Policy Statement

High-dose rate (HDR) prostate brachytherapy may be considered medically necessary as monotherapy or in conjunction with external-beam radiotherapy in the treatment of localized prostate cancer.

High-dose rate (HDR) prostate brachytherapy is considered investigational in the treatment of prostate cancer when used as salvage therapy.

Policy Guidelines

High-dose rate (HDR) brachytherapy as monotherapy is being used in low- and intermediate-risk patients with localized prostate cancer. HDR brachytherapy combined with external-beam radiotherapy (3-dimensional conformal radiotherapy [3D-CRT], intensity-modulated radiotherapy, or proton beam therapy) may be used for more advanced or aggressive prostate cancers. Adequate dose escalation should be achieved with combination HDR temporary brachytherapy and 3D-CRT. Intensity-modulated radiotherapy (IMRT) should be limited only to cases in which 3D-CRT planning is not able to meet dose-volume constraints for normal tissue tolerance. Permanent low-dose rate 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 external-beam radiotherapy (EBRT) is used (sometimes along with androgen deprivation therapy) to treat higher risk disease.

Prostate cancer risk is often defined using the following criteria:

- **Low risk:** prostate-specific antigen (PSA) 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 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

Coding

CPT coding for HDR prostate brachytherapy will consist of a series of codes describing the treatment planning, dosimetry, and delivery of radiotherapy. These codes overlap with those describing brachytherapy using permanent seed implantation. However, because the therapy is given over several days, the last 2 CPT codes listed below may be used more than once:

- **76873**: Ultrasound, transrectal; prostate volume study for brachytherapy treatment planning (separate procedure)
- **77316**: Brachytherapy isodose plan; simple (calculation[s] made from 1 to 4 sources, or remote afterloading brachytherapy, 1 channel), includes basic dosimetry calculation(s)
- **77317**: Brachytherapy isodose plan; intermediate (calculation[s] made from 5 to 10 sources, or remote afterloading brachytherapy, 2-12 channels), includes basic dosimetry calculation(s)
- **77318**: Brachytherapy isodose plan; complex (calculation[s] made from over 10 sources, or remote afterloading brachytherapy, over 12 channels), includes basic dosimetry calculation(s)
- **77778**: Interstitial radiation source application, complex, includes supervision, handling, loading of radiation source, when performed
- **77790**: Supervision, handling, loading of radiation source
The surgical code for placement of the brachytherapy catheter is:
- 55875: Transperineal placement of needles or catheters into prostate for interstitial radioelement application, with or without cystoscopy

There are codes specific to afterloading of HDR brachytherapy:
- 77770: Remote afterloading high dose rate radionuclide interstitial or intracavitary brachytherapy, includes basic dosimetry, when performed; 1 channel
- 77771: Remote afterloading high dose rate radionuclide interstitial or intracavitary brachytherapy, includes basic dosimetry, when performed; 2-12 channels
- 77772: Remote afterloading high dose rate radionuclide interstitial or intracavitary brachytherapy, includes basic dosimetry, when performed; over 12 channels

**Description**

High-dose rate (HDR) temporary prostate brachytherapy is a technique for delivering a high-intensity radiation source directly to the prostate gland to treat cancer. The radiation source is administered through hollow catheters or needles inserted precisely into several areas of the prostate gland using ultrasound guidance and treatment planning computed tomography or ultrasound images. Radiation is applied to target areas until the prescribed dose is reached and is then removed. The goal of treatment is to induce direct tumor necrosis and reduce toxicity and surrounding tissue damage.

**Related Policies**

- Brachytherapy for Clinically Localized Prostate Cancer Using Permanently Implanted Seeds
- Charged-Particle (Proton or Helium Ion) Radiotherapy for Neoplastic Conditions
- 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.

