Clinical Policy Title: Brachytherapy for localized prostate cancer

Clinical Policy Number: 05.02.02

Effective Date: October 1, 2014
Initial Review Date: June 18, 2014
Most Recent Review Date: July 3, 2018
Next Review Date: July 2019

Policy contains:
- Localized prostate cancer.
- Brachytherapy.
- External beam radiation therapy.
- Radical prostatectomy.

Related policies:
None.

ABOUT THIS POLICY: Prestige Health Choice has developed clinical policies to assist with making coverage determinations. Prestige Health Choice’s clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by Prestige Health Choice when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Prestige Health Choice’s clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Prestige Health Choice’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Prestige Health Choice will update its clinical policies as necessary. Prestige Health Choice’s clinical policies are not guarantees of payment.

Coverage policy

Prestige Health Choice considers the use of low-dose brachytherapy to be clinically proven and, therefore, medically necessary when all of the following criteria are met:

- Men with prostate cancer whose tumor is confined to the prostate gland.
- Prostate Specific Antigen score is <10 ng/ml and the Gleason score is <6.
- Patient is assigned Stage T1 or T2, using the American Joint Committee on Cancer staging system. Stage T1 is defined as clinically not apparent/neither palpable nor visible, or incidental finding on tissues during transurethral resection of the prostate. T2 is defined as confined within the prostate, one or both sides.

In addition, high-dose brachytherapy is considered medically necessary when used with external beam radiation therapy for prostate cancer patients with Stages T3 and T4 (Rosenthal, 2011; NICE, 2014; Chin, 2017).
Limitations:

Coverage determinations are subject to benefit limitations and exclusions as delineated by the state Medicaid authority. The Florida Medicaid website may be accessed at http://ahca.myflorida.com/Medicaid/.

Temporary brachytherapy for prostate cancer is not clinically proven, and therefore is considered investigational/experimental.

Alternative covered services:

Watchful waiting, radical prostatectomy or external beam radiation.

Background

Brachytherapy (interstitial radiation) is a form of radiation therapy in which encapsulated sources of radiation (“seeds”), typically radioactive iodine-125 or palladium-103 are implanted directly into or adjacent to tumor tissues, such as prostate cancer. Brachytherapy is based on the principle that radiation doses decrease as a function of the squared distance from the source, thus delivering intensive exposure to cancerous tissue while minimizing exposure and adverse effects to surrounding healthy tissue. Current standard prostate brachytherapy technique achieves a homogeneous dose distribution according to a customized template based on CT and ultrasound assessment of the tumor and computer-optimized dosimetry (ACS, 2016).

Prostate cancer is the most common non-cutaneous malignancy in men, with 164,690 cases expected to be diagnosed in 2018 (Noone, 2018). Ninety percent of men with prostate cancer are over age 60 and have disease believed to be localized to the prostate gland (clinically localized). Common treatments for clinically localized prostate cancer include watchful waiting, surgery to remove the prostate gland (radical prostatectomy), external beam radiation therapy, and interstitial radiation therapy. Prostate cancer is a clinically heterogeneous disease. A substantial proportion of prostate cancer cases detected with current screening methods will never cause symptoms during the patients’ lifetimes.

The Gleason score is a system of grading prostate cancer based on its microscopic appearance. It indicates the sum of predominant histological pattern (graded 1 to 5) and the next most common pattern. Gleason scores range from two to 10, indicating likelihood a tumor will spread. The higher the score is, the higher the likelihood of spread. Needle biopsy specimens (versus those from radical prostatectomy) provide insufficient tissue for complete Gleason scoring and cannot be scored lower than six (3 + 3).

Gleason, prostate-specific antigen levels, and tumor staging together comprise risk stratification for prostate cancer. Specific definitions of low-, intermediate-, and high-risk prostate cancer are:
**Prostate-specific antigen (ng/ml)**

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Intermediate</td>
<td>10 - 20</td>
</tr>
<tr>
<td>High risk</td>
<td>&gt; 20</td>
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</tbody>
</table>

**Gleason score**

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
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<tr>
<td>Intermediate</td>
<td>7</td>
</tr>
<tr>
<td>High risk</td>
<td>8 - 10</td>
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</tbody>
</table>

**Tumor stage**

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>T1 – T2</td>
</tr>
<tr>
<td>Intermediate</td>
<td>T2</td>
</tr>
<tr>
<td>High risk</td>
<td>T3 – T4</td>
</tr>
</tbody>
</table>

The American Society for Radiation Oncology/American College of Radiology guideline indicates transperineal permanent brachytherapy is appropriate for low- and intermediate-risk prostate cancer. Low-risk is defined as clinical stage T1b – T2b, Gleason score equal to or less than six, and prostate-specific antigen equal to or less than 10 ng/ml. Intermediate-risk is defined as clinical stage T2b – T2c, Gleason score of seven, and prostate-specific antigen between 10 and 20. Exclusions include life expectancy under five years, unacceptable operative risk, poor anatomy preventing a quality implant, positive lymph nodes from pathology, significant obstructive uropathy, and distant metastases (Rosenthal, 2011).

