Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

Nonprofit corporations and independent licensees of the Blue Cross and Blue Shield Association

***Current Policy Effective Date: 3/1/25**
(See policy history boxes for previous effective dates)

Title: Focal Treatments for Prostate Cancer

Description/Background

PROSTATE CANCER

Prostate cancer is the most common cancer diagnosed in men and the second leading cause of cancer death among men in the U.S. According to the National Cancer Institute, there were an estimated 299,010 new cases and 35,250 deaths in 2024.[1] Prostate cancer is more likely to develop in older men and in non-Hispanic Black men. About 6 in 10 cases are diagnosed in men who are ≥ 65 years of age, and it is rare in men ≤40 years of age. 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.[2,] 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 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 diagnoses.[3,] However, the 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).[,4,5,6,7,8] 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%[9,10] to 20%[11] to perhaps 27% at 20-year follow-up.[12] 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 the cancer itself. Other very similar-appearing low-risk tumors may progress unexpectedly and rapidly, quickly disseminating and becoming incurable.

Staging of prostate cancer entails the size of the tumor, if lymph nodes are affected, if the tumor has metastasized, and the appropriate course of treatment.

Table: Staging of Prostate Cancer

Table: American Joint Committee on Cancer Clinical TNM (tumor-node-metastases) Criteria [13]

The **T category** describes the original (primary) tumor

Stage	Effects of Cancer
T1	Clinically inapparent tumor that is not palpable
T2	Tumor is palpable and confined within prostate
T3	Extraprostatic tumor that is not fixed or does not invade adjacent structures
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles, such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall
NX	Regional lymph nodes were not assessed
N0	No positive regional lymph nodes
N1	Metastases in regional lymph node(s)
M0	No distant metastasis
M1	Distant metastasis

Treatments

The divergent behavior of localized prostate cancers creates uncertainty about whether to treat immediately.[14,15] A patient may choose definitive treatment upfront.[15] Surgery (radical prostatectomy) or external-beam radiotherapy (EBRT) are frequently used to treat patients with localized prostate cancer.[15,17] 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%).[17]

American Urological Association guidelines state that for patients with low-risk prostate cancer, clinicians should recommend active surveillance.[17] 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.[19,20]

Focal Treatments for Localized Prostate Cancer

Given significant uncertainty in predicting the behavior of individual localized prostate cancers, and the substantial adverse effects associated with definitive treatments, investigators have sought a therapeutic middle ground. The latter seeks to minimize morbidity associated with radical treatment in those who may not actually require 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.[21-25]

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.[25] Thus, appropriate patient selection is imperative for physicians who must decide whether to recommend active surveillance or focal treatment for patients who refuse radical therapy or for whom it is not recommended due to the risk/benefit balance.[27]

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 presumed multifocal disease actually have a unilaterally confined discrete lesion, which, when removed, would "cure" the patient.[28-30] 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.[31] 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 development of a lesion-targeted strategy, which is referred to as "focal therapy" in this evidence review.[32] This involves treating only the largest and highest grade cancerous focus (referred to as the "index lesion"), which has been shown in pathologic studies to determine clinical progression of disease.[32,33] This concept is supported by molecular genetics evidence that suggests a single index tumor focus is usually responsible for disease progression and metastasis.[35,36] 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.[37,38,39] This also leaves available subsequent definitive therapies as needed should disease progress.

Identification of prostate cancer lesions (disease localization) particularly the index lesion, is critical to oncologic success of focal therapy; equally imperative to success is the ability to guide focal ablation energy to the tumor and assess treatment effectiveness. At present, no single modality reliably meets the requirements for all three activities (disease localization, focal ablation energy to the tumor, assessment of treatment effectiveness).[27,31] Systematic transrectal ultrasound–guided biopsy alone has been investigated; however it has been considered insufficient for patient selection or disease localization for focal therapy.[40-44]

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.[26,32,40] Evidence has shown mp-MRI can detect high-grade, large prostate cancer foci with performance similar to transperineal prostate mapping using a brachytherapy template.[45] For example, for the primary end point 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 (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.[46]

Modalities Used to Ablate Lesions

The following ablative methods for which clinical evidence is available are considered herein: focal laser ablation (FLA); high-intensity focused ultrasound (HIFU); cryoablation; radiofrequency ablation (RFA); photodynamic therapy, irreversible electroporation and MRI-guided transurethral ultrasound ablation (TULSA).[21,22.24,25,31,32,35,37,40,47,48,51,71] 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 and MRI-guided TULSA currently rely on ultrasound guidance to the tumor focus of interest; focal laser ablation and MRI-guided TULSA use MRI to guide the probe. NanoTherm uses magnetic nanoparticles and an alternating magnetic field to create heat and local ablation in the ablation of prostate cancer. This technology was undergoing a clinical study NCT05010759 which has been terminated in 2023 due inadequate enrollment and the company changing direction.

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. Tissue is destroyed through 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.[49]

High-Intensity Focused Ultrasound

High-intensity focused ultrasound focuses high-energy ultrasound waves on a single location, which increase 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 uses 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 (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 assessment of necrosis and treatment progress.

Irreversible electroporation
Electroporation generates high-frequent electric pulses between two or more electrodes which produces an electric current that damages the cell membrane and allows molecules to pass into the cell passively. Electroporation can be temporary (reversible electroporation) or permanent (irreversible electroporation or IRE). In IRE the cell membrane is permanently damaged causing cell death due to the inability to maintain homeostasis. IRE achieves its action with no thermal effect. IRE appears to preserve vessels, nerves and the extracellular matrix.[51]

MRI-guided transurethral ultrasound ablation (TULSA)
MRI-guided transurethral ultrasound ablation (TULSA) uses MRI to deliver high-energy sound waves, producing very high temperature to destroy tumor cells in a targeted manner.
It allows for precise targeting and controlled ablation of prostate. This precise approach is part of what defines it as a focal therapy.

