# Medical Policy

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# Title: Brachytherapy for Clinically Localized Prostate Cancer Using Permanently Implanted Seeds

## Description/Background

### Prostate Cancer

In 2021, it has been estimated that 13.1% of all new cancer diagnoses will involve the prostate. In addition, as of 2018, estimates have suggested that over 3.2 million men in the U.S. are living with prostate cancer.(1)

### Brachytherapy

Brachytherapy is a procedure in which a radioactive source (e.g., radioisotope "seeds") is used to provide extremely localized radiation doses. With brachytherapy, the radiation penetrates only short distances; this procedure is intended to deliver tumoricidal radioactivity directly to the tumor and improve local control, while sparing surrounding normal tissue. Local tumor control has been reported to be associated with lower distant metastasis rates and improved patient survival. Seeds can be permanently or temporarily implanted. Permanent (low-dose rate, LDR) brachytherapy is generally used for those with low-risk disease; temporary (high-dose rate, HDR) brachytherapy is typically reserved for intermediate- or high-risk patients. This evidence review only assesses permanent LDR brachytherapy in prostate cancer.

The proposed biologic advantages of brachytherapy compared to external-beam radiation therapy (EBRT) are related to the dose delivered to the target and the dose-delivery rate. The dose rate of brachytherapy sources is generally in the range of 40-60 CGy/h (centigray per hour), whereas conventional fractionated EBRT dose rates exceed 200 cGy/min. Enhanced normal tissue repair occurs at the LDRs. Repair of tumor cells does not occur as quickly, and these cells continue to die during continued exposure. Thus, from a radiobiologic perspective, LDR radiation causes ongoing tumor destruction in the setting of normal tissue repair. In addition, brachytherapy is preferable to the multiple sessions required to deliver EBRT. The total doses of radiation therapy (RT) that can be delivered may also vary between EBRT and brachytherapy, especially with newer forms of EBRT such as 3-dimensional-conformal radiation therapy (3D-CRT) and intensity-modulated radiotherapy.

Brachytherapy has not been considered appropriate for patients with a large prostate or those with a urethral stricture, because the procedure results in short-term swelling of the prostate, which can lead to urinary obstruction. As with all forms of RT, concerns exist regarding the long-term risk of treatment-related secondary malignancies. Reports also suggest that the clinician's level of experience with brachytherapy correlates with disease recurrence rates.

Studies of permanent brachytherapy have generally used either iodine-125 or palladium-103. Use of cesium-131 is also being studied. Use of iodine-125 requires more seeds, thus reducing dosimetric dependence on any single seed. Post-implant dosimetric assessment should be performed to ensure the quality of the implant and optimal source placement (i.e., the targeted tumor areas receive the predetermined radiation dosages while nearby structures and tissues are preserved).

Permanent brachytherapy may be used as monotherapy or as combined with EBRT as a way to boost the dose of radiation therapy delivered to the tumor; CMT can be performed with permanent or temporary brachytherapy. The brachytherapy boost is typically done 2 to 6 weeks after completion of EBRT, although the sequence can vary. In some cases, patients also receive androgen deprivation therapy.

Focal or subtotal prostate brachytherapy is a form of more localized, organ-preserving therapy for small localized prostate cancers. Brachytherapy "seeds" are placed only in the areas where the tumor has been identified rather than throughout the whole prostate gland. The aim of focal therapy is to reduce the occurrence of adverse events that may be associated with brachytherapy, including urinary, bowel, and sexual dysfunction.

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## Regulatory Status:

A large number of permanently implanted seeds for brachytherapy of prostate cancer have become available since 1999. The U.S. Food and Drug Administration (FDA) has cleared these devices through its 510(k) process, including I-Seed® (Theragenics Corp.), Proxcelan™ Cs-131 (IsoRay Medical), and BrachySource® Brachytherapy Seed Implants (C.R. Bard). FDA product code: KXK.

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## Medical Policy Statement

Brachytherapy using permanent transperineal implantation of radioactive seeds has been established as a safe and effective treatment of localized prostate cancer when used as monotherapy or in conjunction with external beam radiation therapy (EBRT).

Focal brachytherapy is experimental/investigational in the treatment of prostate cancer. Its effectiveness in this clinical indication has not been scientifically determined.

## Inclusionary and Exclusionary Guidelines (Clinically based guidelines that may support individual consideration and pre-authorization decisions)

**Inclusions:**
Permanent brachytherapy using only implanted seeds is generally used in patients whose prostate cancer is considered low risk. Active surveillance is generally recommended for very low risk prostate cancer. Permanent brachytherapy combined with EBRT is used (sometimes along with androgen deprivation) to treat higher risk disease.

Prostate cancer risk is often defined using the following criteria:

- Low risk: PSA (prostate-specific antigen) 10 ng/mL or less, Gleason score 6 or less, and clinical stage T1c (very low risk) or T1-T2a.
- Intermediate risk: PSA greater than 10 but 20 ng/mL or less, or Gleason score 7, or clinical stage T2b-T2c.
- High Risk: PSA >20 ng/mL or Gleason score 8–10, or clinical stage T3a for clinically localized disease and T3b-T4 for locally advanced disease.