**Regulatory Status**

A number of devices have been cleared for marketing by the U.S. Food and Drug Administration through the 510(k) process to deliver HDR brachytherapy to the prostate. The Martinez Prostate Template Set and the Photon Technologies HDR Prostate Template and Accessories are examples of radiation application devices. These devices are intended as accessories to commercially available HDR remote afterloader systems for prostate brachytherapy. Food and Drug Administration product code: JAQ.
Rationale

Background
Brachytherapy for prostate cancer can be delivered in a variety of ways. Perhaps the most common technique uses radioactive seeds permanently implanted into prostate tissue. These seeds contain isotopes that slowly emit radiation of relatively low energy. In contrast, temporary prostate brachytherapy involves the use of higher energy radioisotopes such as iridium 192. The latter isotopes deliver radiation at higher dose rates than permanent seeds and may be more effective in destroying rapidly dividing cancer cells. For implantation, needle catheters are placed into the prostate gland using transrectal ultrasound guidance. Once placed, a dosimetric plan is developed, and the radioactive source is inserted into each needle using an afterloading device. The radioactive source is left in the needle for a predetermined time, called the “dwell” time. The radiation usually is delivered once or twice daily over several days. The dwell time can be altered at various positions along the needle’s length to control dose distribution to the target volume and critical surrounding structures (eg, rectum, urethra). This strategy contrasts with permanent seed implantation in which dosimetry is calculated before needle placement and which cannot be altered after seed implantation. Treatment typically consists of delivering a dose of 4000 to 5000 centigray with external-beam radiotherapy (EBRT) to the prostate and periprostatic tissues, while high-dose rate (HDR) brachytherapy is used as the method of dose escalation to the prostate gland. Total boost doses vary. Additionally, studies are also being conducted using HDR brachytherapy as the sole treatment modality (monotherapy) for prostate cancer.

It is accepted that increasing doses of radiotherapy are associated with improved biochemical control (ie, stable levels of prostate-specific antigen), and thus there has been an interest in exploring different techniques of dose escalation, simultaneously limiting both early and late toxicities in surrounding tissues. In patients with the locally advanced disease, it has been hypothesized that local failure might be related to large tumor volume and radioresistant cell clones, both of which might respond to higher radiation doses. HDR brachytherapy has been primarily investigated as an adjunct to EBRT for dose escalation. Other techniques for dose escalation include EBRT using intensity-modulated radiotherapy for treatment planning and delivery, proton beam therapy (which may also use intensity-modulated radiotherapy), or EBRT combined with brachytherapy using interstitial seeds.

Literature Review
Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are 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 to 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 a technology, 2 domains are examined: the relevance and the 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.
High-Dose Rate Brachytherapy Plus External-Beam Radiotherapy

Clinical Context and Therapy Purpose
The purpose of high-dose rate (HDR) temporary brachytherapy plus external-beam radiotherapy (EBRT) in patients who have localized prostate cancer is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does use of HDR temporary brachytherapy plus EBRT improve the net health outcome in patients with localized prostate cancer?

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

Patients
The relevant population of interest is patients with localized prostate cancer.

Interventions
The therapy being considered is HDR temporary brachytherapy plus EBRT.

Comparators
The following therapies are currently being used to make decisions about localized prostate cancer: EBRT, surgery, and cryoablation.

Outcomes
The general outcomes of interest are locoregional recurrence, overall survival (OS), and adverse events.

Timing
Regular follow-up (every 6 to 12 months) are suggested for the first 5 years posttreatment.

Setting
Brachytherapy and EBRT are administered in an outpatient oncology setting.

Systematic Reviews
Zaorsky et al (2014) reviewed 38 prospective and retrospective studies (total N=8008 patients) reporting on HDR brachytherapy boost with EBRT for prostate cancer.1 Five-year freedom from biochemical failure rates were 85% to 100% for low-risk, 80% to 98% for intermediate-risk, 59% to 96% for high-risk patients, and 34% to 85% for locally advanced patients. In all risk groups, 5-year rates of cancer-specific survival, OS, local recurrence, and distant metastases were 99% to 100%, 85% to 100%, 0% to 8%, and 2% to 12%, respectively. Late Radiation Therapy Oncology Group (RTOG) grade 3 or 4 genitourinary (GU) or gastrointestinal (GI) toxicities occurred in less than 6% of patients. Comparisons of HDR brachytherapy with other radiation techniques were inconclusive. Interpretation of results of this systematic review was limited by the number of reports from single-institution studies, the lack of comparative studies, and insufficient reporting on toxicity and quality of life.