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 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 FDA through the 510(k) process for cryoablation of the prostate are: 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 FDA through the 510(k) process for general use for soft tissue cutting and coagulation and ablation by thermal coagulation. Under this general indication, radiofrequency ablation may be used to ablate tumors.
FDA product code: GEI.

Photodynamic Therapy
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 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.

Irreversible electroporation
The NanoKnife System was cleared through the 510(k) process (K102329) in 2011 for the surgical ablation of soft tissue. NanoKnife has not received clearance for the treatment of any specific disease.

MRI-guided transurethral ultrasound ablation (TULSA)
The High Intensity Ultrasound System for Prostate Tissue Ablation, TULSA-PRO System (K191200) received 510(k) Premarket clearance in 2019.

Medical Policy Statement

Cryoablation of the prostate is considered **established** when criteria are met.

High-intensity focused ultrasound (HIFU) ablation of the prostate is considered **established** when criteria are met.

Focal therapy with laser ablation, radiofrequency ablation, photodynamic therapy, magnetic nanoparticles, irreversible electroporation and MRI-guided transurethral ultrasound ablation (TULSA) for the initial or salvage treatment of localized prostate cancer are considered **experimental/investigational**, as they have not been shown to improve net health outcomes.

Inclusionary and Exclusionary Guidelines

Inclusions:
Cryoablation for the **initial treatment** of clinically localized (organ-confined) prostate cancer.

Cryoablation or High-Intensity Focused Ultrasound (HIFU) for local **treatment of recurrent** prostate cancer when:

1. Primary treatment of prostate cancer was radiation therapy; AND
2. All of the following:
   - Original clinical stage T1-T2, NX or N0
   - Life expectancy >10 y
   - PSA now <10 ng/mL; AND
3. Transrectal ultrasound guided biopsy is positive; AND
4. Studies are negative for distant metastases

Exclusions:

- Localized treatment of recurrent prostate cancer with Cryoablation or high-intensity focused ultrasound (HIFU) that does not meet criteria.
- HIFU for the initial treatment of clinically localized prostate cancer.

Focal laser ablation, radiofrequency ablation, photodynamic therapy, magnetic nanoparticles, irreversible electroporation or MRI-guided transurethral ultrasound ablation (TULSA) for the initial or salvage treatment of localized prostate cancer are considered **experimental/investigational.**

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

55880	55873	55899	

Other codes (investigational, not medically necessary, etc.):

51721	55881	55882	
0600T	0601T	0655T	0739T

Individual policy criteria determine the coverage status of the CPT/HCPCS code(s) on this policy. Codes listed in this policy may have different coverage positions (such as established or experimental/investigational) in other medical policies.

Rationale

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function, including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to 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 a technology, 2 domains are examined: the relevance and the 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. RCTs 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.

FOCAL THERAPY OVERVIEW

Clinical Context and Therapy Purpose

The purpose of focal therapy using either laser ablation, high-intensity focused ultrasound (HIFU), 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 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 HIFU, cryoablation, radiofrequency ablation, photodynamic therapy, irreversible electroporation, or MRI-guided transurethral ultrasound ablation (TULSA)

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 quality of life (eg, incontinence, sexual dysfunction) by treating the index lesion. An international multidisciplinary panel of urologists, radiologists and biomedical engineers recommended that follow-up after focal therapy should be a minimum of 5 years and should include multiparametric MRI, biopsies, assessment of erectile function, QoL, urinary symptoms and incontinence.[52]

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 longer 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; however, RCTs comparing focal therapy to radical therapy are underway for focal prostate ablation (NCT03668652, NCT06223295), irreversible electroporation (NCT01835977), and HIFU (NCT03531099); see Table 1. The current evidence is primarily comprised of systematic reviews of noncomparative studies, case series, and other observational studies. The pivotal trial for the irreversible electroporation system (NanoKnife) in the US is a single arm study and has only preliminary results available.[71] Prospective, comparative studies compared to standard therapy are needed therefore, noncomparative studies and case series will not be discussed further.
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)[50]; 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.[53]

The quality of evidence was rated as low to medium, with no study yielding a level of evidence greater than 2b (individual cohort study). Twelve series used HIFU (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 radiofrequency ablation (n=14); and 1 used photodynamic therapy (n=6). In 2 series, focal treatments were mixed or included brachytherapy.

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 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 in 54% to 100%, while physician-reported data showed erectile functional rates of 58% to 85%. Other adverse outcomes were poorly reported, particularly the quality of life 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 treatment of localized prostate cancer.[55] 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.[56] 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.[50] 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."

Hopstaken et al (2022) reported on an updated systematic review on focal therapy in localized prostate cancer in terms of functional and oncological outcomes that included 72 studies published between October 2015 and December 31, 2020.[57] Of the included studies, 27 reported on HIFU, 9 on irreversible electroporation, 11 on cryoablation, 8 each on focal laser ablation and focal brachytherapy, 7 on photodynamic therapy, 2 on FRA, and 1 on prostatic artery embolization. Results revealed photodynamic therapy and HIFU to have potentially promising results. HIFU studies reported a median of 95% pad-free)regarding continence) patients and a median of 85% of patients with no clinically significant cancer in the treated area. No changes in continence were noted and a median of 90% of patients were without clinically significant cancer in the treated area among those receiving photodynamic therapy. Both treatments were well-tolerated. Despite these positive results, the authors noted that the majority of the studies concerning focal therapy are still in an early research stage and that definitive proof of oncological effectiveness of focal therapy against standard of care is still pending.

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, overall survival). 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.[61] Among these patients, 10 (40%) developed in-field recurrence, with 9 undergoing salvage partial gland ablation with various focal treatments.

High-Intensity Focused Ultrasound

Duwe et al (2023) described a prospective series of 29 patients with unilateral prostate cancer treated with focal HIFU between 2016 and 2021 at a single institution in Germany.[62] Median follow-up after HIFU was 23 months. Median age at time of HIFU was 67 years. Prostate cancer was detected in 13/29 (45%) patients histologically at one year. Another 7/29 patients (24%) were diagnosed with prostate cancer at two years. One patient developed local metastatic disease 2 years after HIFU. 70% of patients maintained sufficient erectile function for intercourse and 97% reported maintenance of urinary continence.