The procedure is usually performed in two stages: a prostate volume study (76873) followed at a later date by the implant itself, which is performed in the operating room with the patient under general or epidural anesthesia. Iodine and palladium are the typical isotopes used; the selection of isotope is usually based on physician preference. A computed tomography (CT) scan is usually performed at some stage after the procedure to determine the accuracy of the seed placement.

**Exclusions:**
Focal prostate brachytherapy

## CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

### *Established codes:*

| | | | | | |
|---|---|---|---|---|---|
| 55875 | 76873 | 77316 | 77317 | 77318 | 77402 |
| 77407 | 77412 | 77778 | Q3001 | G0458 | G6003 |
| G6004 | G6005 | G6006 | G6007 | G6008 | G6009 |
| G6010 | G6011 | G6012 | G6013 | G6014 | |

### *Other codes (investigational, not medically necessary, etc.):*

N/A

*Note: The above code(s) may not be covered by all contracts or certificates. Please consult customer or provider inquiry resources at BCBSM or BCN to verify coverage.*

## Rationale

### PERMANENT LOW-DOSE RATE BRACHYTHERAPY PLUS EXTERNAL-BEAM RADIOTHERAPY

#### Clinical Context and Therapy Purpose

The purpose of permanent low-dose rate (LDR) brachytherapy plus external-beam radiotherapy (EBRT) is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as active surveillance, EBRT alone, surgery, and cryoablation, in patients with localized prostate cancer.

The question addressed in this evidence review is: Does the use of permanent LDR brachytherapy in combination with EBRT, improve the net health outcome in patients with prostate cancer?

The following PICOs were used to select literature to inform this review.

***Populations***

The relevant population of interest is individuals with localized prostate cancer.

Brachytherapy has not been considered appropriate for patients with a large prostate or those with a urethral stricture because the procedure results in short-term swelling of the prostate, which can lead to urinary obstruction. As with all forms of radiotherapy, concerns exist with the long-term risk of treatment-related secondary malignancies.

***Interventions***

The therapy being considered is permanent LDR brachytherapy plus EBRT.

Brachytherapy is a procedure in which a radioactive source (eg, radioisotope "seeds") is permanently or temporarily implanted in or near the tumor (eg, placed into the prostate gland to treat localized prostate cancer). The radiation from brachytherapy penetrates only short distances and is intended to deliver tumoricidal radioactivity directly to the tumor to improve local control while sparing surrounding normal tissue.

Studies of permanent brachytherapy have generally used iodine 125 or palladium 103. Use of cesium 131 is also being studied. Use of iodine 125 requires more seeds, thus reducing dosimetric dependence on any single seed.

***Comparators***

Comparators of interest include active surveillance, EBRT alone, surgery, and cryoablation.

Active surveillance, external-beam radiotherapy alone, surgery, and cryoablation is performed by radiologists, surgical oncologists, and primary care providers in an outpatient clinical setting.

### *Outcomes*

The general outcomes of interest are overall survival (OS), disease-specific survival, and treatment-related morbidity.

**Table 1. Outcomes of Interest for Individuals with Localized Prostate Cancer**

| Outcomes | Details | Timing |
|---|---|---|
| Disease-specific survival | Outcomes of interest include progression-free survival and tumor progression | ≥1 year |
| Treatment-related morbidity | Outcomes of interest include treatment-related adverse events such as urinary blockage, sexual dysfunction, or gastrointestinal toxicities | ≥1 year |

### Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

## REVIEW OF EVIDENCE

### Systematic Reviews

Kee et al (2018) published a systematic review and meta-analysis comparing brachytherapy and EBRT boost for patients with prostate cancer.(2) Three RCTs with a total of 703 participants were included. Brachytherapy had a significant benefit over EBRT boost for 5-year progression-free survival (hazard ratio [HR] 0.49; 95% CI 0.37–0.66; p<0.01); there was no significant difference between the 2 treatments for OS (HR 0.92; 95% CI 0.64–1.33; p=0.65). There was also no difference in rates of ≥ grade 3 late genito-urinary (relative risk 2.19; 95% CI 0.76–6.30; p=0.15) or late gastrointestinal toxicities (relative risk 1.85; 95% CI 1.00–3.41; p=0.05). No limitations for this analysis were reported.

### Randomized Controlled Trials

No randomized controlled trials (RCTs) were identified that compared low-dose rate (LDR) brachytherapy plus external-beam radiotherapy (EBRT) with LDR brachytherapy or with EBRT alone in patients who have clinically localized prostate cancer. Morris et al (2017) reported on the ASCENDE-RT trial, which evaluated patients who received androgen deprivation therapy (ADT) and EBRT.(3) The investigators compared EBRT boost with an LDR brachytherapy boost. The primary outcome (biochemical progression-free survival (BPFS) at a median follow-up of 6.5 years significantly favored the LDR brachytherapy group (p=0.004). In a subgroup analysis limited to patients with intermediate-risk prostate cancer (ie clinically localized disease), BPFS was significantly higher in the brachytherapy boost group (p=0.003). Overall survival (OS) and disease-specific survival did not differ significantly between the LDR brachytherapy boost and EBRT boost groups.

