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 20, 2016
Next Review Date: July 2017

Related policies:
None.

ABOUT THIS POLICY: AmeriHealth Caritas Iowa has developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas Iowa’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 AmeriHealth Caritas Iowa 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. AmeriHealth Caritas Iowa’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. AmeriHealth Caritas Iowa’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, AmeriHealth Caritas Iowa will update its clinical policies as necessary. AmeriHealth Caritas Iowa’s clinical policies are not guarantees of payment.

Coverage policy

AmeriHealth Caritas Iowa considers the use of low-dose brachytherapy (BT) 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 (PSA) 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 inapparent/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 BT is considered medically necessary when used as monotherapy or with external beam radiation therapy (EBRT) for prostate cancer patients with Stages T3 and T4.

Limitations:
No other indications for BT are covered.

**Alternative covered services:**

Watchful waiting, radical prostatectomy or external beam radiation.

**Background**

Brachytherapy (BT, or interstitial radiation) is a form of radiation therapy in which encapsulated sources of radiation ("seeds") are implanted directly into or adjacent to tumor tissues, such as prostate cancer. BT 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 BT technique achieves a homogeneous dose distribution according to a customized template based on CT and ultrasound assessment of the tumor and computer-optimized dosimetry.

BT for prostate cancer is well-tolerated, although most patients experience urinary frequency and urgency that can persist for several months. Only 2 to 4 percent of patients are incontinent. Patients who have undergone a previous transurethral resection of the prostate (TURP) have higher complication rates.

Prostate cancer is the most common non-cutaneous malignancy and the second-leading cause of death in men. Ninety percent of men with prostate cancer are over age 60, diagnosed with the prostate specific antigen (PSA) blood test, 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, or RP), external beam radiation therapy (EBRT) and interstitial radiation therapy (BT).

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. Modeling studies based on U.S. incidence data (181,000 new cases per year) suggest over-diagnosis rates ranging from 29 percent to 44 percent of all prostate cancer cases detected by PSA screening. Because patients with “pseudo-disease” receive no benefit from, and may be harmed by, prostate cancer screening and treatment, prostate cancer detection in this population constitutes an important burden. The United States Preventive Services Task Force (USPSTF) in 2002 found insufficient evidence that screening for prostate cancer improved health outcomes, including mortality. It also found little evidence on the harms of the screening process or the natural history of prostate cancer cases detected with screening.

Prostate cancer screening is problematic because it attempts to mitigate a disease which is poorly understood by using a test resulting in substantial over-diagnosis. Side effects of treatment can be considerable and may include lasting effects on urinary, bowel, sexual and vitality functions.
Unfortunately, even patients with clear evidence of indolent disease who are candidates for surveillance suffer from cancer diagnosis. The most common reason patients stop surveillance and have active treatment is anxiety, not disease progression.

Five-year PSA relapse-free survival with current brachytherapy techniques according to pre-treatment PSA levels are as follows:

<table>
<thead>
<tr>
<th>Pre-brachytherapy PSA (ng/ml)</th>
<th>5-year actuarial survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – 4</td>
<td>98</td>
</tr>
<tr>
<td>4 – 10</td>
<td>90</td>
</tr>
<tr>
<td>&gt; 10</td>
<td>89</td>
</tr>
</tbody>
</table>

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 6 (3 + 3).

Gleason, PSA levels and tumor staging together comprise risk stratification for prostate cancer referenced in the reviews tabulated under Summary of clinical evidence:

<table>
<thead>
<tr>
<th>Risk</th>
<th>PSA (ng/ml)</th>
<th>Gleason</th>
<th>Tumor stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>&lt; 10</td>
<td>&lt; 6</td>
<td>T1 – T2</td>
</tr>
<tr>
<td>Intermediate</td>
<td>10 – 20</td>
<td>7</td>
<td>T2</td>
</tr>
<tr>
<td>High</td>
<td>&gt; 20</td>
<td>8 – 10</td>
<td>T3 – T4</td>
</tr>
</tbody>
</table>

**Searches**

AmeriHealth Caritas Iowa 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 July 7, 2016. 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

Survival outcomes for localized prostate cancer (RP, EBRT, and BT) are all relatively high (Wolff, 2015 and Zaorsky, 2016). Patients and their physicians thus choose among options based on adverse event profiles or biochemical outcomes, convenience, and other factors not related exclusively to survival. As generally positive outcomes exist for different treatment modalities, the current knowledge is inadequate to determine definitively the best treatment option, among them brachytherapy.

One large-scale study of 152,614 patients, covering one meta analysis, 30 randomized trials, 55 prospective trials, and 210 retrospective studies concluded that BT and EBRT actually provide superior outcomes to RP (Nilsson, 2004).