Reddy et al (2022) reported results of 1379 participants with 6 months or more of follow-up in the HIFU Evaluation and Assessment of Treatment (HEAT) registry from 2005-2020 in 13 centers in the United Kingdom.[63] Median follow-up was 32 months; 325 (24%) participants had 5 or more years of follow-up. The median age was 66 years. Failure-free survival at 7 years was 69% (95% CI, 64% to 74%). 252 participants had repeat focal treatment due to residual or recurrent cancer. 92 participants required salvage whole-gland treatment.

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.[64] Of the 30 patients who underwent biopsy postablation, 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.

National Comprehensive Cancer Network® (NCCN) Clinical Practice Guidelines in Oncology, Prostate Cancer, state:

> HIFU has been studied for treatment of radiation recurrence. Analysis of a prospective registry of men treated with HIFU for radiation recurrence revealed median biochemical recurrence-free survival at 63 months, 5-year (overall survival) of 88%, and cancer-specific survival of 94%. Morbidity was acceptable, with a grade III/IV complication rate 3.6%. Analysis of a separate prospective registry showed that 48% of men who received HIFU following radiotherapy were able to avoid ADT (androgen deprivation therapy) at a median follow-up of 64 months."[68]

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.[65] 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.[66] 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 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, BRFS 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.[67] 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.

National Comprehensive Cancer Network® Guidelines Version 4.2024 Prostate Cancer offered further evidence:

> "In the initial disease setting, the reported 5-year biochemical disease-free rate after cryotherapy ranged from 65% to 92% in patients with low-risk disease using different definitions of biochemical recurrence. A report suggests that cryotherapy and radical prostatectomy give similar oncologic results for unilateral prostate cancer. A study by Donnelly and colleagues randomly assigned 244 men with T2 or T3 disease to either cryotherapy or EBRT. All patients received neoadjuvant ADT. There was no difference in 3-year OS or DFS. Patients who received cryotherapy reported poorer sexual function. For patients with locally advanced cancer, cryoablation was associated with lower 8-year biochemical progression-free rate compared to EBRT in a small trial of 62 patients, although disease-specific survival and OS were similar.
>
> Cryosurgery has been assessed in patients with recurrent disease after RT. In one registry-based study of 91 patient, the biochemical DFS rates at 1, 3, and 5 years were 95.3%, 72.4%, and 46.5%, respectively. Adverse events included urinary retention (6.6%), incontinence (5.5%), and rectourethral fistula (3.3%)."[68]

Photodynamic Therapy

The evidence available for photodynamic therapy was related to a trial of Tookad, for which the FDA advisory committee voted against recommending approval.

MRI-guided transurethral ultrasound ablation (TULSA)

Dora et al (2021) reported results of a systematic review on MRI-guided transurethral ultrasound ablation of prostate cancer which followed Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. The review was from the inception of PubMed, Embase, and the Cochrane Library to June 2021 and included 10 studies (8 full-text articles and 2 conference abstracts and presentations) with two hundred twenty-four patients

with up to a 5-year follow-up. Studies that reported at least one efficacy, functional, or safety outcome after a single TULSA treatment were included. The indications for treatments were for primary localized prostate cancer (PCa),198 patients, recurrent PCa,16 patients, and palliation for locally advanced PCa, 10 patients. In men who were treated for primary PCa, the proportion of men who went on to need salvage treatment by up to 2 years after one MRI-guided TULSA procedure was 10%. The authors concluded that MRI guided TULSA is safe and effective for prostate tissue ablation in men with primary prostate cancer and results indicate favorable preservation of potency and continence with stability of urinary symptoms. Key limitations found in this review include small sample size, multicenter studies are few, and Level 1 evidence is still underway from a randomized-controlled trial comparing MRI-guided TULSA with radical prostatectomy (NCT 05027477). [72]

SUMMARY OF EVIDENCE

Many therapies have been investigated for the treatment of localized prostate cancer in the initial disease and recurrent setting, with the goals of reducing side effects and matching the cancer control of other therapies. For individuals who have primary localized prostate cancer who receive focal therapy using laser ablation, high-intensity focused ultrasound, cryoablation, radiofrequency ablation or photodynamic therapy, the evidence includes systematic reviews, studies from a registry cohort, and numerous observational studies. Relevant outcomes are overall survival, disease-specific survival, symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. The evidence is highly heterogeneous and inconsistently reports clinical outcomes. For initial treatment of clinically localized prostate cancer, cryosurgery may be considered. Cryosurgery and high-intensity focused ultrasound (HIFU) are recommended for local treatment of recurrent prostate cancer following radiotherapy in the absence of metastatic disease. For the remainder of the above techniques, the evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Irreversible electroporation is a newer technology aimed at focal therapy of tumors. Based on the small multi-center RCT and PRESERVE study, a single arm study available, there is not adequate evidence for proof of effectiveness. Larger studies with long term outcomes are needed to determine the net health outcomes related to this procedure. MRI-guided transurethral ultrasound ablation (TULSA) Dora et al. summarized a systematic review that TULSA is a promising option, offering precise treatment with minimal impact on patients' quality of life, and it may serve as an alternative to more invasive surgeries. It emphasizes the need for further long-term studies to confirm efficacy and safety.