Morris et al (2018) published a reanalysis of the Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy trial comparing biochemical failure using a prostate-specific antigen (PSA) threshold of >0.2 ng/mL to the Phoenix threshold (nadir+2 ng/mL).(4) At follow-up times >4 years, patients receiving LDR-permanent

brachytherapy were less likely to experience biochemical failure (log rank p=0.001). The Kaplan-Meier b-PFS was superior for LDR-permanent brachytherapy compared with dose-escalated EBRT when applying the nadir+2 ng/mL threshold (5-, 7-, and 9-year results were 90%, 88%, and 85% vs 84%, 76%, and 63%).

**Observational Studies**

Pasalic et al (2021) reported on the Comparative Effectiveness Analysis of Surgery and Radiation (CEASAR) study, which was a prospective, multicenter study that evaluated 695 patients who received EBRT alone (n=583) and EBRT plus LDR brachytherapy(n=112) for localized prostate cancer.(5) Adjunctive ADT was given based on a risk-based assessment at the discretion of each clinician. Patient-reported outcomes were the primary outcomes assessed, including Expanded Prostate Cancer Index Composite domains (eg, urinary irritative function, bowel function). After a median follow-up of 73 months, no significant differences were found between EBRT alone and EBRT plus LDR brachytherapy for 5-year OS (92.8% vs 95.2%), 7-year OS (84% vs 91%), 5-year prostate cancer-specific survival (99.6% vs 99%), and 7-year prostate cancer-specific survival (96.9% vs 97.3%). Treatment with EBRT plus LDR brachytherapy was associated with clinically meaningful worse urinary irritative function (adjusted mean difference, -5.4; 95% CI,-9.3 to -1.6; p=.006) and bowel function scores (-4.1; 95% CI, -7.6 to -0.5; p=.027) through 3 years; the differences between treatment groups were no longer considered clinically meaningful at 5 years.

Abugharib et al (2017) reported on 579 patients with localized prostate cancer treated using LDR brachytherapy plus EBRT (n=191) or EBRT alone (n=388).(6) Patients were not randomized to treatment group, and ADT was given at the physician's discretion to patients in both groups. After a median follow-up of 7.5 years, 13 (7%) patients in the combined treatment group and 77 (20%) patients in the EBRT alone group had biochemical recurrence. Actuarial BPFS up to 10 years was significantly higher in the combined treatment than in the EBRT-only group (p=0.014). In addition, local progression-free survival significantly favored the combined treatment group (p=0.042), but distant metastasis-free survival did not differ significantly between groups (p=0.21). There was no significant difference between groups in the rate of gastrointestinal (GI) toxicity (grade ≥2), but the combined treatment group had a significantly higher incidence of grade 3 genitourinary (GU) toxicity than the EBRT-only group.

Serrano et al (2016) evaluated long-term rectal toxicity from LDR brachytherapy patients with prostate cancer (stage T1c-T2b).(7) A total of 245 patients were followed for at least 5 years (median follow-up, 7.5 years). Eighty-five (33.5%) patients received EBRT plus LDR brachytherapy. Sixteen (6.5%) patients developed rectal toxicity (grade ≥2) and 7 (2.9%) developed rectal toxicity (grade ≥3). Six of the seven patients who developed rectal toxicity at grade III or higher had received combined treatment. The authors did not report the number of patients with rectal toxicity at grade 2 or higher who had EBRT only versus LDR brachytherapy plus EBRT. Moreover, survival outcomes were not reported.

Findings of the Radiation Therapy Oncology Group 0019 multicenter study were published by Lawton et al (2012), with data from 131 patients followed for a median of 8.3 years.(8) All patients received EBRT followed by permanent LDR brachytherapy. Late GU and/or GI tract toxicity greater than grade III was estimated to be 15% and most commonly included urinary frequency, dysuria, and proctitis. Grade III impotence was reported in 42% of patients. These adverse effects rates with combined modality therapy were higher than are often reported for either brachytherapy or EBRT treatment alone. Estimates of biochemical failure were 18%

using the Phoenix definition and 21% using the American Society for Radiation Oncology's definition and were similar to either treatment alone.

Long-term efficacy and/or toxicity results are also available from large cohorts treated at single institutions. For example, Sylvester et al (2007) reported on results of treatment with EBRT at 45 gray followed by permanent brachytherapy.(9) In this series, androgen deprivation therapy was not used. This report was based on a series of 223 consecutive patients treated between 1987 and 1993; patients had stage T1–T3 disease. Permanent brachytherapy was performed with radioactive palladium or iodine 4 weeks after EBRT. Fifteen-year biochemical relapse-free survival (BRFS) was 88% in the low-risk group, 80% in the intermediate-risk group, and 53% in the high-risk group. In addition, long-term outcomes were compared with those of two institutions that had results for RP. Results were similar across Gleason score categories, (e.g., the relapse-free survival was 25% to 30% for those with Gleason score 7 for the 3 series of patients but varied for other prognostic factors such as PSA level).

