Brachytherapy for Clinically Localized Prostate Cancer Using Permanently Implanted Seeds

**Policy Statement**

Brachytherapy using permanent transperineal implantation of radioactive seeds may be considered **medically necessary** for the treatment of localized prostate cancer when used for **either** of the following criteria (see Policy Guidelines section):

- **In conjunction with external-beam radiotherapy**
- **As monotherapy**

Focal prostate brachytherapy is considered **investigational** in the treatment of prostate cancer.

**Policy Guidelines**

Permanent brachytherapy with 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 external-beam radiotherapy (3-dimensional conformal radiotherapy [3D-CRT], intensity-modulated radiotherapy, or proton beam therapy) is used, sometimes with androgen deprivation therapy, to treat higher risk disease. Adequate dose escalation should be achieved with combination permanent brachytherapy and 3D-CRT. Intensity-modulated radiotherapy should be limited to cases in which 3D-CRT planning is unable to meet dose-volume constraints for normal tissue tolerance.

Prostate cancer risk is often defined using the following criteria (Epstein):

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

Permanent low-dose rate brachytherapy, as monotherapy, in the treatment of localized prostate cancer may be best used in men older than 60 years with small volume cancer of low-risk disease (Gleason score, less than 7; PSA level, less than 10 mg/mL; stage T1c). Patients in their 50s or younger may not be considered ideal candidates for brachytherapy based on concerns about the durability of treatment and quality of life outcomes. However, favorable outcomes in men 60 years or younger treated with brachytherapy for localized prostate cancer have been reported. Ideally, the cancer should be within a prostate with a volume of less than 60 mL. Patients with locally advanced prostate cancer may be undertreated by permanent brachytherapy alone.

**Coding**

The procedure is usually performed in 2 stages: a prostate volume study (CPT code 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. Typical isotopes include iodine and palladium, and the selection of isotope is usually based on physician preference. A computed tomography scan is usually performed at some stage after the procedure to determine the quality of the seed placement.

The following CPT codes for prostate brachytherapy are consist of a series of codes describing the treatment planning, dosimetry, and delivery of radiotherapy:
Brachytherapy is a procedure in which a radioactive source (e.g., radioisotope “seeds”) is permanently or temporarily implanted in or near the tumor (e.g., 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. This evidence review only assesses permanent low-dose rate (LDR) brachytherapy in prostate cancer.

**Related Policies**

- Charged-Particle (Proton or Helium Ion) Radiotherapy for Neoplastic Conditions
- Focal Treatments for Prostate Cancer
- High-Dose Rate Temporary Prostate Brachytherapy
- Intensity-Modulated Radiotherapy of the Prostate
- Whole Gland Cryoablation of Prostate Cancer

**Benefit Application**

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.
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through the 510(k) process, including I-Seed® (Theragenics), Proxcelan™ Cs-131 (IsoRay Medical), and BrachySource® Brachytherapy Seed Implants (C.R. Bard). Food and Drug Administration product code: KXX.

Rationale

Background

Prostate Cancer

In 2018, it has been estimated that 9.5% of all new cancer diagnoses will involve the prostate. In addition, as of 2015, estimates have suggested that over 3 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. Brachytherapy has been used for localized prostate cancer to provide local tumor control, which has been 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 low-risk disease; temporary (high-dose rate) brachytherapy is typically reserved for intermediate- or high-risk disease. This evidence review only assesses permanent LDR brachytherapy in prostate cancer.

The proposed biologic advantages of brachytherapy compared with external-beam radiotherapy (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 to 60 centigray per hour, whereas conventional fractionated EBRT dose rates exceed 200 centigray per minute. 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. Additionally, brachytherapy is performed as a single procedure in the outpatient setting, which many patients may find preferable to the multiple EBRT sessions. The total doses of radiotherapy that can be delivered may also vary between EBRT and brachytherapy, especially with newer forms of EBRT such as 3-dimensional conformal radiotherapy 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 radiotherapy, concerns exist with the long-term risk of treatment-related secondary malignancies. Reports have also suggested that the clinician’s level of experience with brachytherapy correlates with disease recurrence rates.

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. Postimplant dosimetric assessment should be performed to ensure the quality of the implant and optimal source placement (i.e., targeted tumor areas receive the predetermined radiation dosages while nearby structures and tissues are preserved).

Permanent brachytherapy may be used as monotherapy or as combination therapy with EBRT as a way to boost the dose of radiotherapy delivered to the tumor; this combined modality therapy can be performed with permanent or temporary brachytherapy. The brachytherapy boost is typically done two to six 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 associated with brachytherapy, including urinary, bowel, and sexual dysfunction.