Randomized Controlled Trials
In a multicenter open-label RCT in Sweden, Lennemäes et al (2015) allocated patients with localized and locally advanced (T1b-T3a, N0, M0) prostate cancer to open radical prostatectomy (RP, n=45) or to combined EBRT (3-dimensional conformal radiotherapy, 25×2 Gray [Gy]) and HDR brachytherapy (2×10 Gy) between 1996 and 2001 (n=44).2 All patients received total androgen blockade that comprised a combination of leuprorelin and flutamide for 6 months. Follow-up assessments included digital rectal examinations if serum prostate-specific antigen (PSA) levels exceeded 10 ng/mL. Quality of life changes were assessed using the European Organization of Research and Treatment of Cancer Quality of Life Questionnaire C33.3 Patients completed the RTOG/European Organization of Research and Treatment of Cancer Toxicity Scale at 12, 24, and 60 months posttreatment. No statistically significant between-group differences were reported for any of the European Organization of Research
and Treatment of Cancer Quality of Life Questionnaire C33 variables or treatment-associated toxicities. Sixty-eight (76%) patients were alive at 10-year follow-up; 8 patients (in the RP group, 2 in the 3-dimensional conformal radiotherapy group; 9% total) died of prostate cancer, 13 (n=6 in the RP group, n=7 in the 3-dimensional conformal radiotherapy group) died of other causes.

Hoskin et al (2007) reported on a European single-center randomized trial of 220 patients conducted between 1997 and 2005. It compared EBRT at 55 Gy with EBRT at 35.75 Gy plus HDR brachytherapy in patients with prostate cancer. With a median follow-up of 30 months, an improvement was reported in actuarial biochemical recurrence-free survival (BRFS), as well as a lower incidence of acute rectal discharge. Hoskin et al (2012) later reported on longer term follow-up of 218 patients from this phase 3 trial. Seventy-six percent of patients also received androgen-deprivation therapy. BRFS was greater in the combination treatment group after 4 years (median time to relapse, 116 months) than in the EBRT-only treatment group (median time to relapse, 74 months). Estimates of BRFS rates for the combination group at 5, 7, and 10 years were 75%, 66%, and 46% compared with 61%, 48%, and 39% for the EBRT-only group, all respectively (p=0.04). However, OS did not differ significantly between treatment arms. Estimates of OS rates for the combination group at 5, 7, and 10 years were 88%, 81%, and 67% compared with 89%, 88%, and 79% for the EBRT-only group, all respectively (p=0.2). Severe urinary symptoms (26%-31%) and bowel events (6%-7%) did not differ significantly between groups at 5 years or 7 years. Erectile dysfunction rates were not reported.

**Observational Studies**

Boehm et al (2016) published a single-center retrospective analysis of 5619 patients with clinically localized prostate cancer who were treated between 1999 and 2009 with HDR brachytherapy plus EBRT (n=419) or RP (n=5200). Eligibility criteria included stage cT1 or cT2 prostate cancer, a prostate volume of 60 mL or less, no neoadjuvant androgen suppression therapy, and no urinary retention symptoms. HDR brachytherapy treatment (18 Gy in 2 fractions) preceded EBRT (50.4 Gy, 1.8 Gy per fraction with 5 fractions per week). In an unmatched analysis of the overall cohort (N=5619), 5-year OS rates were 97.1% in the RP group and 92.4% in the HDR brachytherapy plus EBRT group (p<0.01). An analysis was also conducted after matching the 2 groups on a number of variables including age, cardiovascular disease, diabetes, PSA level, Gleason score, clinical stage, and years of treatment. Five-year OS rates in the matched cohort (n=1257) did not differ significantly between groups. Rates were 95.7% after RP and 92.4% after HDR brachytherapy plus EBRT (p=0.5).