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

National Comprehensive Cancer Network® (NCCN) Clinical Practice Guidelines in Oncology, Prostate Cancer, state:
HIFU has been studied for treatment of radiation recurrence. Analysis of a prospective registry of men treated with HIFU for radiation recurrence revealed median biochemical recurrence-free survival at 63 months, 5-year (overall survival) of 88%, and cancer-specific survival of 94%. Morbidity was acceptable, with a grade III/IV complication rate 3.6%. Analysis of a separate prospective registry showed that 48% of men who received HIFU following radiotherapy were able to avoid ADT (androgen deprivation therapy) at a median follow-up of 64 months."[68]

The National Comprehensive Cancer Network (NCCN) guidelines for prostate cancer (v.4.2024) recommend cryosurgery or high-intensity focused ultrasound (HIFU; category 2B) 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.[68]

Options for primary salvage therapy for those with positive biopsy but low suspicion of metastases include localized interventions of cryotherapy, HIFU, and brachytherapy. Treatment, however, needs to be individualized based on the patient's risk of progression, the likelihood of success, and the risks involved with salvage therapy.[68]

Magnetic Nanoparticles, Irreversible Electroporation (NanoKnife) and MRI-guided transurethral ultrasound ablation (TULSA) not mentioned in guidelines for the treatment of prostate cancer.[68]

National Institute for Health and Care Excellence
The National Institute for Health and Care Excellence (2019; updated in 2023) issued guidance on management for localized prostate cancer.[69] Cryoablation and high-intensity ultrasound are not recommended for the treatment of localized prostate cancer because there is a lack of evidence on quality-of-life benefits and long-term survival.

Evidence on the safety of focal therapy using high-intensity focused ultrasound for localized prostate cancer is adequate, but evidence on its efficacy is limited. Therefore, this procedure should only be used with special arrangements for clinical governance, consent, and audit or research. Find out what special arrangements mean on the NICE interventional procedures guidance page.

1.2 Clinicians wanting to do high-intensity focused ultrasound for localized prostate cancer should:

- Inform the clinical governance leads in their healthcare organization.
- Give people (and their families and carers, as appropriate) clear written information to support shared decision making, including NICE's information for the public. Use the recommendations in NICE's guideline on diagnosing and managing prostate cancer for information on treatment options and decision support.
- Ensure that people (and their families and carers, as appropriate) understand the procedure's safety and efficacy, and any uncertainties about these.

- Audit and review clinical outcomes of everyone having the procedure. The main efficacy and safety outcomes identified in this guidance can be entered into NICE's interventional procedure outcomes audit tool (for use at local discretion).
- Discuss the outcomes of the procedure during their annual appraisal to reflect, learn and improve.

1.3 Healthcare organizations should:

- Ensure systems are in place that support clinicians to collect and report data on outcomes and safety for everyone having this procedure.
- Regularly review data on outcomes and safety for this procedure.

1.4 Patient selection should be done by a multidisciplinary team.
1.5 Further research could include registry data or randomised trials. It should include details of patient selection, including size and classification of tumor, technique used and long-term outcomes such as quality of life.

American Urological Association et al
The American Urological Association, in collaboration with the American Society for Radiation Oncology (ASTRO) with additional representation from the American Society of Clinical Oncology (ASCO), and Society of Urologic Oncology (SUO) published updated guidelines on the management of clinically localized prostate cancer in 2022.[18] The guidelines included the following recommendation on focal treatments:

- "Clinicians should inform patients with intermediate-risk prostate cancer considering whole gland or focal ablation that there are a lack of high-quality data comparing ablation outcomes to radiation therapy, surgery, and active surveillance. (Expert Opinion"
- "Clinicians should not recommend whole gland or focal ablation for patients with high-risk prostate cancer outside of a clinical trial. (Expert Opinion)"

National Cancer Institute
The National Cancer Institute (NCI; 2023) updated its information on prostate cancer treatments.[69] The NCI indicated that cryosurgery, high-intensity focused ultrasound therapy and photodynamic therapy were new types of treatment being tested in clinical 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 (2018) published recommendations for prostate cancer screening.[70]

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 (recruiting)

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	108	Oct 2026 (active, not recruiting)
NCT04045756	Short-term Efficacy of Transperineal Laser Ablation (TPLA) with Image Fusion and Multi-parametric (mpMRI) Follow-up in Focal Low-intermediate Risk Prostate Cancer: Interventional Pilot Study	50	Aug 2024 (no records found)
NCT04549688	Active Surveillance Plus (AS+): Local Tumor Contorl with High-intensity Focused Ultrasound (HIFU) in Patients with Localized Prostate Cancer	250	Sep 2030 (recruiting)
NCT06223295	Effectiveness of Focal Therapy in Men With Prostate Cancer (ENFORCE)	356	Feb 2031 (recruiting)
NCT06451445	A Pan-Canadian, Investigator Initiated Clinical Trial With Focal IRE Directed to Intermediate-Risk Prostate Cancer (WIRED)	100	May 2032 (recruiting)
NCT0356188	Phase 2, Multicenter, Prospective Cohort Study, Estimating the Efficacy of Focused HIFU Therapy in Patients with Localized Intermediate Risk Prostate Cancer	170	Sep 2025 (no records found)
NCT05454488	An Evidence-Based Focal Cryotherapy Protocol for Focal Ablation of Intermediate Risk Prostate Cancer	30	Jan 2024 (recruiting)
NCT04972097	Pivotal Study of the NanoKnife System for the Ablation of Prostate Tissue (PRESERVE)	121	Jul 2024 (active, not recruiting)
NCT03668652	A Randomized Control Trial of Focal Prostate Ablation Versus Radical Prostatectomy	200	Sep 2024 (unknown status)
NCT01835977	Multi-Center Randomized Clinical Trial Irreversible Electroporation for the Ablation of Localized Prostate Cancer	106	Jan 2025 (active, not recruiting)
NCT05610852	Prospective Single-Center Randomized Study Of Single-Port Transvesical Partial Prostatectomy Versus High Intensity Focused Ultrasound (HIFU)	276	July 2028 (recruiting)
NCT05027477	Customized Ablation of the Prostate With the TULSA Procedure Against Radical Prostatectomy Treatment: a Randomized Controlled Trial for Localized Prostate Cancer (CAPTAIN)	201	Dec 2032 (recruiting)
Unpublished			
NCT04307056	Evaluation of high intensity focused ultrasound (hifu) in curative treatment of localized prostate cancer at low or intermediate risk and in treatment of recurrence after radiotherapy	3862	Aug 2022 (completed, no results posted)
NCT05010759	Study of Focal Ablation of the Prostate With NanoTherm® Therapy System for Intermediate-Risk Prostate Cancer	3	July 2023 (Terminated)

