Medical Policy
Focal Treatments for Prostate Cancer

Table of Contents
- Policy: Commercial
- Policy: Medicare
- Authorization Information
- Coding Information
- Description
- Policy History
- Information Pertaining to All Policies
- References

Policy Number: 733
BCBSA Reference Number: 8.01.61
NCD/LCD: N/A

Related Policies
- Cryoablation of the Prostate, #149

Policy
Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity
Medicare HMO BlueSM and Medicare PPO BlueSM Members

Use of any focal therapy modality to treat patients with localized prostate cancer is INVESTIGATIONAL.

Prior Authorization Information
Pre-service approval is required for all inpatient services for all products.
See below for situations where prior authorization may be required or may not be required.
Yes indicates that prior authorization is required.
No indicates that prior authorization is not required.
N/A indicates that this service is primarily performed in an inpatient setting.

<table>
<thead>
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<td>Commercial Managed Care (HMO and POS)</td>
<td>This is not a covered service.</td>
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<tr>
<td>Commercial PPO and Indemnity</td>
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<td>Medicare HMO BlueSM</td>
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<td>Medicare PPO BlueSM</td>
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CPT Codes / HCPCS Codes / ICD Codes
Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.
The following codes are included below for informational purposes only; this is not an all-inclusive list.

The following HCPCS code is considered investigational for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

**HCPCS Codes**

<table>
<thead>
<tr>
<th>HCPCS codes:</th>
<th>Code Description</th>
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<tr>
<td>C9747</td>
<td>Ablation of prostate, transrectal, high intensity focused ultrasound (HIFU), including imaging guidance</td>
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**Description**

**Localized Prostate Cancer and Current Management**

Prostate cancer is the second most common cancer diagnosed among men in the United States. According to the National Cancer Institute (NCI), nearly 240,000 new cases are expected to be diagnosed in the United States in 2013 and are associated with around 30,000 deaths. Autopsy studies in the pre-prostate-specific antigen (PSA) screening era have identified incidental cancerous foci in 30% of men 50 years of age, with incidence reaching 75% at age 80 years. However, NCI Surveillance Epidemiology and End Results data show age-adjusted cancer-specific mortality rates for men with prostate cancer have declined from 40 per 100,000 in 1992 to 22 per 100,000 in 2010. This decline has been attributed to a combination of earlier detection via PSA screening and improved therapies.

Localized prostate cancers may appear very similar clinically at diagnosis. However, they often exhibit diverse risk of progression that may not be captured by accepted clinical risk categories (eg, D'Amico criteria) or prognostic tools that are based on clinical findings, including PSA titers, Gleason grade, or tumor stage. In studies of conservative management, the risk of localized disease progression based on prostate cancer-specific survival rates at 10 years may range from 15% to 20% to perhaps 27% at 20-year follow-up. Among elderly men (70 years) with this type of low-risk disease, comorbidities typically supervene as a cause of death; these men will die with prostate cancer present, rather than from the cancer. Other very similar-appearing low-risk tumors may progress unexpectedly rapidly, quickly disseminating and becoming incurable.

The divergent behavior of localized prostate cancers creates uncertainty whether to treat immediately. A patient may choose definitive treatment upfront. Surgery (radical prostatectomy), or EBRT are most commonly used to treat patients with localized prostate cancer. Complications most commonly reported with radical prostatectomy or EBRT and with the greatest variability are incontinence (0%-73%), and other genitourinary toxicities (irritative and obstructive symptoms); hematuria (typically ≤5%); gastrointestinal and bowel toxicity, including nausea and loose stools (25%-50%); proctopathy, including rectal pain and bleeding (10%-39%); and erectile dysfunction, including impotence (50%-90%).

American Urological Association (AUA) guidelines suggest patients with low- and intermediate-risk disease have the option of entering an “active surveillance” protocol that takes into account patient age, patient preferences, and health conditions related to urinary, sexual, and bowel function. With this approach the patient will forgo immediate therapy, but continue regular monitoring until signs or symptoms of disease progression are evident, at which point curative treatment is instituted.