Khor et al (2013) reported on a matched pair analysis that compared 344 patients who received EBRT (46 Gy in 23 fractions) plus HDR brachytherapy (19.5 Gy in 3 fractions) with 344 patients who received only EBRT (74 Gy in 37 fractions) for intermediate- or high-risk prostate cancer. Median biochemical follow-up was 60.5 months. Freedom from biochemical failure at 5 years was 79.8% (95% confidence interval [CI], 74.3% to 85.0%) for the HDR brachytherapy plus EBRT group and 70.9% (95% CI, 65.4% to 76.0%) for the EBRT-only group. However, significantly more grade 3 urethral strictures occurred with HDR brachytherapy (11.8%) than with EBRT (0.3%; p<0.001).

Long-term outcomes of treatment with HDR brachytherapy and EBRT were reported by Yaxley et al (2017). The analysis included 507 patients with localized prostate cancer who were followed for at least 6 years; the median follow-up was 10.3 years. For 271 men with a minimum follow-up of 10 years, the actuarial 10-year OS rate was 85% and the actual 10-year disease-specific survival rate was 90%. The overall urethral stricture rate was 28.9% (28.9% for men treated before 2005 vs 4.2% for men treated after 2005).

**Section Summary: High-Dose Rate Brachytherapy Plus External-Beam Radiotherapy**

Two RCTs comparing HDR brachytherapy plus EBRT with an alternative therapy were identified. One RCT found no statistically significant differences in outcomes between patients treated with HDR brachytherapy and EBRT and those given RP. Another RCT found significantly better BRFS, but not better OS, in patients treated with HDR brachytherapy plus EBRT compared with EBRT alone. Among several controlled observational studies with matched analyses, one reported 5-
year OS rates for HDR brachytherapy plus EBRT similar to those of one of the RCTs. In another study, 4-year BPFS was significantly higher after HDR brachytherapy plus EBRT than after EBRT alone. Long-term (at least 10 years) outcomes after HDR brachytherapy and EBRT were reported in a case series: the actuarial 10-year OS rate was 85%, and the disease-specific survival rate was 90%.

**HDR Brachytherapy as Monotherapy**

The purpose of high-dose rate (HDR) temporary brachytherapy as monotherapy in patients who have localized prostate cancer is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does use of HDR temporary brachytherapy as monotherapy improve the net health outcome in patients with localized prostate cancer?

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

**Patients**
The relevant population of interest is patients with localized prostate cancer.

**Interventions**
The therapy being considered is HDR temporary brachytherapy as monotherapy.

**Comparators**
The following therapies are currently being used to make decisions about localized prostate cancer: EBRT, surgery, and cryoablation.

**Outcomes**
The general outcomes of interest are locoregional recurrence, OS, and adverse events.

**Timing**
Regular follow-up (every 6 to 12 months) are suggested for the first 5 years posttreatment.

**Setting**
Brachytherapy and EBRT are administered in an outpatient oncology setting.

**Systematic Reviews**
Zaorsky et al (2015), in a comparative effectiveness review, assessed the relative clinical effectiveness of HDR brachytherapy as monotherapy and robotic arm stereotactic body radiotherapy (SBRT). This review was performed using Preferred Reporting Items for Systematic Reviews and Meta-Analyses conventions. Studies selected enrolled 35 or more men with localized (T1-T2, N0-Nx, M0) and locally advanced (T3-T4, N0-Nx, M0) prostate cancer who underwent either therapy and were followed for 12 or more months. To be included, studies had to report disease-related outcomes such as BPFS, PSA kinetics, and late GU or GI tract toxicities. For SBRT, BPFS rates were generally 90% or greater at up to 5 years; for HDR brachytherapy as monotherapy, rates were generally 85% or greater at up to 5 years. Median follow-up was 2.9 years, and longest reported actuarial outcomes were at 8 years. For SBRT, late GU RTOG grade 3 or 4 toxicity rates ranged from 0% to 12%; RTOG late grade 3 or 4 GI toxicity rates ranged from 0% to 5% for HDR brachytherapy, these rates were 0% to 26% and 0% to 16%, respectively.

