined as at least 1 positive biopsy or biochemical recurrence. Mean follow-up was 63 months (range, 12 to 92 months). Two (5%) of 40 patients met the criteria for biochemical failure
and 4 (10%) patients experienced treatment failure. Of the men who were potent before cryotherapy, 20 (77%) remained potent after treatment. Ninety-eight percent of the men were completely continent during follow-up.

A matched cohort study by Mendez et al (2015) included 317 men who underwent focal cryoablation with 317 men who underwent whole-gland cryoablation. Patients were entered into the Cryo Online Data Registry between 2007 and 2013. The median age at the time of the procedure was 66 years, and median follow-up was 58 months. All patients were preoperatively potent men who had low-risk disease according to the D'Amico risk criteria and were matched by age at surgery. Outcomes included biochemical recurrence-free survival, defined using ASTRO and Phoenix criteria and assessed by Kaplan-Meier curves. Only patients with PSA nadir data were included in the oncologic outcome analysis.

Functional outcomes were assessed at 6, 12, and 24 months after the procedure for erectile function (defined as the ability to have intercourse with or without erectile aids), urinary continence, urinary retention, and rates of fistula formation. After surgery, 30% (n=95) and 17% (n=55) of the men who underwent whole-gland cryoablation and focal cryoablation, respectively, underwent biopsy, with positive biopsy rates of 12% and 14%, respectively. Biochemical recurrence-free survival rates at 60 months using the Phoenix definition were 80% and 71% in the whole-gland and focal therapy cohorts, respectively, with a HR of 0.827 (p>.1). Using the ASTRO definition, biochemical recurrence-free survival rates were 82% and 73%, respectively (p>.1). Erectile function data at 24 months were available for 172 whole-gland and 160 focal therapy-treated men. Recovery of erectile function was achieved in 47% and 69% of patients in the whole-gland and focal therapy cohorts, respectively (p=.001). Urinary function data at 24 months were available for 307 whole-gland and 313 focal therapy patients. Urinary continence rates were 99% and 100% for the whole-gland and focal therapy groups, respectively (p=.02). Urinary retention rates at 6, 12, and 24 months were reported as 7%, 2%, and 0.6%, respectively, in the whole-gland treated patients versus 5%, 1%, and 0.9%, respectively, in the focal therapy cohort. One fistula was reported in each group.

The Cryo Online Data Registry is a database established and supported by a cryotherapy manufacturer. The data are maintained independently. Physicians submit standardized forms to the database and participation is voluntary. The registry contains case report forms of pretreatment and posttreatment information for patients undergoing whole-gland or partial-gland (focal) prostate cryoablation. Patients are stratified into low-, intermediate-, and high-risk groups. Ward and Jones (2012) have described characteristics of the focal cryoablation registry patients. Biochemical success was defined using the ASTRO definitions. The analysis included 1160 patients treated with focal cryoablation and 5853 treated with whole-gland cryoablation between 1997 and 2007. Reports on the use of focal cryoablation increased dramatically between 1999 (46 reports) and 2005 (567 reports, p<.01). The biochemical success at 36 months for focal cryotherapy was 75.7% and was similar to that of whole-gland cryoablation (75.5%); no significant differences between biochemical success for whole-gland and focal cryoablation
were observed for low-, intermediate-, or high-risk groups (p-values not given). Urinary continence was 98.4% in focal and 96.9% in whole-gland cryoablation.

**Summary of Evidence**
For individuals who have primary localized prostate cancer who receive focal therapy using laser ablation, HIFU, cryoablation, RFA, or photodynamic therapy, the evidence includes systematic reviews, studies from a registry cohort, and numerous observational studies. Relevant outcomes are OS, disease-specific survival, symptoms, change in disease status, functional outcomes, QoL, and treatment-related morbidity. The evidence is highly heterogeneous and inconsistently reports clinical outcomes. No prospective, comparative evidence was found for the majority of focal ablation techniques versus 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 OS 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 that the technology results in an improvement in the net health outcome.

**SUPPLEMENTAL INFORMATION**
The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

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

**National Comprehensive Cancer Network**
The National Comprehensive Cancer Network (NCCN) guidelines for prostate cancer (v.2.2021 ) recommend only cryosurgery and high-intensity focused ultrasound (HIFU) as local therapy options for radiotherapy recurrence in the absence of metastatic disease. Cryotherapy or other local therapies are not recommended as routine primary therapy for localized prostate cancer due to lack of long-term data comparing these treatments to radiation or radical prostatectomy.\(^62\).
**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 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 National Cancer Institute (NCI; 2018) updated its information on prostate cancer treatments. The NCI indicated that cryoablation, photodynamic therapy, 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

<table>
<thead>
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<th>Trial Name</th>
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<th>Completion Date</th>
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<td>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</td>
<td>146</td>
<td>Oct 2025</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

a Denotes industry-sponsored or cosponsored trial.

REFERENCES

25. Passoni NM, Polascik TJ. How to select the right patients for focal therapy of prostate cancer?. Curr Opin Urol. May 2014; 24(3): 203-8. PMID 24625428


Billing Coding/Physician Documentation Information

Billed Coding/Physician Documentation Information

55880 Ablation of malignant prostate tissue, transrectal, with high intensity-focused ultrasound (HIFU), including ultrasound guidance (New Code 1/1/2021)
55899 Unlisted procedure, male genital system; No specific code. See Policy Guidelines
0655T Transperineal focal laser ablation of malignant prostate tissue, including transrectal imaging guidance, with MR-fused images or other enhanced ultrasound imaging (eff 7/01/2021)

ICD-10 Codes
C61 Malignant neoplasm of prostate

Additional Policy Key Words
N/A

Policy Implementation/Update Information
2/1/2022 No policy statement changes.
State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The medical policies contained herein are for informational purposes. The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents Blue KC and are solely responsible for diagnosis, treatment and medical advice. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, photocopying, or otherwise, without permission from Blue KC.