**Literature Review**

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function-including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, two domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

**Permanent Low-Dose Rate Brachytherapy Plus External-Beam Radiotherapy**

**Clinical Context and Therapy Purpose**

The purpose of permanent LDR brachytherapy plus 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 permanent LDR brachytherapy alone or in combination with EBRT or 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.

**Patients**

The relevant population of interest are 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 (e.g., radioisotope "seeds") is permanently or temporarily implanted in or near the tumor (e.g., 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. This evidence review only assesses permanent LDR brachytherapy in prostate cancer.

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. Permanent brachytherapy may be used as monotherapy or as combination therapy with EBRT to boost the dose of radiotherapy delivered to the tumor; this combined modality therapy can be performed with permanent or temporary brachytherapy. Permanent LDR brachytherapy plus EBRT is performed by oncologists and radiologists in an inpatient clinical setting.

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

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Study Selection Criteria
Methodologically credible studies were selected using the following principles:

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

Systematic Reviews
Kee et al (2018) published a systematic review and meta-analysis comparing brachytherapy and EBRT boost for patients with prostate cancer. 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 RCTs were identified that compared LDR brachytherapy plus EBRT with LDR brachytherapy or with EBRT alone in patients who have clinically localized prostate cancer. Morris et al (2017) reported on the Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy trial, which evaluated patients who received androgen deprivation therapy (ADT) and EBRT. 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 (i.e., clinically localized disease), BPFS
was significantly higher in the brachytherapy boost group (p = 0.003). OS and disease-specific survival did not differ significantly between the LDR brachytherapy boost and the 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). 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**

Abuhabib et al (2017) reported on 579 patients with localized prostate cancer treated using LDR brachytherapy plus EBRT (n = 191) or EBRT alone (n = 388). Patients were not randomized to a 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 a biochemical recurrence. Acturetimes BPFS up to 10 years was significantly higher in the combined treatment than in the EBRT-only group (p = 0.014). Additionally, local progression-free survival significantly favored the combined treatment group (p = 0.042), but distant metastases-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 2 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). 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 7 patients who developed grade 3 or 4 rectal toxicity had received combined treatment. The authors did not report the number of patients with grade 2, 3, or 4 rectal toxicity in either group. Moreover, survival outcomes were not reported.

Findings of the Radiation Therapy Oncology Group 0019 multicenter study, published by Lawton et al (2012), evaluated data from 131 patients followed for a median of 8.3 years. All patients received EBRT followed by permanent LDR brachytherapy. Late GU and/or GI tract toxicity greater than grade 3 was estimated to be 15% and most commonly included urinary frequency, dysuria, and proctitis. Grade 3 impotence was reported in 42% of patients. These adverse events rates with combined modality therapy were higher than often reported for either brachytherapy or EBRT treatment alone. Estimates of biochemical failure were 18% using the Phoenix definition, 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. In this series, ADT was not used. This report was based on a series of 223 consecutive patients treated between 1987 and 1993; patients had stage T1 to T3 disease. Permanent brachytherapy was performed with radioactive palladium or iodine four weeks after EBRT. Fifteen-year BPFS was 88% in the low-risk group, 80% in the intermediate-risk group, and 53% in the high-risk group. Additionally, long-term outcomes were compared with those of two institutions that had results for radical prostatectomy (RP). Results were similar across Gleason score categories (e.g., the relapse-free survival was 25%-30% for those with a 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 3-dimensional conformal radiotherapy followed by permanent (palladium) brachytherapy. This 2007 study involved 282 intermediate- and high-risk patients treated from 1992 to 1996. Fourteen-year BPFS in the intermediate-risk group was 87% and 72% in the high-risk group.

**Section Summary: Permanent LDR 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 BPFS but not OS or disease-specific survival in patients who had combined treatment. There are also a number of observational studies, including a nonrandomized study comparing LDR brachytherapy plus EBRT with EBRT alone. The BPFS rate was significantly higher in the combined treatment group; rates of GU but not GI toxicity were significantly higher with combined treatment. Multicenter and single-center uncontrolled studies have found relatively high rates of BPFS after LDR brachytherapy plus EBRT.

**Permanent LDR 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 permanent LDR brachytherapy alone or in combination with EBRT or 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.