Demanes and Ghilezan (2014) published a systematic review analyzing evidence on HDR brachytherapy as monotherapy for prostate cancer. Thirteen studies met selection criteria; they presented clinical outcomes and toxicity data with follow-up ranging from 1.5 to 8.0 years. All risk groups (low, intermediate, high) were represented in selected articles, and a variety of dose and fractionation schedules were reported. Information on study designs, study quality, and other study and patient characteristics were very limited in this review. BPFS rates reported among the studies ranged from 79% to 100%, and local control rates ranged from 97% to 100%.
Grade 3 GU toxicity rates, mainly related to urinary urgency or frequency, ranged from 0% to 16% grade 3 GI tract toxicity rates ranged from 0% to 2%. Erectile functional preservation rates ranged from 67% to 89%.

Observational Studies
Hegde et al (2018) reported on 437 patients with intermediate-risk prostate cancer who were treated with HDR brachytherapy (n=137) or SBRT (n=300).5 After a median follow-up of 4 years, the BRFS rate was 98.5% in the HDR brachytherapy group and 95.3% in the SBRT group (p=0.17). There were no statistically significant differences in subgroup analyses (eg, comparing patients with a PSA level <10 and ≥10 ng/mL or clinical stage T1 with T2). OS and disease-specific survival were not reported.

A study by Chiang and Liu (2016) reported on a nonrandomized comparison of outcomes after HDR brachytherapy (n=161), RP (n=97), cryoablation (n=114), or high-intensity focused ultrasound (HIFU; n=12).6 The study included patients with clinically localized prostate cancer (stage T3a or lower). Mean follow-up was approximately 3 years. In an unadjusted analysis, the length of PSA BRFS differed significantly across the 4 groups (p<0.001). The mean number of months of BRFS was 21.2 in the HDR group, 22.1 in the RP group, 26.4 in the cryotherapy group, and 27.7 in the HIFU group. There was a longer duration of BRFS in the HDR brachytherapy group than in the other 3 groups. Moreover, patients treated with HDR brachytherapy had a significantly lower metastasis-free rate (90.7%) than those who received other treatments (94.8% in the RP group, 99.1% in the cryotherapy group, 99.2% in the HIFU group; p<0.001). OS and disease-specific survival were not reported. The study was not randomized, and baseline differences across groups might have affected outcomes. For example, patients differed at baseline in a number of characteristics, including age, preoperative prostate volume, and Gleason score. The authors did not report adjusted analyses.

Strom et al (2015) published a nonrandomized comparative study assessing 413 men who had low- or intermediate-risk prostate cancer.7 Patients received HDR brachytherapy (n=85), low-dose rate brachytherapy (n=249), or intensity-modulated radiotherapy (n=79). Median follow-up was 32 months. Primary outcomes were patient-reported and validated health-related quality of life (HRQOL) measures obtained before treatment and at 1, 3, 5, 12, and 18 months posttreatment. Sixty-percent of patients completed pre- and posttreatment HRQOL questionnaires. HRQOL outcomes were mixed. At 1 and 3 months posttreatment, HDR brachytherapy patients reported significantly less deterioration in urinary HRQOL than low-dose rate brachytherapy patients (p=0.005). However, HDR brachytherapy patients had significantly worse sexual HRQOL than low-dose rate brachytherapy at 1, 6, 9, and 18 months after irradiation (p=0.02, p=0.003, p=0.006, p=0.02, respectively). At 18 months, the intensity-modulated radiotherapy group had significantly worse bowel HRQOL scores than either brachytherapy group (p=0.007 for both comparisons).

