FEP Medical Policy Manual

FEP 8.01.61 Focal Treatments for Prostate Cancer

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Related Policies:

7.01.109 - Magnetic Resonance Imaging-Guided Focused Ultrasound
7.01.121 - Saturation Biopsy for Diagnosis, Staging, and Management of Prostate Cancer

Focal Treatments for Prostate Cancer

Description

Description

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

Prostate cancer is the second most common cancer diagnosed among men in the U.S. According to the National Cancer Institute, nearly 268,490 new cases are estimated to be diagnosed in the U.S. in 2022 , associated with around 34,500 deaths.[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 that age-adjusted cancer-specific mortality rates for men with prostate cancer declined from 40 per 100,000 in 1992 to 19 per 100,000 in 2018. This decline has been attributed to a combination of earlier detection via PSA screening and improved therapies.

Diagnosis

From a clinical standpoint, different types of localized prostate cancers may appear similar during initial diagnosis.[3,] However, prostate cancer often exhibits varying degrees of risk progression that may not be captured by accepted clinical risk categories (eg, D'Amico criteria) or prognostic tools based on clinical findings (eg, PSA titers, Gleason grade, or tumor stage).[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 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 about whether to treat immediately.[13,14,] A patient may choose definitive treatment up front.[15,] Surgery (radical prostatectomy) or external-beam radiotherapy are frequently used to treat patients with localized prostate cancer.[14,16,] 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%).[16,]

American Urological Association guidelines state that for patients with low-risk prostate cancer, clinicians should recommend active surveillance.[17,] With this approach, patients forego immediate therapy but continue regular monitoring until signs or symptoms of disease progression are evident, at which point curative treatment is instituted.[18,19,]

Focal Treatments for Localized Prostate Cancer

Given significant uncertainty in predicting the behavior of individual localized prostate cancers, and the substantial adverse events associated with definitive treatments, investigators have sought a therapeutic middle ground. The latter seeks to minimize morbidity associated with radical treatment in those who may not actually require surgery while reducing tumor burden to an extent that reduces the chances for rapid progression to incurability. This approach is termed *focal treatment*, in that it seeks to remove, using any of several ablative methods described next, cancerous lesions at high-risk of progression, leaving behind uninvolved glandular parenchyma. The overall goal of any focal treatment is to minimize the risk of early tumor progression and preserve erectile, urinary, and rectal functions by reducing damage to the neurovascular bundles, external sphincter, bladder neck, and rectum.[20,21,22,23,24,] Although focal treatments are offered as an alternative middle approach to manage localized prostate cancer, several key issues must be considered in choosing it. These include patient selection, lesion selection, therapy monitoring, and modalities used to ablate lesions.

Patient Selection

A proportion of men with localized prostate cancer have been reported to have (or develop) serious misgivings and psychosocial problems in accepting active surveillance, sometimes leading to inappropriately discontinuing it.[25,] 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.[26,]

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.[27,28,29,] 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.[30,] 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.[31,] 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.[32,33,] This concept is supported by molecular genetics evidence that suggests that a single index tumor focus is usually responsible for disease progression and metastasis.[34,35] 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.[36,37,38] 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).[26,31] Systematic transrectal ultrasound-guided biopsy alone has been investigated; however, it has been considered insufficient for patient selection or disease localization for focal therapy.[39,40,41,42,43] See evidence review 7.01.121 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.[25,31,39] Evidence has shown mpMRI can detect high-grade, large prostate cancer foci with performance similar to transperineal prostate mapping using a brachytherapy template.[44] 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 (eg, mpMRI requires highly specialized MRI-compatible equipment; biopsy within the magnetic resonance imaging (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.[45]

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.[39] 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.[39] Finally, although investigators have indicated that PSA levels should be monitored, PSA levels are not considered valid endpoints because the utility of PSA kinetics in tissue preservation treatments has not been established.[36]

Modalities Used to Ablate Lesions

Five ablative methods for which clinical evidence is available are considered herein: focal laser ablation; high-intensity focused ultrasound (HIFU); cryoablation; radiofrequency ablation (RFA); and photodynamic therapy.[20,21,23,24,30,31,34,36,39,46,47] 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 evidence review 8.01.14).

Focal Laser Ablation

Focal laser ablation refers to the destruction of tissue using a focused beam of electromagnetic radiation emitted from a laser fiber introduced transperineally or transrectally into the cancer focus. The tissue is destroyed through the thermal conversion of the focused electromagnetic energy into heat, causing coagulative necrosis. Other terms for focal laser ablation include photothermal therapy, laser interstitial therapy, and laser interstitial photocoagulation.[48]

High-Intensity Focused Ultrasound

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

Cryoablation

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

Radiofrequency Ablation

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

Photodynamic Therapy

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

OBJECTIVE

The objective of this evidence review is to determine whether the use of focal therapy administered with different ablative techniques improves the net health outcome in individuals with primary localized prostate cancer.