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

Government Regulations
National:

National Coverage Determination (NCD) for Cryosurgery of Prostate (230.9)
Effective Date 7/1/2001
Implementation Date 7/1/2001

Item/Service Description

Cryosurgery of the prostate gland, also known as cryosurgical ablation of the prostate (CSAP), destroys prostate tissue by applying extremely cold temperatures in order to reduce the size of the prostate gland. It is safe and effective, as well as medically necessary and appropriate, as **primary treatment** for patients with clinically localized prostate cancer, Stages T1-T3.

Indications and Limitations of Coverage
Cryosurgery of the prostate as a salvage therapy is not covered for any services performed prior to June 30, 2001.

Salvage Cryosurgery of Prostate After Radiation Failure. Salvage cryosurgery of the prostate for recurrent cancer is medically necessary and appropriate only for those patients with localized disease who:
1. Have failed a trial of radiation therapy as their primary treatment; and
2. Meet one of the following conditions: Stage T2B or below, Gleason score <9, PSA <8 ng/mL.

Cryosurgery as salvage therapy is therefore not covered under Medicare after failure of other therapies as the primary treatment. Cryosurgery as salvage is only covered after the failure of a trial of radiation therapy, under the conditions noted above.

Article - Billing and Coding: Salvage High-intensity Focused Ultrasound (HIFU) Treatment in Prostate Cancer (PCa) (A56702) A56702 Effective Date: 04/01/2020 Revision Effective Date: 01/01/2021 Revision Ending Date: 10/20/2022 Retirement Date 10/20/2022

This article contains coding guidelines that complement the Local Coverage Determination (LCD) for Salvage High-intensity Focused Ultrasound (HIFU) Treatment in Prostate Cancer (PCa)

Coding Information:

Procedure codes may be subject to National Correct Coding Initiative (NCCI) edits or OPPS packaging edits. Refer to NCCI and OPPS requirements prior to billing Medicare.

For services requiring a referring/ordering physician, the name and NPI of the referring/ordering physician must be reported on the claim.

A claim submitted without a valid ICD-10-CM diagnosis code will be returned to the provider as an incomplete claim under Section 1833(e) of the Social Security Act.

The diagnosis code(s) must best describe the patient's condition for which the service was performed.
CPT assigned HIFU a code (C9747) on 7/1/17.

Local:
Wisconsin Physicians Service Insurance Corporation
Article Title: High Intensity Focused Ultrasound (HIFU) in the Treatment of Recurrent Prostate Cancer (A56019)
Original Article Effective Date: 08/15/2018, Revision Effective Date: 08/15/2018 Revision Ending Date 10/17/2019, Retired 10/17/2019

High intensity focused ultrasound (HIFU) is a minimally-invasive surgical technique for the thermal ablation of both malignant and benign tumors. It utilizes a probe to image the structure and deliver timed bursts of heat to create coagulation necrosis in a targeted area. A unique benefit is that it causes little damage to the adjacent tissue. A cooling balloon surrounding the probe protects the surrounding mucosa from the high temperature. HIFU has been proposed as an alternative to surgery for the treatment of cancer and other tumor types such as prostate, breast, brain, liver, and renal cancer. It is also being studied for palliation of pain in tumor metastasis to bone, uterine fibroids, essential tremors, thyroid nodules, glaucoma, and benign prostatic hypertrophy (BPH).

This document focuses on the coverage of HIFU for recurrent prostate cancer. It should primarily serve as a billing and coding guideline.
Treatment options for localized prostate cancer include watchful waiting, active surveillance, radical prostatectomy, radiotherapy, brachytherapy, cryotherapy, and intensity-modulated radiation therapy (IMRT). Treatment of recurrent cancer depends on factors such as the primary treatment method, extent of the cancer, and site of recurrence.

HIFU is considered medically necessary as a local treatment for recurrent prostate cancer following external beam radiation when both of the following criteria are met:

1) Positive, recent (i.e. repeat) transrectal ultrasound guided (TRUS) biopsy completed due to suspicion of local recurrent of prostate cancer
2) Candidate for local therapy alone as evidenced by all of the following:

- Original clinical state T1-T2, NX or N0
- Recent PSA < 10ng/mL
- Absence of distant metastases

This procedure is typically carried out in an outpatient setting and is performed under a spinal or general anesthesia with IV sedation.

HIFU is not represented by a true code at this time. Place HIFU in line 19 of the CMS 1500 Health Insurance Claim Form.

2024 Medicare Physician Fee Schedule

0600T, 0601T, 0655T,0739T is not listed as a payable code

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Brachytherapy for Clinically Localized Prostate Cancer Using Permanently Implanted Seeds
- Cryosurgical Ablation of the Prostate (Retired 11/18/03)

- Magnetic Resonance-Guided Focused Ultrasound (MRGFUS)
- Saturation Biopsy for Diagnosis and Staging of Prostate Cancer

