High-Dose Rate Temporary Prostate Brachytherapy

Description

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

Background

Prostate brachytherapy can be delivered in a variety of ways. Perhaps the most familiar technique is the use of 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 use of higher energy radioisotopes such as iridium-192. These isotopes deliver radiation at higher dose rates, which may be more effective in destroying rapidly dividing cancer cells. In this technique, needle catheters are placed into the prostate gland using transrectal ultrasound guidance. Once the needles are 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 a course of 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, such as the rectum or urethra. This strategy contrasts with permanent seed implantation in which dosimetry is calculated prior to needle placement and which cannot be altered after seed implantation. The treatment typically consists of 4,000 to 5,000 cGy delivered with external beam radiation therapy (EBRT) to the prostate and periprostatic tissues, while the high-dose rate (HDR) brachytherapy is used as the method of dose escalation to the prostate gland. The total boost doses are variable. In addition, studies are also being conducted using HDR brachytherapy as the sole treatment modality (monotherapy) in those with prostate cancer.

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

**Regulatory Status**

A number of devices have been cleared through the U.S. Food and Drug Administration (FDA) 510(k) process to deliver high-dose brachytherapy radiation to the prostate. The Martinez Prostate Template Set and the Photon Technologies HDR Prostate Template and Accessories are 2 examples of radiation application devices. These devices are intended to be used as accessories to commercially available high-dose rate remote afterloader systems for prostate brachytherapy. FDA product code: JAQ.

**Related Policies**

6.01.10  Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy
7.01.79  Cryoablation of Prostate Cancer
8.01.10  Charged-Particle (Proton or Helium Ion) Radiation Therapy
8.01.14  Brachytherapy for Clinically Localized Prostate Cancer Using Permanently Implanted Seeds

**Policy**

*This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.*

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 prostate brachytherapy is considered **investigational** in the treatment of prostate cancer when used as salvage therapy.

**Policy Guidelines**

High-dose rate brachytherapy as monotherapy is being used in low- and intermediate-risk patients with localized prostate cancer. High-dose rate brachytherapy combined with EBRT (3-dimensional conformal radiotherapy [3D-CRT], intensity-modulated radiotherapy [IMRT] or proton) may be used for more advanced or aggressive prostate cancers. Adequate dose escalation should be achieved with combination high-dose rate temporary brachytherapy and 3D-CRT. 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 (LDR) brachytherapy using only implanted seeds is generally used in patients whose prostate cancer is considered low risk. Active surveillance is generally recommended.
for very low-risk prostate cancer. Permanent brachytherapy combined with EBRT is used (sometimes along with androgen deprivation) to treat higher risk disease.

Prostate cancer risk is often defined using the following criteria:

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

### Rationale

An evidence-based approach to the analysis of data on the various treatment options for prostate cancer is problematic for the following reasons:

- The lack of controlled clinical trials comparing various different treatment options in homogeneous groups of patients. Thus far, the only randomized trials of alternatives for managing early stage prostate cancer compared active surveillance with radical prostatectomy (1) and external-beam radiation therapy (EBRT) with high-dose rate (HDR) brachytherapy with EBRT alone. (2, 3)
- Similar trials are lacking to compare surgery with radiation or to compare different methods of radiation. In a recent review of 2991 consecutive patients receiving a variety of therapies for localized prostate cancer, the authors concluded that it is still not possible to determine which of the treatment options leads to the best metastasis free or overall survival (OS). Therefore, at the present time, there is no evidence-based standard of treatment, which limits the ability to assess emerging approaches. (4)
- The numerous patient variables, including tumor stage, size of tumor (ie, percent positive biopsy score), Gleason score, and prostate-specific antigen (PSA) level.
- The indolent natural history of many early-stage prostate cancers, requiring prolonged follow-up to determine final patient outcomes.
- A variety of intermediate outcomes have been used, most commonly biochemical failure as evidenced by rising PSA levels.
- The evolving nature of radiation therapy. Over the past 10 years, major advances have occurred in the planning and delivery of radiation therapy, including conformal therapy and intensity modulated radiation therapy (IMRT), both of which permit dose escalation. There are variables in the total dosage of radiation therapy, variations in the planning and delivery of radiation therapy, and multiple different combinations of therapy (ie, external beam radiation therapy [EBRT] plus brachytherapy). Fractionation of doses is another treatment variable that intends to balance the treatment effectiveness with both early and late morbidities to surrounding normal tissues.
- The role of dose escalation in radiation therapy of prostate cancer. A dose-response relationship in the treatment of prostate cancer is generally accepted among clinicians and physicists, and in fact serves as the scientific rationale of high-dose rate (HDR) brachytherapy,
as well as other recent techniques for radiation planning and delivery (i.e., IMRT). While a few randomized controlled trials (RCTs) have examined this issue, the data suggest that dose escalation is associated with improved biochemical control. (5) However, data regarding the impact of total radiation dose on survival among patients with different prognostic factors are minimal. In addition, the optimal radiation therapy dose is unknown. (6)

