8.01.61	Focal Treatments for Prostate Cancer		
Original Policy Date:	July 31, 2015	**Effective Date:**	November 1, 2021
Section:	8.0 Therapy	**Page:**	Page 1 of 18

Policy Statement

Use of any focal therapy modality to treat patients with localized prostate cancer is considered **investigational**.

Note: Treatment of benign prostatic hyperplasia is not addressed in this policy (e.g., Rezum for BPH). The policy: *2.01.49 Transurethral Water Vapor Thermal Therapy for Benign Prostatic Hyperplasia* was archived on March 1, 2020 and is no longer in effect.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

Effective January 1, 2021, the following CPT code will replace **HCPCS code C9747** to represent a high intensity ultrasound procedure:

- **55880**: Ablation of malignant prostate tissue, transrectal, with high intensity-focused ultrasound (HIFU), including ultrasound guidance

The following CPT code may also be used for this service:

- **55899**: Unlisted procedure, male genital system

The following CPT code describes ultrasound guided transurethral ablation of prostate tissue for treating prostate cancer using thermotherapy with water vapor generated by high energy direct current:

- **0582T:** Transurethral ablation of malignant prostate tissue by high-energy water vapor thermotherapy, including intraoperative imaging and needle guidance

The following CPT code describes radiofrequency generated water vapor thermotherapy:

- **53854**: Transurethral destruction of prostate tissue; by radiofrequency generated water vapor thermotherapy

Effective August 1, 2021, the following CPT code describes transperineal focal laser ablation of malignant prostate tissue with ultrasound guidance:

- **0655T**: Transperineal focal laser ablation of malignant prostate tissue, including transrectal imaging guidance, with MR-fused images or other enhanced ultrasound imaging

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 (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).

Related Policies

- Brachytherapy for Clinically Localized Prostate Cancer Using Permanently Implanted Seeds
- Magnetic Resonance-Guided Focused Ultrasound
- Saturation Biopsy for Diagnosis, Staging, and Management of Prostate Cancer
- Whole Gland Cryoablation of Prostate Cancer

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

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. 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.

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

Background

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.[1.] 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

From a clinical standpoint, different types of localized prostate cancers may appear similar during initial diagnosis.[2.] However, prostate cancer often exhibits varying degrees of risk 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).[3,4,5,6,7.] 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%[8,9.] to 20%[10.] to perhaps 27% at 20-year follow-up.[11.] Among elderly men (³70 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.[12,13.] A patient may choose definitive treatment upfront.[14.] Surgery (radical prostatectomy) or external-beam radiotherapy are frequently used to treat patients with localized prostate cancer.[13,15.] 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 ≤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%).[15.]

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.[16.] 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.[17,18.]

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 remove¾using 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. 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.[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 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.[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).[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.[38,39,40,41,42] See Blue Shield of California Medical Policy: Saturation Biopsy for Diagnosis, Staging, and Management of Prostate Cancer 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.[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. [43] For example, for the primary endpoint definition (lesion, ≥4 mm; Gleason score, ≥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 (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 transperineal prostate mapping.[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.[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.[38,] 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.[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.[19,20,22,23,29,30,33,35,38,45,46,] 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 (see Blue Shield of California Medical Policy: Brachytherapy for Clinically Localized Prostate Cancer Using Permanently Implanted Seeds).

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.[47,]

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.

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 (i.e., 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.

Literature Review
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 (e.g., 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)[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.[49] This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[50] 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.[51.] 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.[52.] 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.[53.] 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.[48.] 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 (e.g., 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.

Cryoablation

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.[60,] 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 cryotherapy registry patients.[61] 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 (e.g., 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.[45.] 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.[16.] 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.[63.] 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.[64.] 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
Ongoing			
NCT04049747	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 2025

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

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Documentation for Clinical Review

- No records required

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	0582T	Transurethral ablation of malignant prostate tissue by high-energy water vapor thermotherapy, including intraoperative imaging and needle guidance
	0655T	Transperineal focal laser ablation of malignant prostate tissue, including transrectal imaging guidance, with MR-fused images or other enhanced ultrasound imaging ***(Code effective 8/1/2021)***
	53854	Transurethral destruction of prostate tissue; by radiofrequency generated water vapor thermotherapy
	55880	Ablation of malignant prostate tissue, transrectal, with high intensity-focused ultrasound (HIFU), including ultrasound guidance ***(Code effective 1/1/2021)***
	55899	Unlisted procedure, male genital system
HCPCS	C9747	Ablation of prostate, transrectal, high intensity focused ultrasound (HIFU), including imaging guidance

Type	Code	Description
		(Deleted code effective 1/1/2021)

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
07/31/2015	BCBSA Medical Policy adoption
11/01/2016	Policy revision without position change
07/01/2017	Coding update
11/01/2017	Policy revision without position change
11/01/2018	Policy revision without position change
02/01/2019	Coding update
12/01/2019	Policy revision without position change
03/01/2020	Coding update
11/01/2020	Annual review. No change to policy statement. Literature review updated.
01/01/2021	Coding Update
02/01/2021	Coding Update
08/01/2021	Coding Update
11/01/2021	Annual review. Policy statement and literature updated.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE	**AFTER** **Blue font: Verbiage Changes/Additions**
Focal Treatments for Prostate Cancer 8.01.61 **Policy Statement:** Use of any focal therapy modality to treat patients with localized prostate cancer is considered **investigational**.	**Focal Treatments for Prostate Cancer 8.01.61** **Policy Statement:** Use of any focal therapy modality to treat patients with localized prostate cancer is considered **investigational**. Note: Treatment of benign prostatic hyperplasia is not addressed in this policy (e.g., Rezum for BPH). The policy: *2.01.49 Transurethral Water Vapor Thermal Therapy for Benign Prostatic Hyperplasia* was archived on March 1, 2020 and is no longer in effect.