---

References

1. National Cancer Institute. 2024 https://seer.cancer.gov/statfacts/html/common.html Accessed 10/21/24
2. Dall'Era MA, Cooperberg MR, Chan JM, et al. Active surveillance for early-stage prostate cancer: review of the current literature. Cancer. Apr 15 2008;112(8):1650-1659. PMID 18306379
3. Bangma CH, Roemeling S, Schroder FH. Overdiagnosis and overtreatment of early detected prostate cancer. World J Urol. Mar 2007;25(1):3-9. PMID 17364211
4. Johansson JE, Andren O, Andersson SO, et al. Natural history of early, localized prostate cancer. JAMA. Jun 9 2004;291(22):2713-2719. PMID 15187052
5. Ploussard G, Epstein JI, Montironi R, et al. The contemporary concept of significant versus insignificant prostate cancer. Eur Urol. Aug 2011;60(2):291-303. PMID 21601982
6. Harnden P, Naylor B, Shelley MD, et al. The clinical management of patients with a small volume of prostatic cancer on biopsy: what are the risks of progression? A systematic review and meta-analysis. Cancer. Mar 1 2008;112(5):971-981. PMID 18186496
7. Brimo F, Montironi R, Egevad L, et al. Contemporary grading for prostate cancer: implications for patient care. Eur Urol. May 2013;63(5):892-901. PMID 23092544
8. Eylert MF, Persad R. Management of prostate cancer. Br J Hosp Med (Lond). Feb 2012;73(2):95-99. PMID 22504752
9. Eastham JA, Kattan MW, Fearn P, et al. Local progression among men with conservatively treated localized prostate cancer: results from the Transatlantic Prostate Group. Eur Urol. Feb 2008;53(2):347-354. PMID 17544572
10. Bill-Axelson A, Holmberg L, Ruutu M, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. N Engl J Med. May 12 2005;352(19):1977-1984. PMID 15888698
11. Thompson IM, Jr., Goodman PJ, Tangen CM, et al. Long-term survival of participants in the prostate cancer prevention trial. N Engl J Med. Aug 15 2013;369(7):603-610. PMID 23944298
12. Albertsen PC, Hanley JA, Fine J. 20-year outcomes following conservative management of clinically localized prostate cancer. JAMA. May 4 2005;293(17):2095-2101. PMID 15870412
13. Definitions of American Joint Committee on Cancer TNM Criteria: Table - PMC (nih.gov) accessed 10/21/24
14. Borley N, Feneley MR. Prostate cancer: diagnosis and staging. Asian J Androl. Jan 2009;11(1):74-80. PMID 19050692
15. Freedland SJ. Screening, risk assessment, and the approach to therapy in patients with prostate cancer. Cancer. Mar 15 2011;117(6):1123-1135. PMID 20960523
16. Ip S, Dahabreh IJ, Chung M, et al. An evidence review of active surveillance in men with localized prostate cancer. Evidence Report/Technology Assessment no. 204 (AHRQ Publication No. 12-E003-EF). Rockville, MD: Agency for Research and Quality; 2011.
17. American Urological Association. Guideline for management of clinically localized prostate cancer: 2007 update. Linthicum, MD: American Urological Association Education and Research; 2007.
18. Eastham JA, Auffenberg GB, Barocas DA, et al. Clinically Localized Prostate Cancer: AUA/ASTRO Guideline. 2022; https://www.auanet.org/guidelines/guidelines/clinically-localized-prostate-cancer-aua/astro-guideline-2022. Accessed 9/28/23.

19. Whitson JM, Carroll PR. Active surveillance for early-stage prostate cancer: defining the triggers for intervention. J Clin Oncol. Jun 10 2010;28(17):2807-2809. PMID 20439633
20. Albertsen PC. Treatment of localized prostate cancer: when is active surveillance appropriate? Nat Rev Clin Oncol. Jul 2010;7(7):394-400. PMID 20440282
21. Jacome-Pita F, Sanchez-Salas R, Barret E, et al. Focal therapy in prostate cancer: the current situation. Ecancermedicalscience. 2014;8:435. PMID 24944577
22. Nguyen CT, Jones JS. Focal therapy in the management of localized prostate cancer. BJU Int. May 2011;107(9):1362-1368. PMID 21223478
23. Lindner U, Lawrentschuk N, Schatloff O, et al. Evolution from active surveillance to focal therapy in the management of prostate cancer. Future Oncol. Jun 2011;7(6):775-787. PMID 21675840
24. Iberti CT, Mohamed N, Palese MA. A review of focal therapy techniques in prostate cancer: clinical results for high-intensity focused ultrasound and focal cryoablation. Rev Urol. 2011;13(4):e196-202. PMID 22232569
25. Lecornet E, Ahmed HU, Moore CM, et al. Conceptual basis for focal therapy in prostate cancer. J Endourol. May 2010;24(5):811-818. PMID 20443699
26. Tay KJ, Mendez M, Moul JW, et al. Active surveillance for prostate cancer: can we modernize contemporary protocols to improve patient selection and outcomes in the focal therapy era? Curr Opin Urol. Mar 12 2015. PMID 25768694
27. Passoni NM, Polascik TJ. How to select the right patients for focal therapy of prostate cancer? Curr Opin Urol. May 2014;24(3):203-208. PMID 24625428
28. Scales CD, Jr., Presti JC, Jr., Kane CJ, et al. Predicting unilateral prostate cancer based on biopsy features: implications for focal ablative therapy--results from the SEARCH database. J Urol. Oct 2007;178(4 Pt 1):1249-1252. PMID 17698131
29. Mouraviev V, Mayes JM, Sun L, et al. Prostate cancer laterality as a rationale of focal ablative therapy for the treatment of clinically localized prostate cancer. Cancer. Aug 15 2007;110(4):906-910. PMID 17587207
30. Mouraviev V, Mayes JM, Madden JF, et al. Analysis of laterality and percentage of tumor involvement in 1386 prostatectomized specimens for selection of unilateral focal cryotherapy. Technol Cancer Res Treat. Apr 2007;6(2):91-95. PMID 17375971
31. Muto S, Yoshii T, Saito K, et al. Focal therapy with high-intensity-focused ultrasound in the treatment of localized prostate cancer. Jpn J Clin Oncol. Mar 2008;38(3):192-199. PMID 18281309
32. Kasivisvanathan V, Emberton M, Ahmed HU. Focal therapy for prostate cancer: rationale and treatment opportunities. Clin Oncol (R Coll Radiol). Aug 2013;25(8):461-473. PMID 23759249
33. Mouraviev V, Villers A, Bostwick DG, et al. Understanding the pathological features of focality, grade and tumour volume of early-stage prostate cancer as a foundation for parenchyma-sparing prostate cancer therapies: active surveillance and focal targeted therapy. BJU Int. Oct 2011;108(7):1074-1085. PMID 21489116
34. Mouraviev V, Mayes JM, Polascik TJ. Pathologic basis of focal therapy for early-stage prostate cancer. Nat Rev Urol. Apr 2009;6(4):205-215. PMID 19352395
35. Liu W, Laitinen S, Khan S, et al. Copy number analysis indicates monoclonal origin of lethal metastatic prostate cancer. Nat Med. May 2009;15(5):559-565. PMID 19363497
36. Guo CC, Wang Y, Xiao L, et al. The relationship of TMPRSS2-ERG gene fusion between primary and metastatic prostate cancers. Hum Pathol. May 2012;43(5):644-649. PMID 21937078
37. Ahmed HU, Emberton M. Active surveillance and radical therapy in prostate cancer: can focal therapy offer the middle way? World J Urol. Oct 2008;26(5):457-467. PMID 18704441

