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 15, 2015
Next Review Date: July 2016

Related policies:
None.

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

Coverage policy

Arbor Health Plan considers the use of brachytherapy to be clinically proven and, therefore, medically necessary when the following criteria are met:
- Men with prostate cancer whose tumor is confined to the prostate gland.
- Stage 1 or 2 (defined below).

Tumor (T) staging for prostate cancer:

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
</tr>
</thead>
</table>
| T1    | Clinically inapparent: neither palpable nor visible:  
         • Incidental finding on tissues resected during TURP.  
         • Identified on needle biopsy initiated by elevated PSA. |
| T2    | Confined within the prostate: one or both lobes. |
| T3    | Tumor spreads through capsule or present at resection margin:  
         • Uni- or bilateral extra-capsular extension.  
         • Seminal vesicles involved. |
| T4    | Fixed to or invades adjacent structures. |
Limitations:

No other indications for brachytherapy are covered.

Alternative covered services:

Watchful waiting, radical prostatectomy or external beam radiation.

Background

Brachytherapy (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. It 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.

Brachytherapy for prostate cancer is well-tolerated, although most patients experience urinary frequency and urgency that can persist for several months. Only 2 percent 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 noncutaneous 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), external beam radiation therapy and interstitial radiation therapy (brachytherapy).

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 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 of which we have a poor understanding by using a test not well-suited to the job, with rates of over-diagnosis estimated at 20 percent to 50 percent for a disease with a current annual incidence > 186,000 in the United States alone. 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. Indeed, 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:

<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>1 – 2</td>
</tr>
<tr>
<td>Intermediate</td>
<td>10 – 20</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>High</td>
<td>&gt; 20</td>
<td>8 – 10</td>
<td>3 – 4</td>
</tr>
</tbody>
</table>

**Searches:**

Arbor Health Plan 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 performed searches in July 2015, using the term “brachytherapy.” 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**
• The only brachytherapy indication documented as consistently effective is localized prostate cancer.
• Management options for localized prostate cancer (radical prostatectomy, external beam radiation and brachytherapy) appear to be fundamentally equivalent in terms of survival outcomes. 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.
• The current research evidence base is inadequate to determine definitively the best treatment option, among them brachytherapy, with the optimal balance of benefits and harms for well-defined groups of patients.
• Outstanding research issues for prostate cancer include early identification of those men with PSA screening-detected tumors who should receive immediate or aggressive therapy because the tumors actually will impact survival, i.e., those patients who will die from their tumors rather than with them.

Summary of clinical evidence:

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content</th>
</tr>
</thead>
</table>
| Andras (Cochrane; 2014) | **Key points:**

Intravascular brachytherapy for peripheral vascular disease
- Randomized controlled trials (RCTs), – August 2013.
- Eight moderate-quality trials (1,090 subjects); brachytherapy as adjunct to stent or balloon.
- Insufficient evidence. |
| Hayes (2013) | **Key points:**

Cost-effectiveness of observation vs. immediate treatment for low-risk prostate cancer
- Costs and outcomes data from Medicare and published literature for brachytherapy, intensity-modulated radiation or radical prostatectomy for men ages 65 – 75 with newly diagnosed low-risk disease.
- Observation (watchful waiting) more effective and less costly than immediate treatment.
- Brachytherapy was the most effective and least expensive immediate treatment. |
| Kearns (2013) | **Key points:**

Cost-effectiveness of enhancements to angioplasty for infrainguinal arterial disease
Poor reporting and insufficient evidence. |
| Lansbury (2013) | **Key points:**

Non-metastatic squamous cell carcinoma of the skin
Insufficient evidence. |
| Liu (2013) | **Key points:**

High vs. low dose rate for early stage oral cancer |
<table>
<thead>
<tr>
<th>Citation</th>
<th>Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bonet (2012)</td>
<td><strong>Key points:</strong></td>
</tr>
</tbody>
</table>
- Surgery plus radiation significantly better than surgery alone for cholangiocarcinoma. |
| Reveiz (Cochrane; 2012)        | **Key points:**                                                                                                                        |
- Fourteen trials (953 subjects).  
- Insufficient evidence. |
| Varela (2012): Galicia (Spain) HTA Agency | **Key points:**                                                                                                                        |
| High dose for head and neck cancer | Insufficient evidence.                                                                                                                  |
| Hayes, Inc. (2011)             | **Key points:**                                                                                                                        |
| Breast cancer                  | - Moderate evidence: for early-stage breast cancer brachytherapy is safe and as an adjunct to lumpectomy and whole breast irradiation improves tumor control and survival.  
- Combination of three interventions is equivalently effective to mastectomy.  
- One well-designed study suggests brachytherapy can also improve outcomes of non-surgical breast-conserving therapy, but a single study is insufficient for definitive conclusions.  
- Pending additional research, current evidence insufficient to replace whole-breast radiation with brachytherapy. |
| Peinemann (Cochrane; 2011)     | **Key points:**                                                                                                                        |
| Low dose rate brachytherapy for localized prostate cancer | - RCTs for low dose rate vs. radical prostatectomy, external beam or no treatment – 2010.  
- One (N = 200) vs. radical prostatectomy trial with high risk of bias and no primary outcomes reported.  
- Insufficient evidence. |
| Wang (Cochrane; 2010)          | **Key points:**                                                                                                                        |
| Locally advanced cervical cancer | - RCTs, – Nov 2009.  
- Four trials (N = 1265).  
- NS differences with comparators except for small bowel complications with high dose rate. |
| Flynn (2009)                   | **Key points:**                                                                                                                        |
| Localized prostate cancer       |                                                                                                                                         |
Citation | Content
--- | ---

- Nineteen reviews, including Wilt (2008) and Graham (2009), below.
- Treatment options equivalent in terms of survival; selections made for other reasons.
- Outstanding research issues: early identification of men whose tumors will impact survival or quality of life.