The American Society for Radiation Oncology/American College of Radiology guideline was corroborated by a 2017 guideline by the American Society of Clinical Oncology/Cancer Care Ontario Joint Guideline update (Chin, 2017). A 2014 guideline from the National Institute for Health and Care Excellence supported use of high-dose brachytherapy with external beam radiation therapy for men with intermediate- and high-risk localized prostate cancer, but not brachytherapy alone in cases of high-risk prostate cancer (NICE, 2014). The American Brachytherapy Society’s task forces have issued guidelines on both high-dose and low-dose use of treatment for prostate cancer (Hsu, 2008; Merrick, 2008).

**Searches**

Prestige Health Choice searched PubMed and the databases of:

- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality Guideline Clearinghouse and evidence-based practice centers.
- The Centers for Medicare & Medicaid Services (CMS).

We conducted searches on May 2, 2018. Search terms were: “brachytherapy prostate cancer.”
We included:

- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.

- **Guidelines based on systematic reviews.**

- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**

In general, survival rates for men with prostate cancer are high. A recent review of 14 studies of prostate cancer found that progression-free survival varied by study, among low-risk (85 to 100 percent) and high-risk (79 to 92 percent) patients at 5 years (Sanchez-Gomez, 2017). Similar rates for low-, intermediate-, or high-risk prostate cancer were reported as 85 to 100, 80 to 98, and 59 to 96 percent, along with 34 to 85 percent for locally advanced patients (Zaorsky, 2014), figures that were consistent with a later article by the same research team (Zaorsky, 2016).

In a systematic review of 13 articles, males with prostate cancer given high dose brachytherapy were followed for 1.5 to 8.0 years. The prostate-specific antigen progression-free survival ranged from 79 to 100 percent; local control from 97 to 100 percent; and erectile function preservation from 67 to 89 percent (Demanes, 2014).

A 2016 review of six studies (n= 34,338 males with metastatic prostate cancer) documented that survival for local treatment, radiotherapy, surgery, or brachytherapy was greater than those receiving no treatment at three years (64.2 versus. 44.5 percent) and five years (51.9 versus 23.6 percent) (Carneiro, 2016). Another review of six studies of 3011 prostate cancer patients undergoing brachytherapy and followed 4 - 6 years found that 27.4 to 50.0 percent had a prostate-specific antigen “bounce”, defined as an increase of at least 0.2 ng/mL from the nadir (Bernstein, 2013).

Some studies compare outcomes for various types of treatment for prostate cancer. One of the first of these compared brachytherapy with radical prostatectomy, but could identify only one randomized controlled trial, thus limiting any conclusions (Peinemann, 2011). Since this review, other articles have compared brachytherapy with other treatments:

- A study of 371 males with early stage prostate cancer (tumor stage T1 or T2 with Gleason score 6 or 7 and prostate-specific antigen score under 20) underwent radical prostatectomy (n=279) or brachytherapy (n=92), and followed for 7.2 to 7.6 years. Five-year biochemical recurrence-free survival was 96.1 and 90.6 percent for low- and intermediate-risk disease after radical prostatectomy (p=.003) and 92.5 and 95.8 percent after brachytherapy (p=.017). Differences
between the two techniques are insignificant (Fisher, 2012).

- A review of 36 randomized controlled trials of localized prostate cancer showed brachytherapy had similar efficacy as radical prostatectomy in terms of quality of life and progression-free survival, and brachytherapy had better outcomes for patient satisfaction and sexual function (Wolff, 2015).

- A review of 18 studies (n=6986) found overall survival and progression free survival in high-risk prostate cancer was lower for brachytherapy compared to radical prostatectomy, but cancer-specific mortality was equal; compared to radiation therapy, brachytherapy had a non-significantly higher five-year progression free survival (Lei, 2015).

- A comparison of low-dose rate brachytherapy and external beam radiation therapy for patients with low- or intermediate-risk prostate cancer patients found those undergoing brachytherapy had fewer 2nd primary cancers and lower rates of impotence, but higher rates of genitourinary and gastrointestinal toxicity (Rodrigues, 2013).

- In a study of three systematic reviews and four prospective studies, comparing robotic prostatectomy for localized prostate cancer with brachytherapy, the latter group had more improved questionnaire scores for urinary and sexual domains three years after treatment, along with a lower incontinence rate (Martin-Lopez, 2015).

- A meta-analysis of nine studies (n=55,139) compared radical prostatectomy and brachytherapy outcomes, finding no significant differences. The (radical prostatectomy) risk ratio for biochemical recurrence was 0.71 (p=.15), 1.02 (p=.98), and 1.09 (p=.92) for low-, intermediate-, and high-dose patients. Ratios for all-cause mortality (1.34, p=.25) and prostate cancer-specific mortality were 1.34 (p=.25) and (1.62, p=.13) (Cozzi, 2017).