In another single-center report, results were summarized for combined modality therapy using three-dimensional conformal radiotherapy followed by permanent (palladium) brachytherapy.(10) This 2007 study involved 282 intermediate- and high-risk patients treated from 1992 to 1996. Fourteen-year freedom from biochemical progression in the intermediate-risk group was 87% and 72% in the high-risk group.

**Section Summary: Permanent Low-Dose Rate Brachytherapy Combined with EBRT**
No RCTs have compared permanent LDR brachytherapy plus EBRT with EBRT alone in patients having clinically localized prostate cancer. One RCT compared boost LDR brachytherapy plus boost EBRT with EBRT alone. It found better biochemical PFS but not OS or disease-specific survival in patients who had combined treatment. There are also a number of observational studies, including 2 nonrandomized studies comparing of LDR brachytherapy plus EBRT with EBRT alone. One found that the BPFS rate was significantly higher in the combined treatment group; rates of GU but not GI toxicity were significantly higher with combined treatment. The other found differences in urinary irritative function and bowel function were significantly worse at 3 years with combination treatment, but the differences were no longer clinically meaningful at 5 years. Multicenter and single-center uncontrolled studies found relatively high rates of BPFS after LDR brachytherapy plus EBRT.

## PERMANENT LOW-DOSE RATE BRACHYTHERAPY AS MONOTHERAPY

### Clinical Context and Therapy Purpose

The purpose of permanent LDR brachytherapy as monotherapy is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as active surveillance, EBRT alone, surgery, and cryoablation, in patients with localized prostate cancer.

The question addressed in this evidence review is: Does the use of permanent LDR brachytherapy alone improve the net health outcome in patients with prostate cancer?

The following PICOs were used to select literature to inform this review.

#### *Populations*

The relevant population of interest are individuals with localized prostate cancer.

### *Interventions*
The therapy being considered is permanent LDR brachytherapy as monotherapy.

Brachytherapy is a procedure in which a radioactive source (eg, radioisotope "seeds") is permanently or temporarily implanted in or near the tumor (eg, placed into the prostate gland to treat localized prostate cancer). The radiation from brachytherapy penetrates only short distances and is intended to deliver tumoricidal radioactivity directly to the tumor to improve local control while sparing surrounding normal tissue.

Studies of permanent brachytherapy have generally used iodine 125 or palladium 103. Use of cesium 131 is also being studied. Use of iodine 125 requires more seeds, thus reducing dosimetric dependence on any single seed.

### *Comparators*
Comparators of interest include active surveillance, EBRT alone, surgery, and cryoablation.

### *Outcomes*
The general outcomes of interest are OS, disease-specific survival, and treatment-related morbidity.

**Table 2. Outcomes of Interest for Individuals with Localized Prostate Cancer**

| Outcomes | Details |
|---|---|
| Disease-specific survival | Outcomes of interest include progression-free survival and tumor progression [Timing ≥ 1 year] |
| Treatment-related morbidity | Outcomes of interest include treatment-related adverse events such as urinary blockage, sexual dysfunction, or gastrointestinal toxicities [Timing ≥ 1 year] |

### Study Selection Criteria
See methodological criteria listed above.

## REVIEW OF EVIDENCE

### Systematic Reviews
A Cochrane review by Peinemann et al (2011) evaluated literature on low-dose brachytherapy for prostate cancer.(11) Reviewers focused on the only identified RCT, Giberti et al (2009).(12) The Giberti trial (detailed below) compared brachytherapy with radical prostatectomy (RP) and was considered to have a high risk of bias. Peinemann et al (2011) also conducted a systematic review of brachytherapy.(13) In this review, the Giberti et al (2009) RCT and 30 nonrandomized studies were included, all of which were also found to have a high risk of bias.

### Randomized Controlled Trials
The Giberti et al (2009) RCT reported results for 200 low-risk prostate cancer patients randomized to RP or to brachytherapy.(12) Biochemical progression-free survival (BPFS) rates at five years were 90% for RP and 91.7% for brachytherapy. Both treatment groups experienced decreases in quality of life at six months and one-year post-treatment, although brachytherapy patients reported more urinary disorders but better erectile function than the RP group. At five-year follow-up, functional outcomes did not differ between arms.

**Observational Studies**

Several nonrandomized comparative studies have reported on outcomes in patients with localized prostate cancer who received one of several treatments. Williams et al (2012) compared data from the U.S. Surveillance, Epidemiology, and End Results Medicare-linked data on 10,928 patients with localized prostate cancer treated with primary cryoablation or brachytherapy.(14) Urinary dysfunction occurred more frequently with cryoablation (41.4%) than with brachytherapy (22.2%; p<0.001). Erectile dysfunction was also more common after cryoablation (34.7%) than brachytherapy (21.0%; p<0.001). Additionally, use of ADT was significantly more common after cryoablation than after brachytherapy, suggesting a higher rate of prostate cancer recurrence after cryoablation (1.4 vs 0.5 per 100 person-years). Bowel complications, however, occurred significantly more frequently with brachytherapy (19%) than cryoablation (12.1%).