Related policy No. 8.01.14, on conventional brachytherapy (using permanently implanted seeds), notes that while final health outcomes are not available, thus limiting scientific conclusions, conventional brachytherapy had become widely accepted by patients and physicians and may be considered a reasonable treatment option. Large case series of conventional brachytherapy have reported data on both morbidity and the intermediate outcome of biochemical relapse-free survival (RFS) (i.e., survival-free from increasing PSA levels). These studies show that conventional brachytherapy is associated with similar outcomes when compared with the alternative (EBRT). Therefore, given the uncertainty for choosing between the established treatment options of watchful waiting, radical prostatectomy, EBRT, or conventional brachytherapy, some may consider patient preference to be particularly appropriate in selecting conventional brachytherapy. Questions have also been asked about patient acceptance of HDR brachytherapy compared to low-dose rate (LDR) brachytherapy. Given these significant limitations, the following results have been reported for HDR as an adjunct to EBRT.

**Systematic Reviews and Literature Reviews on HDR Brachytherapy± EBRT**

Zaorsky et al published a comparative effectiveness review (CER) in 2015 in which they assessed the relative clinical effectiveness of HDR brachytherapy monotherapy and robotic arm stereotactic body radiotherapy (SBRT). (7) This CER was performed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses convention. The electronic search of MEDLINE via PubMed encompassed the years 1970 through 2013, including only English language publications. Studies that were included 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 must have reported disease-related outcomes such as biochemical PFS, PSA kinetics, and late genitourinary (GU) or gastrointestinal (GI) tract toxicities. For SBRT, the biochemical PFS rates were generally 90% or greater at up to 5 years. Biochemical PFS rates with HDR brachytherapy monotherapy were generally 85% or greater at up to 5 years; the median follow-up was 2.9 years and longest reported actuarial outcomes were at 8 years. For SBRT, late GU Radiation Therapy Oncology Group (RTOG) grade 3 to 4 toxicity rates ranged from 0% to 12%; RTOG late-grade 3 to 4 GI toxicity rates ranged from 0% to 5%; for HDR brachytherapy, these rates were 0% to 26%, and 0% to 16%, respectively.

Demanes et al published a systematic review of the literature in 2014 in which they analyzed published evidence on HDR brachytherapy as monotherapy for prostate cancer. (8) Among more than 80 individual articles and abstracts published between 1990 and 2013, 13 met selection criteria, presenting clinical outcome and toxicity evidence with follow-up ranging from 1.5 to 8.0 years. All risk groups (low, intermediate, high) were represented in the included articles, and a variety of dose and fractionation schedules were reported. Information on study design, study quality, and other study and patient characteristics was very limited in this review. Biochemical PFS 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%.

In 2014, Zaorsky reviewed 38 prospective and retrospective studies reporting on a total of 8008 patients treated with high-dose rate (HDR) brachytherapy for prostate cancer. (9) Five-year freedom from biochemical failure rates were 85% to 100% for low-risk, 80-98% for intermediate-risk, 59% to 96% for high-risk and 34% to 85% for locally advanced patients. In all risk groups, 5-year rates of cancer-specific survival, overall survival, local recurrence and distant metastases were 99% to 100%, 85% to 100%, 0% to 8%, and 2% to 12%, respectively. Late RTOG Grade 3-4 genitourinary or gastrointestinal toxicities occurred in less than 6% of patients. Comparisons of HDR brachytherapy to other radiation techniques were inconclusive. Interpretation of results from the review is limited by reports from single-institution studies, the lack of comparative studies and insufficient reporting on toxicity and quality of life.