Graham (2009): UK Institute for Clinical Excellence | Key points:
--- | ---
**Research recommendations**
- “Further research is required into the identification of prognostic indicators in order to differentiate effectively between men who may die with prostate cancer and those who might die from prostate cancer.”
- The 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.
- With the diagnosis of prostate cancer being made more frequently in asymptomatic men, it is of growing importance to know which of these men are likely to benefit from aggressive treatment.
- Research is required into the clinical and cost effectiveness of treatments aimed at the elimination of disease in men with localized prostate cancer, with locally advanced disease and with locally recurrent disease.
- This research should include a rigorous examination of procedures, such as brachytherapy (localized disease only), cryotherapy and high-intensity focused ultrasound, as well as combinations of surgery and radiotherapy with hormonal therapy and chemotherapy. The endpoints should include survival, local recurrence, toxicity and quality of life.

Wilt (AHRQ; 2008) | Key points:
--- | ---
**Description of included studies (18 RCTs and 473 observational)**
- No treatment option had consistent results from at least two high-quality RCTs with adequate follow up and statistical power.
- Three RCTs compared major treatment categories (RP vs. RT or WW) and no trials enrolled men with primarily PSA-detected disease.
- Many RCTs were inadequately powered to provide long-term survival outcomes; most reported biochemical progression or recurrence as main outcomes.
- No RCT evaluated cryotherapy, laparoscopic or robotic-assisted RP, primary androgen deprivation, high-intensity focused ultrasound, proton beam, or intensity-modulated radiation.
- Non-randomized studies varied widely in treatment effectiveness and harms, definitions, and reporting of outcomes.
- Many studies included patients with locally advanced disease but did not analyze separately by stage.

**Results from 18 RCTs and one pooled analysis of three trials**
- There were 14,595 patients total.
- Fifteen trials evaluated variations of a particular treatment approach (different doses, isotopes or duration of RT).
- Six trials included men with locally advanced disease (24% of all patients).
- Only some studies reported age, ethnicity, tumor stage or Gleason score.
- Most studies began enrollment before widespread PSA testing.
- Erectile dysfunction occurred frequently after all treatments (RP 58%; RT 43%; androgen deprivation 86%).
- 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.
Conclusions

"Assessment of the comparative effectiveness and harms of localized prostate cancer treatments is difficult because of limitations in the evidence."

Glossary

Prostate-specific antigen (PSA) — An enzyme (biochemical catalyst) produced by malignant and nonmalignant prostate epithelial cells, making it prostate-specific, but not prostate cancer-specific. It also increases from prostatitis and benign prostatic hyperplasia.

PSA testing for early detection of prostate cancer was approved by the FDA in 1994 and widespread testing has played a significant role in the proportion of men diagnosed with early-stage cancers; newly diagnosed cancers are organ-confined or localized in more than 70 percent to 80 percent of men. As noted above, PSA levels are strongly associated with risk and outcomes of prostate cancer treatment.

Radical prostatectomy — Surgical removal of the prostate.

Intensity-modulated radiation therapy (IMRT) — Along with conformal therapy, radiation oncology techniques developed in the 1990s to capitalize on computers’ abilities to plan radiation delivery more precisely, thus maximizing exposure of tumors while avoiding surrounding tissues.

Watchful waiting or active surveillance — An approach to low-risk, localized prostate cancer involving regular PSA testing, digital rectal exam and prostate biopsy that avoids the adverse effects associated with the immediate treatment options (erectile dysfunction, urinary leakage or incontinence) and defers treatment until mandated by symptoms or objective signs of tumor progression.

References

Professional society guidelines:


**Peer-reviewed references:**


Clinical trials:

Reviews in the Summary of clinical evidence (Pages 4–6) cover trials published through 2013.

**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>ICD-9 Code</th>
<th>Description</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>185</td>
<td>Malignant neoplasm of the prostate</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>55875</td>
<td>Transperineal placement of needles or catheters into prostate for interstitial radioelement application</td>
<td></td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
<td></td>
</tr>
<tr>
<td>--------</td>
<td>------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>77776</td>
<td>Interstitial radiation source application; simple</td>
<td></td>
</tr>
<tr>
<td>77777</td>
<td>Interstitial radiation source application; intermediate</td>
<td></td>
</tr>
<tr>
<td>77778</td>
<td>Interstitial radiation source application; complex</td>
<td></td>
</tr>
</tbody>
</table>