Nepple et al (2013) analyzed data prospectively from 2 centers on 4,459 men treated with RP, 972 men treated with brachytherapy and 1,261 men treated with EBRT.(15) After treatment, median follow-up was 7.2 years. Brachytherapy did not significantly increase prostate cancer mortality compared with RP using Cox analysis or competing risk analysis; however, EBRT did increase prostate cancer mortality under Cox analysis. Overall mortality increased with both brachytherapy (hazard ratio [HR]: 1.78; 95% confidence interval [CI]: 1.37-2.31) and EBRT (HR: 1.71; 95% CI: 1.40-2.08) compared with RP.

Several observational studies have used matching to control for potential confounding due to lack of randomization. Loblaw et al (2017) evaluated data on men with clinically localized prostate cancer from the Genitourinary Radiation Oncologists of Canada (GUROC) prostate cancer database.(16) They identified 458 treated with LDR brachytherapy, 64 treated with EBRT, and 90 treated with stereotactic ablative body radiotherapy (SABR), a high-precision EBRT technique. The investigators created 2 sets of matched cohorts to control for confounding factors: SABR versus LDR brachytherapy and SABR versus EBRT. Cohorts were matched on age, baseline PSA, T stage, and number of positive cores. The SABR versus LDR cohorts included 284 patients, 71 of whom received SABR and 213 of whom received LDR brachytherapy. Analysis of SABR versus LDR brachytherapy outcomes found no significant differences between groups in BPFS or OS either before matching (p=0.52 and p=0.71, respectively) or after matching (p=0.33 and 0.56, respectively).

In a 1:1 matched-pair design, Pickles et al (2010) prospectively followed 278 low- and intermediate-risk, localized prostate cancer patients treated with brachytherapy or conformal EBRT (139 patients in each group).(17) The biochemical control (nadir + 2) at five years was 95% in the brachytherapy group and 85% in the EBRT group (p<0.001). This rate was unchanged at seven years in the brachytherapy group but decreased to 75% in the EBRT group. Brachytherapy patients experienced more urinary complaints whereas EBRT patients had more rectal and bowel issues.

Several large uncontrolled observational studies have also been published. A large multicenter study from Italy, published by Fellin et al (2016), included with 2237 patients with clinically localized prostate cancer who were treated with LDR brachytherapy as monotherapy and followed for at least 2 years.(18) Median follow-up was 65 months. Three-, 5-, and 7-year OS rates were 96.7%, 94.0%, and 89.2%, respectively. Three-, 5-, and 7-year disease-specific survival rates were 99.7%, 99.5%, and 98.4%, respectively. A total of 207 patients experienced

biochemical failure after a median of 42 months. The 3-, 5-, and 7-year BPFS rates were 95.7%, 91.9%, and 88.5%, respectively.

An analysis by Pham et al (2016) evaluated outcomes of permanent brachytherapy alone in men with large prostates (>60 mL).(19) The study included 2076 men with prostate cancer from a prospectively collected database who were treated with iodine-125 brachytherapy without androgen deprivation therapy. Two hundred sixty-nine (13%) of the 2076 patients had prostate volumes greater than 60 mL (median volume, 72.5 mL). Men with prostates volumes greater than 60 mL were significantly older than men with prostates volumes of 60 mL or less, and a significantly larger proportion had Gleason score of six and higher initial PSA levels. Median follow-up was 55 months. The five-year biochemical relapse-free survival (BPFS), the primary efficacy outcome, was 96.7% (95% CI, 94.4% to 98.9%) in men with prostates volumes greater than 60 mL and 92.9% (95% CI, 91.4% to 94.3%) in men with prostates volumes of 60 mL or less (p=0.02). Men with prostate volumes greater than 60 mL had significantly higher rates of grade III and IV GU and GI toxicity at five years (7.2%) than men with prostates volumes of 60 mL or less (3.2%; p<0.001). In multivariate analyses, a prostate volume greater than 60 mL was a statistically significant predictor for better BRFS and for higher rates of late grade III and IV GU toxicity.

Delouya et al (2017) published a retrospective, single-center cohort study analyzing patients with D'Amico intermediate-risk prostate cancer treated with brachytherapy or EBRT.(20) Of the 475 patients identified, 222 were treated with brachytherapy and 253 with EBRT. Median follow-up for patients without biochemical failure was 56 months, and median time to biochemical failure was 44.5 months. The brachytherapy group had a significantly less biochemical failure than EBRT (5.4% vs 14.2%, respectively; p=0.036), and the 7-year biochemical recurrence-free survival rates were 91% and 83%, respectively. In multivariate analysis, only Cancer of the Prostate Risk Assessment (CAPRA) score was a significant predictor of biochemical failure. Of patients with CAPRA scores of 0, 1, or 2, a better outcome was observed in those treated with brachytherapy (p=0.042), but there was no difference in patients with CAPRA scores of 3, 4, or 5 (p=0.5). The study was limited by its retrospective design and did not report toxicity data.