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

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

**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.

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**Systematic Reviews**
A Cochrane review by Peinemann et al (2011) evaluated the literature on LDR brachytherapy for prostate cancer. Reviewers focused on the only identified RCT, Giberti et al (2009). The Giberti et al (2009) trial (detailed below) compared brachytherapy with RP and was considered to have a high-risk of bias. Peinemann et al (2011) also conducted a systematic review of brachytherapy. 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 on results for 200 low-risk prostate cancer patients randomized to RP or to brachytherapy. BPFS rates at 5 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 posttreatment, 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 outcomes in patients with localized prostate cancer who received one of the several treatments. Williams et al (2012) compared data from the U.S. Surveillance, Epidemiology, and End Results Program, Medicare-linked data on 10928 patients with localized prostate cancer treated with primary cryoablation or brachytherapy. 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 after brachytherapy (21.0% \( p<0.001 \)). Additionally, the 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 with cryoablation (12.1%).

Nepple et al (2013) analyzed data prospectively from 2 centers on 4459 men treated with RP, 972 men treated with brachytherapy, and 1261 men treated with EBRT. After treatment, the 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 (HR, 1.78; 95% confidence interval [CI], 1.37 to 2.31) and EBRT (HR,1.71; 95% CI, 1.40 to 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 prostate cancer database. 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 two sets of matched cohorts to control for confounding factors: SABR vs LDR brachytherapy and SABR vs EBRT. Cohorts were matched on age, baseline PSA level, T stage, and the number of positive cores. The SABR vs LDR cohorts included 284 patients, 71 of whom received SABR and 213 of whom received LDR brachytherapy. Analysis of SABR vs 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 EBRT (139 patients in each group). The biochemical control (nadir + 2 ng/mL) at 5 years was 95% in the brachytherapy group and 85% in the EBRT group (\( p<0.001 \)). This rate was unchanged at 7 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 2237 patients with clinically localized prostate cancer, who were treated with LDR brachytherapy as monotherapy and followed for at least 2 years. 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). The study included 2076 men with prostate cancer from a prospectively collected database who were treated with iodine-125 brachytherapy without ADT. 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 scores of 6 and higher for initial PSA levels. Median follow-up was 55 months. The 5-year BPFS rate (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 volume greater than 60 mL had significantly higher rates of grade 3 and 4 GU and GI toxicity at 5 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 biochemical recurrence-free survival and for higher rates of late grade 3 and 4 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. 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 the 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 the 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 LDR Brachytherapy as Monotherapy**

One RCT compared LDR brachytherapy as monotherapy with RP and found the five-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 combined 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 permanent LDR brachytherapy alone or in combination with EBRT or 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.

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

**Interventions**
The therapy being considered is focal permanent LDR brachytherapy alone or combined with EBRT.
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                                                                                      | 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 |

Systematic 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.20 Only one series on focal brachytherapy was included. In that study by Nguyen et al (2012), 318 men received brachytherapy only to the peripheral zone.21 In low-risk and intermediate-risk cases, freedom from PSA failure (nadir + 2 ng/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 posttreatment 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.22 The other study, by Cosset et al (2013), included 21 patients who underwent permanent iodine seed implants for low-risk prostate cancer.23 The series reported on toxicity but not on biochemical control or survival outcomes. One patient experienced mild rectal toxicity at 2 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.)

Section Summary: Focal Brachytherapy
Systematic reviews of focal prostate cancer therapies have identified two case series evaluating focal brachytherapy. Survival outcomes were not reported. More data are needed, preferably from RCTs or nonrandomized comparative studies, 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 LDR brachytherapy plus EBRT, the evidence includes an RCT on a related comparison and observational studies. The relevant outcomes are 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 BPFS but not OS or disease-specific survival in patients who had combined treatment. A comparative observational study found a significantly higher BPFS rate in patients who received LDR brachytherapy plus EBRT than with EBRT alone. Rates of GU but not GI toxicity were significantly higher with combined treatment. 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 a meaningful improvement in the net health outcome.
For individuals who have localized prostate cancer who receive permanent LDR brachytherapy as monotherapy, the evidence includes RCTs, systematic reviews, and observational studies. The 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 a meaningful 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 case series and systematic reviews. The relevant outcomes are OS, disease-specific survival, and treatment-related morbidity. Systematic reviews of focal prostate cancer therapies have only identified a few case series evaluating focal brachytherapy. Survival outcomes were not reported. Controlled studies in larger numbers of patients are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information
Practice Guidelines and Position Statements

National Comprehensive Cancer Network
National Comprehensive Cancer Network (v.2.2019) guidelines for prostate cancer note that low-dose rate (LDR) brachytherapy as monotherapy is indicated for patients with low-risk cancers and select patients with low-volume immediate-risk cancers. Intermediate-risk cancers may be treated by combining LDR brachytherapy with external-beam radiotherapy (EBRT; 40-50 gray) and approximately 4 to 6 months of neoadjuvant, concomitant, or adjuvant androgen deprivation therapy (ADT). Patients with high-risk cancers may be treated with a combination of EBRT (40-50 gray) plus LDR brachytherapy and approximately 2 to 3 years of neoadjuvant, concomitant, or adjuvant ADT.