Given the uncertainty in predicting behavior of individual localized prostate cancers, and the substantial adverse effects associated with definitive treatments in patients with such disease, investigators have sought a middle ground that seeks to minimize morbidity associated with radical treatment in those who may not actually require it 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 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.\textsuperscript{18-22} Although focal treatment is offered as an alternative middle approach to management of localized prostate cancer, several key issues must be considered in choosing it. These include patient selection, lesion selection, therapy monitoring, and the modality used to ablate lesions.

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.\textsuperscript{23} Thus, appropriate patient selection is imperative for physicians who must decide whether to recommend active surveillance or focal treatment for individual patients who refuse radical therapy or for whom it is not recommended due to the adverse balance of certain harms with unclear long-term benefit.\textsuperscript{24}

Proper lesion selection is a second key consideration in choosing to undertake focal treatment of localized prostate cancer. Although prostate cancer has always been regarded as a multifocal disease, clinical evidence shows 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.\textsuperscript{25-27} This view presumably drove the use of region-targeted focal treatment variants, such as hemi-ablation of the half of the gland containing tumor, or subtotal prostate ablation via the “hockey stick” method.\textsuperscript{28} While these approaches could 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 usually comprise most of the tumor burden in a patient with organ-confined prostate cancer led to development of the lesion-targeted strategy, which is referred to as “focal therapy” in this Policy.\textsuperscript{29} This involves treating only the largest and highest grade tumor (referred to as the “index lesion”), which has been shown in pathologic studies to determine clinical progression of disease.\textsuperscript{30-31} This concept is supported by molecular genetics evidence that suggests a single index tumor focus is usually responsible for disease progression and metastasis.\textsuperscript{32-33} The index lesion approach leaves in place small foci less than 0.5 cm\(^3\) in volume, with Gleason score less than 7 that are considered unlikely to progress over a 10- to 20-year period.\textsuperscript{34-36} 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. The ability to guide focal ablation energy to the tumor, and assess treatment effectiveness, are additionally important to treatment success. At present, no single modality meets the requirements for all 3 activities.\textsuperscript{24-29} Systematic transrectal ultrasound (TRUS)-guided biopsy alone has been investigated, but is considered insufficient for the purpose of patient selection and disease localization for focal therapy.\textsuperscript{37-41} A 5mm transperineal prostate mapping (TPM) biopsy using a brachytherapy template is the current recommended standard by the European Association of Urology in their 2012 guidelines. TPM can provide 3-dimensional coordinates of cancerous lesions, and has about 87% to 95% accuracy rates in detecting and ruling out clinically significant cancer of all sizes.\textsuperscript{43,44} However, TPM is resource intensive, requires general anesthesia, and has been associated with adverse events including urinary retention (6%), prostatitis (4%), and local events such as perineal hematoma, bruising or pain (5%). The risk of complications of general anesthesia, and the cost of processing multiple biopsy specimens have been considered to limit the practicality and widespread applicability of this approach.\textsuperscript{23}

Multiparametric magnetic resonance imaging (mp-MRI), typically including T1, T2, diffusion-weighted imaging, and dynamic contrast-enhanced imaging, has been recognized as a promising modality to riskstratify prostate cancer and select patients and lesions for focal therapy.\textsuperscript{23,29,37} Evidence is available to show mp-MRI can detect high grade, large prostate cancer foci with performance similar to TPM.\textsuperscript{46} In this cohort study, for the primary end point definition (lesion, \(\geq 4\) mm; and Gleason score, \(\geq 3+4\)), with TPM as the reference standard, sensitivity, negative predictive value, and negative likelihood ratios with mp-MRI 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 mp-MRI appears sufficient to rule out clinically significant prostate cancer and may have clinical use in this setting. However, although mp-MRI technology has capability to detect and risk stratify prostate cancer, several issues constrain its widespread use for these purposes. Thus, it is still necessary to histologically confirm suspicious lesions using TPM; mp-MRI requires highly specialized MRI-compatible equipment; biopsy within the MRI scanner is challenging; and, interpretation of prostate MRI images requires experienced uroradiologists.47