**Section Summary: Permanent Low-Dose Rate Brachytherapy as Monotherapy**
One RCT compared LDR brachytherapy as monotherapy and RP and found the 5-year BPFS rate was as high for brachytherapy as it was for RP and erectile function was better after brachytherapy. Comparative observational studies have found similar survival outcomes with LDR brachytherapy and other treatments; there were lower rates of some adverse events and higher rates of others.

## FOCAL PROSTATE BRACHYTHERAPY ALONE OR COMBINED WITH EBRT

### Clinical Context and Therapy Purpose
The purpose of focal permanent LDR brachytherapy alone or in combination with EBRT is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as active surveillance, EBRT alone, surgery, and cryoablation, in patients with localized prostate cancer.

The question addressed in this evidence review is: Does the use of permanent LDR brachytherapy provided as focal therapy improve the net health outcome in patients with prostate cancer?

The following PICOs were used to select literature to inform this review.

### *Populations*
The relevant population of interest is individuals with localized prostate cancer.

### *Interventions*
The therapy being considered is focal permanent LDR brachytherapy alone or in combination with EBRT.

Brachytherapy is a procedure in which a radioactive source (eg, radioisotope "seeds") is permanently or temporarily implanted in or near the tumor (eg, placed into the prostate gland to treat localized prostate cancer). The radiation from brachytherapy penetrates only short distances and is intended to deliver tumoricidal radioactivity directly to the tumor to improve local control while sparing surrounding normal tissue. Focal (subtotal) prostate brachytherapy is a form of organ-preserving therapy for small localized prostate cancers.

Studies of permanent brachytherapy have generally used iodine 125 or palladium 103. Use of cesium 131 is also being studied. Use of iodine 125 requires more seeds, thus reducing dosimetric dependence on any single seed.

### *Comparators*
Comparators of interest include active surveillance, EBRT alone, surgery, and cryoablation.

### *Outcomes*
The general outcomes of interest are OS, disease-specific survival, and treatment-related morbidity.

**Table 3. Outcomes of Interest for Individuals with Localized Prostate Cancer**

| Outcomes | Details |
|---|---|
| Disease-specific survival | Outcomes of interest include progression-free survival and tumor progression [Timing: ≥ 1 year] |
| Treatment-related morbidity | Outcomes of interest include treatment-related adverse events such as urinary blockage, sexual dysfunction, or gastrointestinal toxicities [Timing: ≥ 1 year] |

## Study Selection Criteria
See methodological criteria listed above.

## REVIEW OF EVIDENCE

## Systemic Reviews
Evidence in the published literature on focal prostate brachytherapy is limited. Reports have primarily focused on methods to delineate and evaluate tumor areas to identify appropriate candidates for focal prostate therapy and treatment-planning approaches. Original clinical reports on patient outcomes after focal brachytherapy are limited.

In a systematic review, Valerio et al (2014) assessed studies on focal prostate cancer therapies.(21) Only 1 series on focal brachytherapy was included. In that study by Nguyen et al (2012), 318 men received brachytherapy only to the peripheral zone.(22) In low-risk and intermediate-risk cases, freedom from PSA failure (nadir + 2ng/ml) was 95.1% and 73% at 5 years and 80.4% and 66.4% at 8 years, respectively. Many questions remain, including treatment effectiveness, patient selection criteria, and post-treatment monitoring approaches.

A systematic review by Baydoun et al (2017) assessing focal therapy for prostate cancer identified the Nguyen et al (2012) series (described above) and another relevant series.(23) The other study, by Cosset et al (2013), included 21 patients who underwent permanent iodine seed implants for low-risk prostate cancer.(24) The series reported on toxicity but not on biochemical control or survival outcomes. One patient experienced mild rectal toxicity at two months and no rectal toxicity was reported at 6 or 12 months. The mean score on the International Index of Erectile Function 5 scale was 20.1 at baseline and 19.8 at 12 months. (This scale ranges from 0 to 25, with a higher score indicating better function.)

**Observational Studies**

A nonrandomized comparative study by Kim et al (2020) has reported outcomes in patients with localized prostate cancer who received focal or partial LDR brachytherapy or whole gland LDR brachytherapy.(25) Sixty patients were identified retrospectively that received focal/partial LDR brachytherapy (n=30) or whole gland LDR brachytherapy (n=30) without supplemental EBRT at a single institution between January 2015 and January 2017. After a median follow-up duration of 45 months, the 3-year biochemical recurrence-free survival was 91.8% and 89.6% for the focal/partial LDR brachytherapy group and whole gland LDR brachytherapy group, respectively, which was not significantly different (p=.554). However, the proportion of patients who reached the 3-year follow-up was significantly lower in the focal/partial LDR brachytherapy group (60%) versus the whole gland LDR brachytherapy group (86.7%). The incidence of GU symptoms was significantly greater with whole gland LDR brachytherapy, as measured by the change in the International Prostate Symptom Score from baseline to 6 months (whole vs focal/partial change, 5.0 vs 3.0; p=.018). The incidence of rectal toxicity was numerically higher, but not statistically significant, with whole gland LDR brachytherapy versus focal/partial LDR brachytherapy (33.3% vs 16.7%, p=.136).