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 an increased risk of adverse events. In cases of an enlarged prostate, neoadjuvant ADT may be used to shrink the prostate. However, increased toxicity would be expected, and prostate size may not shrink.

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. Relevant recommendations are:

“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.”

American College of Radiology
The American College of Radiology (2017) published appropriateness criteria for permanent brachytherapy for prostate cancer. 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."

**U.S. Preventive Services Task Force Recommendations**

Not applicable.

**Medicare National Coverage**

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

**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**

<table>
<thead>
<tr>
<th>NCTNo.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<tbody>
<tr>
<td>Ongoing</td>
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<tr>
<td>NCT02895854</td>
<td>LDR Brachytherapy Versus SBRT for Low and Intermediate Risk Prostate Cancer Patients (BRAVEROBO)</td>
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<td>Dec 2019</td>
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<tr>
<td>NCT02692105</td>
<td>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</td>
<td>60</td>
<td>Apr 2026</td>
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<tr>
<td>Unpublished</td>
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<tr>
<td>NCT00063882</td>
<td>A Phase III Study Comparing Combined External Beam Radiation and Transperineal Interstitial Permanent Brachytherapy With Brachytherapy Alone for Selected Patients With Intermediate Risk Prostatic Carcinoma</td>
<td>588</td>
<td>May 2017 (Unknown)</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

**References**

8.01.14 Brachytherapy for Clinically Localized Prostate Cancer Using Permanently Implanted Seeds

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**Documentation for Clinical Review**

Please provide the following documentation (if/when requested):

- History and physical and/or consultation notes including:
  - Tumor classification
  - Past medical and/or surgical treatment(s) and response(s)
- Pathology report(s)
- Radiation treatment plan including: type of brachytherapy, therapy schedule and number of treatments

**Post Service**

- Daily radiation treatment records (If applicable)
- Operative/procedure report(s)

**Coding**

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

**MN/IE**

The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>CPT®</td>
<td>55875</td>
<td>Transperineal placement of needles or catheters into prostate for interstitial radioelement application, with or without cystoscopy</td>
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<tr>
<td></td>
<td>76873</td>
<td>Ultrasound, transrectal; prostate volume study for brachytherapy treatment planning (separate procedure)</td>
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<td>77316</td>
<td>Brachytherapy isodose plan; simple (calculation[s] made from 1 to 4 sources, or remote afterloading brachytherapy, 1 channel), includes basic dosimetry calculation(s)</td>
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<td>77407</td>
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<td>Brachytherapy needle</td>
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<tr>
<td>0VH031Z</td>
<td>Insertion of Radioactive Element into Prostate, Percutaneous Approach</td>
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<tr>
<td>0VH041Z</td>
<td>Insertion of Radioactive Element into Prostate, Percutaneous Endoscopic Approach</td>
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<td>0VH071Z</td>
<td>Insertion of Radioactive Element into Prostate, Via Natural or Artificial Opening</td>
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<td>0VH081Z</td>
<td>Insertion of Radioactive Element into Prostate, Via Natural or Artificial Opening Endoscopic</td>
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<td>High Dose Rate (HDR) Brachytherapy of Prostate using Iridium 192 (Ir-192)</td>
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<td>High Dose Rate (HDR) Brachytherapy of Prostate using Iodine 125 (I-125)</td>
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Brachytherapy for Clinically Localized Prostate Cancer Using Permanently Implanted Seeds

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

<table>
<thead>
<tr>
<th>Effective Date</th>
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<th>Reason</th>
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<tr>
<td>01/01/2008</td>
<td>New Policy Adoption Combined the following BSC policies and addressed medical necessity for additional cancer diagnoses.</td>
<td>Medical Policy Committee</td>
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<tr>
<td></td>
<td>• Brachytherapy for Prostate Cancer</td>
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<td></td>
<td>• Breast Brachytherapy after Breast-Conserving Surgery, as Boost with Whole Breast Irradiation, or Alone as Accelerated Partial Breast Irradiation (APBI)</td>
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<td>• Interstitial or Balloon Breast Brachytherapy</td>
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<td>03/01/2009</td>
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<td>02/22/2013</td>
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<td>Policy title change from Brachytherapy for Oncologic Indications</td>
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<td>BCBSA Medical Policy adoption</td>
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<tr>
<td>09/01/2019</td>
<td>Policy revision without position change</td>
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Definitions of Decision Determinations

Medically Necessary: A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.
**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

**Prior Authorization Requirements (as applicable to your plan)**

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member’s health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member’s eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.