38. Stamey TA, Freiha FS, McNeal JE, et al. Localized prostate cancer. Relationship of tumor volume to clinical significance for treatment of prostate cancer. Cancer. Feb 1 1993;71(3 Suppl):933-938. PMID 7679045
39. Nelson BA, Shappell SB, Chang SS, et al. Tumour volume is an independent predictor of prostate-specific antigen recurrence in patients undergoing radical prostatectomy for clinically localized prostate cancer. BJU Int. Jun 2006;97(6):1169-1172. PMID 16686706
40. van den Bos W, Muller BG, Ahmed H, et al. Focal therapy in prostate cancer: international multidisciplinary consensus on trial design. Eur Urol. Jun 2014;65(6):1078-1083. PMID 24444476
41. Mayes JM, Mouraviev V, Sun L, et al. Can the conventional sextant prostate biopsy accurately predict unilateral prostate cancer in low-risk, localized, prostate cancer? Urol Oncol. Mar-Apr 2011;29(2):166-170. PMID 19451000
42. Sinnott M, Falzarano SM, Hernandez AV, et al. Discrepancy in prostate cancer localization between biopsy and prostatectomy specimens in patients with unilateral positive biopsy: implications for focal therapy. Prostate. Aug 1 2012;72(11):1179-1186. PMID 22161896
43. Gallina A, Maccagnano C, Suardi N, et al. Unilateral positive biopsies in low risk prostate cancer patients diagnosed with extended transrectal ultrasound-guided biopsy schemes do not predict unilateral prostate cancer at radical prostatectomy. BJU Int. Jul 2012;110(2 Pt 2):E64-68. PMID 22093108
44. Briganti A, Tutolo M, Suardi N, et al. There is no way to identify patients who will harbor small volume, unilateral prostate cancer at final pathology. implications for focal therapies. Prostate. Jun 1 2012;72(8):925-930. PMID 21965006
45. Arumainayagam N, Ahmed HU, Moore CM, et al. Multiparametric MR imaging for detection of clinically significant prostate cancer: a validation cohort study with transperineal template prostate mapping as the reference standard. Radiology. Sep 2013;268(3):761-769. PMID 23564713
46. Dickinson L, Ahmed HU, Allen C, et al. Magnetic resonance imaging for the detection, localisation, and characterisation of prostate cancer: recommendations from a European consensus meeting. Eur Urol. Apr 2011;59(4):477-494. PMID 21195536
47. National Institute for Health and Care Excellence (NICE). Prostate cancer: diagnosis and management. [NG131]. 2019; https://www.nice.org.uk/guidance/ng131/chapter/Recommendations. Accessed 10/21/24.
48. National Institute for Health and Care Excellence (NICE). Focal Therapy Using High-Intensity Focused Ultrasound for Localized Prostate Cancer . April 2023; Focal therapy using high-intensity focused ultrasound for localised prostate cancer (nice.org.uk). Accessed 10/21/24.
49. Lee T, Mendhiratta N, Sperling D, et al. Focal laser ablation for localized prostate cancer: principles, clinical trials, and our initial experience. Rev Urol. 2014;16(2):55-66. PMID 25009445
50. Azzouzi AR, Vincendeau S, Barret E, et al. Padeliporfin vascular-targeted photodynamic therapy versus active surveillance in men with low-risk prostate cancer (CLIN1001 PCM301): an open-label, phase 3, randomized controlled trial. Lancet Oncol. Feb 2017; 18(2): 181-191. PMID 28007457
51. Scheltema MJ, van den Bos W, de Bruin DM, et al. Focal vs extended ablation in localized prostate cancer with irreversible electroporation; a multi-center randomized controlled trial. BMC Cancer. May 05 2016; 16: 299. PMID 27150293
52. Muller BG, van den Bos W, Brausi M, et al. Follow-up modalities in focal therapy for prostate cancer: results from a Delphi consensus project. World J Urol. Oct 2015; 33(10): 1503-9. PMID 25559111