Several uncontrolled observational studies have also been published that have reported longer-term survival outcomes. Saito et al (2021) examined outcomes of hemi-gland LDR brachytherapy for intermediate-risk, unilateral prostate cancer.(26) Twenty-four patients were included and followed for a median of 61 months. Biochemical failure (PSA failure [nadir + 2 ng/mL])-free survival rates at 3 and5 years were 86% and 71%, respectively. Treatment failure-free survival (freedom from radical or systemic therapy, metastases, and cancer-specific mortality) rates at 3 and 5 years were 95% and 90%, respectively. The 5-year rate of metastasis-free survival was100%. Ta et al (2021) reported on outcomes of focal LDR brachytherapy for low- to intermediate-risk prostate cancer.(27) Thirty-nine patients were included and followed for a mean of 65 months. Biochemical relapse-free survival at 5 years, disease-free survival, and OS were 96.8% ± 0.032%, 79.5% ± 0.076%, and 100%, respectively.

**Section Summary: Focal Brachytherapy**
Systematic reviews of focal prostate cancer therapies have identified case series evaluating focal brachytherapy. One nonrandomized comparative study reported similar 3-year biochemical recurrence-free survival with focal/partial LDR brachytherapy versus whole gland LDR brachytherapy. Small, single center observational studies have reported favorable medium-term oncologic outcomes. Clinical outcomes in larger studies, preferably from RCTs or nonrandomized comparative studies, and long-term follow-up are needed before conclusions can be drawn about the effect of focal brachytherapy on health outcomes in patients with localized prostate cancer.

## SUMMARY OF EVIDENCE

For individuals who have localized prostate cancer who receive permanent low-dose rate (LDR) brachytherapy plus external beam radiotherapy (EBRT), the evidence includes a randomized controlled trial (RCT) on a related comparison and observational studies. Relevant outcomes are overall survival (OS), disease-specific survival, and treatment-related morbidity. No RCTs have compared permanent LDR brachytherapy plus EBRT with EBRT alone in patients who have clinically localized prostate cancer. An RCT comparing boost LDR brachytherapy plus boost EBRT with EBRT alone found better biochemical progression-free survival (BPFS) but not overall survival or disease-specific survival in patients who had combined treatment. Another comparative observational study found differences in urinary irritative function and bowel function were significantly worse at 3 years with combination treatment, but the differences were no longer clinically meaningful at 5 years. Multicenter and single-center uncontrolled studies found relatively high rates of BPFS after LDR brachytherapy plus EBRT. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have localized prostate cancer who receive permanent LDR brachytherapy as monotherapy, the evidence includes RCTs, systemic reviews and observational studies. Relevant outcomes are OS, disease-specific survival, and treatment-related morbidity. One RCT compared LDR brachytherapy as monotherapy with radical prostatectomy and found that the five-year BPFS rate was as high for brachytherapy as it was for radical prostatectomy and erectile function was better after brachytherapy. Comparative observational studies have found similar survival outcomes with LDR brachytherapy compared with other treatments; there were lower rates of some adverse events and higher rates of others. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with localized prostate cancer who receive focal permanent LDR brachytherapy alone or combined with EBRT, the evidence includes observational studies and systematic reviews of case series. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity. Systematic reviews of focal prostate cancer therapies have only identified a few case series evaluating focal brachytherapy. One nonrandomized comparative study reported similar 3-year biochemical recurrence-free survival with focal/partial LDR brachytherapy versus whole gland LDR brachytherapy. Small, single center observational studies have reported favorable medium-term oncologic outcomes. 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

#### American College of Radiology

The American College of Radiology (2017) published appropriateness criteria for permanent brachytherapy for prostate cancer.(28) Relevant recommendations are:

- "PPB (permanent prostate brachytherapy) monotherapy remains an appropriate and effective curative treatment for low-risk prostate cancer patients."
- "PPB monotherapy can be considered for select intermediate-risk patients. Multiparametric MRI (magnetic resonance imaging) may be useful in selecting such patients."
- "High-risk localized prostate cancer treated with PPB should be managed in conjunction with EBRT and ADT.

#### American Society of Clinical Oncology and Cancer Care Ontario

The American Society of Clinical Oncology and Cancer Care Ontario (2017) issued joint guidelines on brachytherapy for prostate cancer that included the following statement:(29)

"For patients with intermediate-risk prostate cancer choosing EBRT with or without androgen-deprivation therapy (ADT), brachytherapy boost (LDR or high–dose rate [HDR]) should be offered to eligible patients. For low-intermediate risk prostate cancer (Gleason 7, prostate-specific antigen, 10 ng/mL or Gleason 6, prostate-specific antigen, 10 to 20 ng/mL) LDR brachytherapy alone may be offered as monotherapy. For patients with high-risk prostate cancer receiving EBRT and ADT, brachytherapy boost (LDR or HDR) should be offered to eligible patients."