Some controversy exists as to the proper end points for focal therapy of prostate cancer. The primary end point of focal ablation of clinically significant disease with negative biopsies evaluated at 12 months after treatment is generally agreed on according to a European consensus report.37 The clinical validity of MRI to analyze the presence of residual or recurrent cancer compared with histologic findings is offered as a secondary end point. However, MRI findings alone are not considered sufficient in follow-up. Finally, although investigators indicate PSA levels should be monitored, they are not considered as valid end points because the utility of PSA kinetics in tissue preservation treatments has not been established.34

Methods Used for Focal Treatment of Localized Prostate Cancer
Five ablative methods for which clinical evidence is available are considered in this Policy: FLA; HIFU; cryoablation; RFA; and PDT.18,19,21,22,28,29,32,34,37,48,49 Each method requires placement of a needle probe into a tumor volume followed by delivery of some type of energy that causes destruction of the tissue in a controlled manner. All methods except FLA currently rely on ultrasound guidance to the tumor focus of interest; FLA uses MRI to guide the probe.

Focal laser ablation refers to the destruction of tissue using a focused beam of electromagnetic radiation emitted from a laser. It is accomplished through transperineal or transrectal introduction of a laser fiber into the cancer focus, with emission of energy. Tissue is destroyed by FLA through thermal conversion of the focused electromagnetic energy into heat, causing coagulative necrosis. Other terms for FLA include photothermal therapy, laser interstitial therapy, and laser interstitial photocoagulation.50

High-intensity focused ultrasound (US) works by focusing high-energy US 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, carry out, and monitor treatment in a real-time sequence to ablate the entire gland, or small discrete lesions.

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. It is performed by transperineal insertion under TRUS guidance of a varying number of cryoprobe needles into the tumor, using a TPM template.

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

PDT involves the use of an intravenous photosensitizing agent that distributes to prostate tissue, followed by delivery of light via transperineally inserted needles. The light induces a photochemical reaction that causes production of reactive oxygen species that are highly toxic and reactive with tissue causing functional and structural damage, hence cell death. A major concern with PDT 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.

Summary
No comparative evidence is available that assesses the use of the focal ablation techniques addressed in this Policy versus current standard treatment of prostate cancer, and therefore, no conclusions can be drawn between outcomes of focal therapies versus radical treatments versus active surveillance. In addition, no studies have been conducted that examine which, if any, of the focal techniques leads to better functional and oncologic outcomes. The body of evidence on the use of focal therapies for localized
prostate cancer comprises case series or other observational studies; they are highly heterogeneous and inconsistently report clinical outcomes. Although high cancer-specific survival rates have been reported, the short follow-up periods and small sample sizes preclude conclusions on the effectiveness of any of these techniques. In addition, there is no standardization as to which and how many identified cancerous lesions should be treated. Although the adverse effect rates associated with focal therapies appear to be superior to those associated with radical treatments such as radical prostatectomy or external beam radiotherapy (EBRT), the evidence is limited in its reporting and scope.

Policy History

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<td>7/2017</td>
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<td>10/2016</td>
<td>New references added from BCBSA National medical policy.</td>
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<tr>
<td>11/2015</td>
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Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:

- Medical Policy Terms of Use
- Managed Care Guidelines
- Indemnity/PPO Guidelines
- Clinical Exception Process
- Medical Technology Assessment Guidelines

References


44. Hu Y, Ahmed HU, Carter T, et al. A biopsy simulation study to assess the accuracy of several transrectal ultrasonography (TRUS)-biopsy strategies compared with template prostate mapping biopsies in patients who have undergone radical prostatectomy. BJU Int. Sep 2012;110(6):812-820. PMID 22394583