Other than survival, quality of life is perhaps the most widely-studied type of outcome after prostate cancer treatment. While one systematic review stated that data is of insufficient quality to generate conclusions on efficacy of various treatments (Whiting, 2016), others have made such conclusions. One found the quality of life on the SF-12 physical scale, plus post-surgical urinary and sexual functioning, to be superior in patients undergoing BT, three years after treatment (Martin-Lopez, 2015). Another found erectile function in BT patients superior to all other types of treatment (Robinson, 2002). A study comparing patient outcomes for BT combined with EBRT had less urinary incontinence and sexual impotency, but more urinary irritation and rectal morbidity (Rodriguez, 2013).

Other measures of efficacy include the rate of distant metastases after surgery; a recent systematic review found no difference between BT and EBRT (Zaorsky, 2016). Another meta analysis found a low rate of second cancers after BT, compared to other types of prostate cancer treatment (Wallis, 2016).

While the majority of articles in the literature addressed localized prostate cancer, some looked at high dose rate outcomes for intermediate- and high-risk forms of the disease. Survival outcomes for these cases were similarly high when either BT or EBRT was used (Zaorsky, 2016), while genitourinary and gastrointestinal toxicity was low (Demanes, 2014). However, another meta-analysis reported that radiation therapy, including BT, had higher cancer-specific and overall mortality rates compared to RP (Lei, 2015).

One study reported on trends in BT 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 BT plus EBRT 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:

The inclusion of high-dose temporary brachytherapy as a medically necessary service to the coverage section in July 2016 occurred based on the current peer-reviewed literature. The Results and Summary of Clinical Evidence sections were expanded with the addition of this new evidence. Two (2) professional society guidelines and six (6) peer reviewed references were removed (as they addressed cancers other than prostate), while two guidelines and 14 peer reviewed references (10 of which are meta-analyses or systematic reviews published after 2013) were added.

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% higher  
                                                        • No differences between BT and other therapies in overall survival, cancer-specific mortality, rate of distant metastases |
| 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% |
| Rodrigues (2013)| Key points:                      |
| 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 |
<p>| Flynn (2009)   | Keypoints:                        |
| Localized prostate cancer survival by type of | • 19 reviews, treatment options equivalent in terms of survival |</p>
<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>treatment</td>
<td>● Key issue - early identification of men whose tumors will impact survival or quality of life</td>
</tr>
<tr>
<td>Graham (2009)</td>
<td><strong>Key points:</strong></td>
</tr>
<tr>
<td></td>
<td>● More research is required into the identification of prognostic indicators to differentiate between men who may die with prostate cancer and those who might die from prostate cancer</td>
</tr>
<tr>
<td></td>
<td>● Greatest uncertainties are around the identification of which cancers are of clinical significance and over the choice of radical treatment, and in which settings they are appropriate</td>
</tr>
<tr>
<td></td>
<td>● Research should include a rigorous examination of procedures, such as brachytherapy (localized disease only), cryotherapy and high-intensity focused ultrasound, as well as combinations. The endpoints should include survival, local recurrence, toxicity, and quality of life</td>
</tr>
<tr>
<td>Wilt (2008)</td>
<td><strong>Key points:</strong></td>
</tr>
<tr>
<td></td>
<td>● 18 trials, one pooled analysis of three trials, 14,595 patients</td>
</tr>
<tr>
<td></td>
<td>● Erectile dysfunction occurred frequently after all treatments (RP 58%; RT 43%; androgen deprivation 86%)</td>
</tr>
<tr>
<td></td>
<td>● A higher risk score incorporating histologic grade, PSA level and tumor stage was associated with increased risk for disease progression or recurrence regardless of treatment</td>
</tr>
</tbody>
</table>

**Glossary**

**Brachytherapy (BT)** — A form of radiation therapy in which encapsulated sources of radiation ("seeds") are implanted directly into or adjacent to tumor tissues, such as prostate cancer.

**External beam radiation therapy (EBRT)** — The most common form of radiation therapy, from a machine (typically linear accelerators) outside the body, focused on the cancer site.

**Prostate-specific antigen (PSA)** — An enzyme (biochemical catalyst) produced by malignant and nonmalignant prostate epithelial cells, used to detect presence of prostate cancer (when elevated)

**Radical prostatectomy (RP)** — Surgical removal of the prostate.

**References**

**Professional society guidelines/other:**


Peer-reviewed references:


**Clinical trials:**

Searched clinicaltrials.gov on July 7, 2016 using terms “brachytherapy prostate cancer.” | Open Studies. 152 studies found, 90 not completed or terminated.

**CMS National Coverage Determinations (NCDs):**

None found as of the writing of this policy.

**Local Coverage Determinations (LCDs):**


**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.

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
<th>Comment</th>
</tr>
</thead>
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<tr>
<td>77778</td>
<td>Interstitial radiation source application; complex</td>
<td></td>
</tr>
<tr>
<td>77799</td>
<td>Unlisted procedure, clinical brachytherapy</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ICD-10 Code</th>
<th>Description</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>C61</td>
<td>Malignant neoplasm of the prostate</td>
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</table>

<table>
<thead>
<tr>
<th>HCPCS Level II</th>
<th>Description</th>
<th>Comment</th>
</tr>
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<tbody>
<tr>
<td>N/A</td>
<td></td>
<td></td>
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