Long-term survival data have also been reported in uncontrolled series. For example, Demanes et al (2011) reported on 298 patients with previously untreated low- to intermediate-risk localized prostate cancer (median PSA, 6.0 ng/mL) treated with HDR brachytherapy as monotherapy between 1996 and 2005, using 2 treatment protocols.8 Forty-two gray units in six 7-Gy fractions were delivered using computed tomography for treatment planning in 1 protocol; the other treatment planning delivered 38 Gy units in four 9.5-Gy fractions using ultrasonography. At 8-year follow-up, outcomes included 99% local control, 97% biochemical control (using the Phoenix definition of PSA nadir plus 2 ng/mL), 99% distant metastasis-free survival, 99% cause-specific survival, and 95% OS rate. Grade 2 urinary frequency or urgency was transient in 10% of patients, whereas grade 3 urinary retention was experienced in 3% of patients. GI toxicity was reported as less than 1%.

Hauswald et al (2016) reported on 448 previously untreated men with low- to intermediate-risk localized prostate cancer patients treated with HDR brachytherapy.9 Median follow-up was 78 months (range, 3-216 months). The actuarial 10-year OS rate was 76.7% (95% CI, 69.9% to 82.2%)
and the actuarial 10-year BPFS rate was 97.8% (95% CI, 95.5% to 98.9%). The incidence of grade 3 or 4 GU toxicity during follow-up was 4.9%. No grade 3 or 4 GI toxicity occurred.

Section Summary: HDR Brachytherapy as Monotherapy
A number of observational studies, controlled and uncontrolled, have been published. Systematic reviews have reported BRFS rates of 80% to 100%. One nonrandomized comparative study found similar rates of BRFS in patients treated with HDR brachytherapy and SBRT. However, another comparative study found significantly shorter BRFS and a lower metastases-free rate in patients who were treated with HDR brachytherapy compared with those treated with RP, cryotherapy, or HIFU. As a nonrandomized study, patients differences in baseline characteristics might have affected outcomes. Long-term survival data are available from case series; one found an 8-year OS rate of 95% and another reported an actuarial 10-year survival rate of 77%.

HDR Brachytherapy as Salvage Treatment
The purpose of high-dose rate (HDR) temporary brachytherapy as salvage treatment with or without EBRT in patients who have treatment-resistant or recurrent prostate cancer and no disseminated disease is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does use of HDR temporary brachytherapy as salvage treatment with or without EBRT improve the net health outcome in patients with localized prostate cancer?

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

Patients
The relevant population of interest is patients with localized prostate cancer.

Interventions
The therapy being considered is HDR temporary brachytherapy as salvage treatment with or without EBRT.

Comparators
The following therapies are currently being used to make decisions about localized prostate cancer: active surveillance, surgery, and cryoablation.

Outcomes
The general outcomes of interest are locoregional recurrence, OS, and adverse events.

Timing
Regular follow-up (every 6 to 12 months) are suggested for the first 5 years posttreatment.

Setting
Brachytherapy and EBRT are administered in an outpatient oncology setting.

Case Series
Data on HDR brachytherapy as salvage treatment after failed prior radiotherapy are limited; there are no RCTs or nonrandomized comparative studies. Several retrospective case series reporting survival outcomes are described next.

Wojcieszek et al (2016) reported retrospectively on 83 men with locally recurrent prostate cancer treated with salvage HDR brachytherapy (30 Gy in three 10-Gy fractions). Median follow-up was 41 months. OS rates were 93% at 3 years and 86% at 5 years. Biochemical disease-free survival was 76% at 3 years and 67% at 5 years. The most common adverse event was GU toxicity. Acute grade 2 GU toxicity occurred in 29 (33%) men and a acute grade 3 GU toxicity in 1
(1%) man. Comparable rates for late GU toxicity were 32 (39%) for grade 2 and 11 (13%) for grade 3. No grade 4 toxicities were reported.

Chen et al (2013) retrospectively analyzed 52 men with locally recurrent prostate cancer treated with salvage HDR brachytherapy (36 Gy in 6 fractions).\textsuperscript{17} Median follow-up was 59.6 months. At reporting, median survival had not yet been reached, but the estimated 5-year OS rate was 92% (95% CI, 80% to 97%), and the 5-year biochemical control rate using the Phoenix definition was 51% (95% CI, 34% to 66%). Acute (grade ≥2) GI tract events were not reported. Late grade 2 GI events occurred in 4% of patients. Acute grade 3 GU toxicity occurred in 2%, and late grade 3 GU toxicity occurred in 2%.