- A review of 359 patients compared cryotherapy and brachytherapy. Five-year biochemical progression-free survival was significantly higher in the brachytherapy group (89.6 versus 57.9 percent, p<.0001), for high- and intermediate risk patients (Gestaut, 2017).

Efficacy of combined brachytherapy and external beam radiation for high-risk prostate cancer is well established. The concern over the toxicity of brachytherapy has been reduced over time, according to studies in the professional literature, through improvement in implant quality and toxicity profile of brachytherapy (Spratt, 2017).

A meta-analysis of 60 studies compared patient-reported outcomes for various treatment modes for localized prostate cancer, one year after treatment. Brachytherapy patients reported small deterioration in urinary incontinence, irritative obstructive symptoms, sexual function, and bowel bother, patterns persisting up to five years. External radiotherapy patients reported moderate worsening in three categories; and radical prostatectomy patients reported one small improvement and two large deteriorations. The authors observed that evidence supports brachytherapy as an option for patients seeking a treatment limiting risk for urinary incontinence and sexual dysfunction (Avila, 2018).

One study reported on trends in brachytherapy use for intermediate- and high-risk prostate cancer. Using the U.S. National Cancer Database, researchers from Boston’s Dana-Farber Cancer Institute at Brigham and Women’s Hospital found that between 2004 and 2012, the percent of men with
intermediate- and high-risk prostate cancer treated with brachytherapy plus external beam radiation therapy fell from 19 to 11 in nonacademic centers, and from 15 to 8 percent in academic centers, prompting the authors to speculate that “it is unclear whether academic centers are prepared to train the next generation of residents in this critical modality” (Orio, 2016).

Policy updates:

A total of 7 guidelines/other and 7 peer-reviewed references were added to this policy; 22 peer-reviewed references were removed in May 2017.

A total of four guidelines/other and five peer-reviewed references were added and six guidelines/other and four peer-reviewed references were removed from this policy in May 2018.

Summary of clinical evidence:

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zaorsky (2016)</td>
<td>Key points:</td>
</tr>
</tbody>
</table>
| Review of outcomes and toxicity of prostate cancer therapy | • 26 trials (16 EBRT, 10 BT), studies of > 70 patients.  
• 5 year survival of BT patients are high (>85% low-risk, 69-97% intermediate, 63-80% high-risk.  
• No differences between BT and other therapies in overall survival, cancer-specific mortality, rate of distant metastases. |
| Lei (2015)          | Key points:                        |
| Survival outcomes of different treatments in high-risk prostate cancer | • Systematic review of 18 studies (n=6986) of treatment for high-risk prostate cancer.  
• Comparison of radical prostatectomy (RP), radiation therapy (RT), brachytherapy (BT), androgen-deprivation therapy (ADT), and watchful waiting (WW).  
• RP had significantly better overall survival than RT or BT.  
• RP had similar cancer-specific mortality as did RT and BT.  
• BT had an insignificantly higher 5-year progression free survival as did RT. |
| Wolff (2015)        | Key points:                        |
| Comparing effectiveness of various local prostate cancer therapies | • 34 trials, survival based outcomes.  
• All major therapies found effective (EBRT, RP, BT).  
• No strong evidence to support one therapy over another. |
| Demanes (2014)      | Key points:                        |
| Evaluation of high-dose brachytherapy as monotherapy for prostate cancer | • 13 studies, followed 1.5 to 8.0 years after treatment.  
• Progression-free survival for PSA was 79 to 100%.  
• Genitourinary and gastrointestinal toxicity were 0-16% and 0-2%. |
<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
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<tbody>
<tr>
<td>Rodrigues (2013)</td>
<td><strong>Key points:</strong></td>
</tr>
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</table>
| Evaluation of side effects from low dose BT, compared with EBRT and RP | - 36 studies, patients followed 6 months to 3 years post-treatment.  
- BT had less urinary incontinence and sexual impotency than EBRT.  
- BT had more urinary irritation and rectal morbidity than RP.  
- BT has equal efficacy to EBRT and RP. |
| Flynn (2009)      | **Key points:**                    |
| Localized prostate cancer survival by type of treatment | - 19 reviews, treatment options equivalent in terms of survival.  
- Key issue - early identification of men whose tumors will impact survival or quality of life. |

**References**

**Professional society guidelines/other:**


Peer-reviewed references:


CMS National Coverage Determinations (NCDs):

No NCDs identified as of the writing of this policy.

Local Coverage Determinations (LCDs):

No LCDs identified as of the writing of this policy.

Commonly submitted codes

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

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<td>77778</td>
<td>Interstitial radiation source application; complex</td>
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<tr>
<td>77799</td>
<td>Unlisted procedure, clinical brachytherapy</td>
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<table>
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<table>
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