53. Valerio M, Ahmed HU, Emberton M, et al. The role of focal therapy in the management of localised prostate cancer: a systematic review. Eur Urol. Oct 2014;66(4):732-751. PMID 23769825
54. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol. Oct 2009;62(10):e1-34. PMID 19631507
55. Wolff RF, Ryder S, Bossi A, et al. A systematic review of randomised controlled trials of radiotherapy for localised prostate cancer. Eur J Cancer. Nov 2015;51(16):2345-2367. PMID 26254809
56. Bates AS, Ayers J, Kostakopoulos N, et al. A Systematic Review of Focal Ablative Therapy for Clinically Localised Prostate Cancer in Comparison with Standard Management Options: Limitations of the Available Evidence and Recommendations for Clinical Practice and Further Research. Eur Urol Oncol. Jun 2021; 4(3): 405-423. PMID 33423943
57. Hopstaken JS, Bomers JGR, Sedelaar MJP, et al. An Updated Systematic Review on Focal Therapy in Localized Prostate Cancer: What Has Changed over the Past 5 Years?. Eur Urol. Jan 2022; 81(1): 5-33. PMID 34489140
58. Lepor H, Llukani E, Sperling D, et al. Complications, recovery, and early functional outcomes and oncologic control following in-bore focal laser ablation of prostate cancer. Eur Urol. Dec 2015;68(6):924-926. PMID 25979568
59. Natarajan S, Raman S, Priester AM, et al. Focal laser ablation of prostate cancer: phase I clinical trial. J Urol. Jul 2016;196(1):68-75. PMID 26748164
60. Mehralivand S, George AK, Hoang AN, et al. MRI-guided focal laser ablation of prostate cancer: a prospective single-arm, single-center trial with 3 years of follow-up. Diagn Interv Radiol. May 2021; 27(3): 394-400. PMID 34003127
61. Chao B, Lepor H. 5-Year Outcomes Following Focal Laser Ablation of Prostate Cancer. Urology. Jun 04 2021. PMID 34090887
62. Duwe G, Boehm K, Haack M, et al. Single-center, prospective phase 2 trial of high-intensity focused ultrasound (HIFU) in patients with unilateral localized prostate cancer: good functional results but oncologically not as safe as expected. World J Urol. May 2023; 41(5): 1293-1299. PMID 36920492
63. Reddy D, Peters M, Shah TT, et al. Cancer Control Outcomes Following Focal Therapy Using High-intensity Focused Ultrasound in 1379 Men with Nonmetastatic Prostate Cancer: A Multi-institute 15-year Experience. Eur Urol. Apr 2022; 81(4): 407-413. PMID 35123819
64. Nahar B, Bhat A, Reis IM, et al. Prospective Evaluation of Focal High Intensity Focused Ultrasound for Localized Prostate Cancer. J Urol. Sep 2020; 204(3): 483-489. PMID 32167866
65. Lian H, Zhuang J, Yang R, et al. Focal cryoablation for unilateral low-intermediate-risk prostate cancer: 63-month mean follow-up results of 41 patients. Int Urol Nephrol. Jan 2016;48(1):85-90. PMID 26531063
66. Mendez MH, Passoni NM, Pow-Sang J, et al. Comparison of outcomes between preoperatively potent men treated with focal versus whole gland cryotherapy in a matched population. J Endourol. Jul 13 2015. PMID 26058496
67. Ward JF, Jones JS. Focal cryotherapy for localized prostate cancer: a report from the national Cryo On-Line Database (COLD) Registry. BJU Int. Jun 2012;109(11):1648-1654. PMID 22035200
68. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: prostate cancer. Version 4.2024, May 17, 2024. prostate.pdf (nccn.org) Accessed 10/21/24.
69. National Cancer Institute. Prostate Cancer Treatment (PDQ®)–Patient Version: Treatment Option Overview. 2021

https://www.cancer.gov/types/prostate/patient/prostate-treatment-pdq Accessed 10/21/24.
70. U.S. Preventive Services Task Force. Final Recommendation Statement: Prostate Cancer: Screening. 2018; Search Results | United States Preventive Services Taskforce (uspreventiveservicestaskforce.org) Accessed 12/2/24.
71. George AK, Miocinovic R, Patel AR, et al. A Description and Safety Overview of Irreversible Electroporation for Prostate Tissue Ablation in Intermediate-Risk Prostate Cancer Patients: Preliminary Results from the PRESERVE Trial. Cancers (Basel). Jun 08 2024; 16(12). PMID 38927884
72. Dora C, Clarke GM, Frey G, Sella D. Magnetic Resonance Imaging-Guided Transurethral Ultrasound Ablation of Prostate Cancer: A Systematic Review. J Endourol. 2022 Jun;36(6):841-854. doi: 10.1089/end.2021.0866. Epub 2022 Mar 7. PMID: 35029127; PMCID: PMC9231661. https://doi.org/10.1089/end.2021.0866

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 10/21/24, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
5/1/17	2/21/17	2/21/17	Joint policy established
3/1/18	12/12/17	12/12/17	Routine maintenance
3/1/19	1/24/19		Routine maintenance Added local Medicare coverage information for HIFU; added procedure code C9747 Position change: cryosurgery and HIFU established if criteria met MPS updated Rationale and references updated
3/1/20	12/17/19		Routine maintenance
3/1/21	12/15/20		Routine maintenance Code 55880 added Code C9747 deleted from CPT, eff 1/1/21. Deleted from this policy
11/1/21	8/17/21		Added code 0655T eff 7/1/21 as E/I
3/1/22	12/14/21		Routine maintenance Added ref 53,56,57,58
3/1/23	12/20/22		Routine maintenance (jf) Added ref 1,17, 55, Added Tumor Criteria language, Sonoblate literature review
3/1/24	12/19/23		Routine maintenance (jf) Vendor Managed: NA Added ref: 1,60, 61 Added under regulatory section: Magnetic Nanoparticles MagForce® USA, Inc. is conducting a clinical study evaluating NanoTherm -Edit to the Description, Medical Policy Statement and exclusions -Added code 0739T as E/I
3/1/25	12/17/24		Routine maintenance (jf) Vendor Managed: NA o New indication added for irreversible electroporation under description, regulatory section and

			rationale, summary of evidence, inclusions and exclusions Added ref: 69, 70,71,72,73,74 Add 0600T and 0601T codes as E/I to represent Irreversible electroporation (Nanoknife System) New codes EFD 1/1/25 E/I 51721, 55881, 55882 to represent MRI-guided transurethral ultrasound ablation (TULSA) Edits to MPS, description, rationale, summary of evidence, inclusions and exclusions

Next Review Date: 4th Qtr, 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: FOCAL TREATMENTS FOR PROSTATE CANCER

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered if criteria is met.
BCNA (Medicare Advantage)	See Government Regulations section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.