Jiang et al (2017) published a retrospective series assessing 29 patients with local failure after EBRT who received HDR brachytherapy as salvage therapy.\textsuperscript{18} The minimum length of follow-up was 60 months. The 5-year OS rate was 95.5%, and the 5-year biochemical control rate was 45%. There were no grade 3 or 4 late GI toxicities, but 2 patients experienced grade 2 late GI toxicity. Two patients also experienced urinary incontinence and another experienced urinary tract obstruction.

**Section Summary: HDR Brachytherapy as Salvage Treatment**

No controlled studies were identified; several retrospective case series with sample sizes ranging from 29 to 83 patients were. In the series, median 5-year OS rates after salvage HDR brachytherapy ranged from 83% to 95.5% and median 5-year biochemical control rates ranged from 45% to 67%. Rates of grade 3 or 4 toxicities were relatively low.

**Summary of Evidence**

For individuals who have localized prostate cancer who receive HDR temporary brachytherapy plus EBRT, the evidence includes RCTs, observational studies, and a systematic review. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity. One of the RCTs found no statistically significant differences in outcomes between patients treated with HDR brachytherapy plus EBRT and those receiving radical prostatectomy. The other RCT found significantly better biochemical recurrence-free survival, but not better overall survival, in patients treated with HDR brachytherapy plus EBRT compared with EBRT alone. Among several controlled observational studies with matched analyses, one has reported 5-year overall survival rates for HDR brachytherapy plus EBRT similar to those of one of the RCTs. In another study, 4-year biochemical recurrence-free survival was significantly higher after HDR brachytherapy plus EBRT than after EBRT alone. 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 HDR temporary brachytherapy as monotherapy, the evidence includes large observational studies and systematic reviews. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity. A number of observational studies, controlled and uncontrolled, have been published. Systematic reviews have found biochemical recurrence-free survival rates of 80% to 100%. Long-term survival data are available from case series; one found an 8-year survival rate of 95% and another found an actuarial 10-year survival rate of 77%. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome. For individuals who have treatment-resistant or recurrent prostate cancer and no disseminated disease who receive HDR temporary brachytherapy as salvage treatment with or without EBRT, the evidence includes case series. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity. Only 3 cases series have reported survival outcomes; no comparative studies have been published. In these series, median 5-year overall survival rates after salvage HDR brachytherapy ranged from 83% to 95.5% and the median 5-year biochemical control rate ranged from 45% to 67%. Rates of grade 3 or 4 toxicities were relatively low. The evidence is insufficient to determine the effects of the technology on health outcomes.
Supplemental Information
Clinical Input from Physician Specialty Societies and Academic Medical Centers
While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 2 physician specialty societies (4 reviews) and 2 academic medical centers while this policy was under review in 2009. There was generally strong support for the use of high-dose rate (as monotherapy and with external-beam radiotherapy) as a treatment option for prostate cancer.

Practice Guidelines and Position Statements
National Comprehensive Cancer Network
The National Comprehensive Cancer Network guidelines (v.2.2018) on the treatment of prostate cancer state that brachytherapy monotherapy is indicated for patients with very low and low-risk prostate cancer as well patients at intermediate risk with “favorable or good” prognosis.19 For intermediate-, high-, and very high risk cancers, combination brachytherapy, including high-dose rate (HDR) brachytherapy, with external-beam radiotherapy (EBRT; 40-50.4 gray) is indicated. Permanent low-dose radiotherapy or temporary HDR is indicated for local recurrence following EBRT or primary brachytherapy.

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 20:

“For patients with intermediate-risk prostate cancer choosing EBRT with or without androgen-deprivation therapy, brachytherapy boost (LDR [low-dose rate] 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 androgen-deprivation therapy, brachytherapy boost (LDR or HDR) should be offered to eligible patients.”