#### National Comprehensive Cancer Network

National Comprehensive Cancer Network guidelines for prostate cancer (v.2.2022) note that LDR brachytherapy as monotherapy is indicated for patients with very low-, low-, or favorable intermedidate-risk prostate cancers.(30) Additionally, "LDR or HDR brachytherapy can be added as a boost to EBRT plus ADT in men with unfavorable intermediate-, high-, or very high-risk prostate cancer being treated with curative intent. Combining EBRT and brachytherapy allows dose escalation while minimizing acute or late toxicity in patients with high-risk localized or locally advanced cancer."

The guidelines further state that patients with very large or very small prostates (size cutoffs were not discussed), symptoms of bladder outlet obstruction, or previous transurethral resection of the prostate are more difficult to implant and may suffer increased risk of adverse effects. In cases of enlarged prostate, neoadjuvant ADT may be used to shrink the prostate. However, increased toxicity would be expected and prostate size may not shrink.

### U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable.

### Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 4.

**Table 4. Summary of Key Trials**

| NCT No. | Trial Name | Planned Enrollment | Completion Date |
|---|---|---|---|
| **Ongoing** | | | |
| NCT02692105 | A Phase III Randomized Pilot Study of Low Dose Rate Compared to High Dose Rate Prostate Brachytherapy for Favourable Risk and Low Tier Intermediate Risk Prostate Cancer | 60 | Apr 2026 |
| NCT02960087 | A Randomized Phase II Trial Evaluating High Dose Rate Brachytherapy and Low Dose Rate Brachytherapy as Monotherapy in Localized Prostate Cancer | 232 | Mar 2028 |
| NCT02290366 | Prospective Evaluation of Focal Brachytherapy Using Cesium-131 For Patients with Low-Risk Prostate Cancer | 100 | Feb 2022 |
| NCT02895854 | LDR Brachytherapy Versus Hypofractionated SBRT for Low and Intermediate Risk Prostate Cancer Patients | 44 | Dec 2021 |

NCT: national clinical trial.

## Government Regulations

### National:

There is no National Coverage Determination for brachytherapy.

### Local:

There is a retired Local Coverage Determination (LCD 30320) that addresses brachytherapy for prostate cancer.

"Patients with PROSTATE cancers that are eligible for seed implantation fall within a set of guidelines established by the treating radiation oncologist and urologist."

*(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)*

## Related Policies

- Charged-Particle (Proton or Helium Ion) Radiotherapy for Neoplastic Conditions
- Intensity-Modulated Radiation Therapy of the Prostate
- Intraoperative Radiotherapy
- Stereotactic Radiosurgery and Stereotactic Body Radiotherapy

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*The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 12/8/21, the date the research was completed.*

## Joint BCBSM/BCN Medical Policy History

| Policy Effective Date | BCBSM Signature Date | BCN Signature Date | Comments |
|---|---|---|---|
| 7/1/02 | Joint policy established | 7/1/02 | Joint policy established |
| 11/18/03 | Policy retired | 11/18/03 | Policy retired |
| 7/1/12 | 4/10/12 | 5/15/12 | Policy unretired; entire policy description and rationale sections updated; inclusion criteria revised; Medical policy statement revised from previous version; code 55875 replaced 55859 and multiple related codes added. |
| 3/1/14 | 12/10/13 | 1/6/14 | Routine maintenance; added statement to Medical Policy Statement and Exclusions that focal and subtotal prostate brachytherapy are experimental/investigational. |
| 5/1/15 | 2/17/15 | 2/27/15 | Routine maintenance; references and rationale updated; new codes G6003-G6014 added effective 1/1/15; codes 77403-77406 deleted effective 1/1/15; nomenclature revised for code 77402 effective 1/1/15. |
| 7/1/16 | 4/19/16 | 4/19/16 | Routine maintenance<br>Added codes 76873, 77407, 77412, 77316-77318 |
| 1/1/17 | 10/11/16 | 10/11/16 | Routine maintenance |
| 1/1/18 | 10/19/17 | 10/19/17 | Routine maintenance |
| 1/1/19 | 10/16/18 | 10/16/18 | Routine maintenance |
| 5/1/19 | 2/19/19 | | Routine maintenance |
| 5/1/20 | 2/18/20 | | Routine maintenance |
| 5/1/21 | 2/16/21 | | Routine maintenance |
| 5/1/22 | 2/15/22 | | Routine maintenance |

Next Review Date: 1st Qtr, 2023

# BLUE CARE NETWORK BENEFIT COVERAGE
# POLICY: BRACHYTHERAPY FOR CLINICALLY LOCALIZED PROSTATE CANCER USING PERMANENTLY IMPLANTED SEEDS

## I. Coverage Determination:

| | |
|---|---|
| **Commercial HMO (includes Self-Funded groups unless otherwise specified)** | Covered |
| **BCNA (Medicare Advantage)** | Refer to the Medicare information under the Government Regulations section of this policy. |
| **BCN65 (Medicare Complementary)** | Coinsurance covered if primary Medicare covers the service. |

## II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.
- Duplicate (back-up) equipment is not a covered benefit.