POLICY STATEMENT

Use of any focal therapy modality to treat individuals with localized prostate cancer is **not medically necessary**.

POLICY GUIDELINES

There are no specific CPT codes for focal therapy using cryoablation, focal therapy using radiofrequency ablation, or focal therapy using photodynamic therapy. It is likely they are reported with an unlisted procedure, male genital system.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

FDA REGULATORY STATUS

Focal Laser Ablation

In 2010, the Visualase Thermal Therapy System (Medtronic) and, in 2015, the TRANBERG CLS|Laser fiber (Clinical Laserthermia Systems) were cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process to necrotize or coagulate soft tissue through interstitial irradiation or thermal therapy under MRI guidance for multiple indications including urology, at wavelengths from 800 to 1064 nm. In 2021, the FDA granted a breakthrough device designation to a novel artificial intelligence (AI)-enabled focal therapy system for the treatment of localized prostate cancer. The Avenda Health Focal Therapy System combines an AI-based margin prediction software algorithm with focal laser ablation to deliver treatment directly to the prostate tumor. FDA product code: LLZ, GEX, FRN.

High-Intensity Focused Ultrasound

In October 2015, the Sonablate 450 (SonaCare Medical) was cleared for marketing through the 510(k) process after approval of a de novo request and classification as class II under the generic name "high intensity ultrasound system for prostate tissue ablation". This device was the first of its kind to be approved in the U.S. In November 2015, Ablatherm-HIFU (EDAP TMS) was cleared for marketing by the FDA through the 510(k) process. In June 2018, EDAP received 510(k) clearance for its Focal-One HIFU device designed for prostate tissue ablation procedures. This device fuses magnetic resonance and 3D biopsy data with real-time ultrasound imaging, allowing urologists to view detailed images of the prostate on a large monitor and direct high-intensity ultrasound waves to ablate the targeted area.

Cryoablation

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

Radiofrequency Ablation

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

Photodynamic Therapy

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

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

Magnetic Nanoparticles

MagForce USA, Inc. is conducting a clinical study evaluating NanoTherm under an FDA Investigational Device Exemption (IDE) (NCT05010759). NanoTherm uses magnetic nanoparticles and an alternating magnetic field to create heat and local ablation in the ablation of prostate cancer.

RATIONALE

Summary of Evidence

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

SUPPLEMENTAL INFORMATION

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.

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.[17] 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 Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN) guidelines for prostate cancer (v1.2023) recommend only cryosurgery and high-intensity focused ultrasound (HIFU) as local therapy options for radiotherapy *recurrence* in the absence of metastatic disease (category 2B). 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.[64]

National Cancer Institute

The National Cancer Institute (NCI; 2021) updated its information on prostate cancer treatments.[65] 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.

National Institute for Health and Care Excellence

The National Institute for Health and Care Excellence (2019; updated in 2021) issued guidance on the use of cryoablation for localized prostate cancer.[46,] 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.

U.S. Preventive Services Task Force Recommendations

The U.S. Preventive Services Task Force published recommendations for prostate cancer screening.[66,] 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.

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
June 2015	New policy	Policy created with literature review through March 3, 2015. Use of any focal therapy modality is considered investigational for treatment of localized prostate cancer.
December 2016	Replace policy	Policy updated with literature review through July 26, 2016; references 55-57, and 59-64 were added. Policy statement unchanged.
December 2017	Replace policy	Policy updated with literature review through July 20, 2017; reference 16 added. Policy statement unchanged.
December 2018	Replace policy	Policy updated with literature review through July 9, 2018; reference 57 added; reference 61 updated; several references removed. Policy statement unchanged.
December 2019	Replace policy	Policy updated with literature review through July 8, 2019; reference on NCCN updated. Policy statement unchanged.
December 2020	Replace policy	Policy updated with literature review through August 5, 2020; no references added. Policy statement unchanged.
December 2021	Replace policy	Policy updated with literature review through July 28, 2021; references added. Policy statement unchanged.
December 2022	Replace policy	Policy updated with literature review through August 2, 2022; references added. Minor editorial refinements to policy statements; intent unchanged.
December 2023	Replace policy	Policy updated with literature review through July 11, 2023; references added. Policy statement unchanged.
December 2023	Replace policy	Policy updated with literature review through July 11, 2023; references added. Policy statement unchanged.