These guidelines did not address HDR brachytherapy as salvage treatment.

American College of Radiology
American College of Radiology Appropriateness Criteria for use of HDR brachytherapy to treat prostate cancer were issued in 2014.21 The College indicated HDR monotherapy, HDR plus EBRT, and HDR as salvage treatment might be appropriate treatment options.

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 1.

Table 1. Summary of Key Trials

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<td>NC00913939</td>
<td>HDR Brachytherapy</td>
<td>100</td>
<td>May 2019</td>
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<tr>
<td>NC02692105</td>
<td>Comparison of HDR vs. LDR Brachytherapy as Monotherapy for Intermediate Risk Prostate Cancer</td>
<td>60</td>
<td>Apr 2026</td>
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<tr>
<td>NCTNo.</td>
<td>Trial Name</td>
<td>Planned Enrollment</td>
<td>Completion Date</td>
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<tr>
<td>NCT02303327</td>
<td>Comparative Study of Radiotherapy Treatments to Treat High Risk Prostate Cancer Patients</td>
<td>296</td>
<td>Jan 2029</td>
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</tbody>
</table>

NCT: national clinical trial.

References


**Documentation for Clinical Review**

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

- History and physical
- Oncological radiation consultation notes including: tumor classification, and past medical and/or surgical treatment and response
- Operative report(s) or procedure report(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)

**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.

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### Type Code Description

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT®</td>
<td>55875</td>
<td>Transperineal placement of needles or catheters into prostate for interstitial radionuclide application, with or without cystoscopy</td>
</tr>
<tr>
<td></td>
<td>76873</td>
<td>Ultrasound, transrectal; prostate volume study for brachytherapy treatment planning (separate procedure)</td>
</tr>
<tr>
<td></td>
<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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<tr>
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<td>77317</td>
<td>Brachytherapy isodose plan; intermediate (calculation[s] made from 5 to 10 sources, or remote afterloading brachytherapy, 2-12 channels), includes basic dosimetry calculation(s)</td>
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<tr>
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<td>77318</td>
<td>Brachytherapy isodose plan; complex (calculation[s] made from over 10 sources, or remote afterloading brachytherapy, over 12 channels), includes basic dosimetry calculation(s)</td>
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<td>77770</td>
<td>Remote afterloading high dose rate radionuclide interstitial or intracavitary brachytherapy, includes basic dosimetry, when performed; 1 channel</td>
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<tr>
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<td>77771</td>
<td>Remote afterloading high dose rate radionuclide interstitial or intracavitary brachytherapy, includes basic dosimetry, when performed; 2-12 channels</td>
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<td>77772</td>
<td>Remote afterloading high dose rate radionuclide interstitial or intracavitary brachytherapy, includes basic dosimetry, when performed; over 12 channels</td>
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<td>77778</td>
<td>Interstitial radiation source application, complex, includes supervision, handling, loading of radiation source, when performed</td>
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<td>77790</td>
<td>Supervision, handling, loading of radiation source</td>
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<td>HCPCS</td>
<td>C1717</td>
<td>Brachytherapy source, nonstranded, high dose rate iridium-192, per source</td>
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<td>Q3001</td>
<td>Radioelements for brachytherapy, any type, each</td>
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<tr>
<td>ICD-10 Procedure</td>
<td>0VH031Z</td>
<td>Insertion of Radioactive Element into Prostate, Percutaneous Approach</td>
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</table>

### 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>
<th>Action</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>06/30/2015</td>
<td>BCBSA Medical Policy adoption</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>09/30/2015</td>
<td>Coding Update</td>
<td>Administrative Review</td>
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<tr>
<td>01/01/2016</td>
<td>Coding update</td>
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<td>09/01/2016</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>09/01/2017</td>
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<td>Medical Policy Committee</td>
</tr>
<tr>
<td>09/01/2018</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
</tbody>
</table>

### 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.

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### 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.