In 2011, Bannuru et al analyzed 75 studies (10 RCTs and 65 nonrandomized comparative studies) on radiotherapy for clinically localized prostate cancer. (10) Radiotherapies included brachytherapy, high-dose rate (HDR) brachytherapy and EBRT (conformal radiation, IMRT, or proton therapy). Overall, evidence was insufficient to compare the effectiveness of different forms of radiation treatments. Additionally, the effects of radiation treatments on patient survival were unclear compared with no treatment or no initial treatment. However, evidence considered to be of moderate strength showed higher EBRT dosages were consistently associated with increased long-term biochemical control rates compared with EBRT delivered at lower dosages.

Yamada et al conducted a review of the literature and published consensus guidelines for HDR brachytherapy for the American Brachytherapy Society in 2012.11 Dosing schedule differences and heterogeneous studies make HDR brachytherapy difficult to evaluate systematically. However, HDR brachytherapy was found to have favorable 5-year biochemical disease control ranging from 85% to 100% for low-risk, 83% to 98% for intermediate-risk, and 51% to 96% for high-risk prostate cancer.

**HDR brachytherapy Plus external-beam radiation therapy (EBRT)**

*Randomized, controlled trials*

A multicenter open-label RCT in Sweden allocated patients with localized and locally advanced (T1b-T3a, N0, M0) prostate cancer to either open radical prostatectomy (RP; n=45) or combined EBRT (3D-CRT, 25x2 Gy) and HDR brachytherapy (2x10 Gy) between 1996 and 2001 (n=44). (12) 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 PSA exceeded 10 ng/mL. Quality-of-life changes were assessed using the European Organization of Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C33 (EORTC QLQ-C33). (13) Patients completed the RTOG/EORTC toxicity scale questionnaire at 12, 24 and 60 months after treatment. No statistically significant between group differences were reported for any of the EORTC QLQ-C33 variables or treatment-associated toxicities. A total of 68 patients (76%) were alive at 10-year follow-up; 8 patients (6 in the RP group, 2 in the RT group, 9% total) died of prostate cancer, 13 (n=6 in the RP group, n=7 in the RT group) died of other causes (p=NS).
Hoskin et al reported on a European single-center randomized trial of 220 patients that was conducted between 1997 and 2005, which compared 55 Gy of EBRT to 35.75 Gy of EBRT with HDR brachytherapy. (3) With a median follow-up of 30 months, the authors noted an improvement in actuarial biochemical RFS, as well as a lower incidence of acute rectal discharge. In 2012, Hoskin et al. subsequently reported on longer term follow-up of 218 patients from this Phase 3 trial. (2) Seventy-six percent of patients also received androgen-deprivation therapy (ADT). Biochemical relapse-free survival (RFS) was greater in the combination treatment group after 4 years, with a median time to relapse of 116 months versus 74 months in the EBRT-only treatment group. Estimates of biochemical relapse-free survival for the combination group at 5, 7, and 10 years were 75%, 66%, and 46% versus 61%, 48% and 39% for the EBRT-only group, all respectively (p=0.04). However, overall survival (OS) was not significantly different between treatment arms. Estimates of OS for the combination group at 5, 7, and 10 years were 88%, 81% and 67% versus 89%, 88% and 79% for the EBRT-only group, all respectively (p=0.2). Severe urinary symptoms (26% to 31%) and bowel events (6% to 7%) were not significantly different between groups at 5 and 7 years. Erectile dysfunction rates were not reported.

Non-randomized Comparative Studies

In a case series Martinez et al reported on 472 patients with intermediate- to high-risk prostate cancer (PSA level of ≥10 ng/mL; and/or a Gleason score of ≥7; and/or clinical stage ≥T2b) treated with pelvic EBRT and an HDR boost using ultrasound guidance during the period of 1992 to 2007. (14) Patients received a hypofractionated regimen of pelvic EBRT delivered in 23 fractions of 2 Gy for a total dose of 46 Gy over a 5-week period. Initially, HDR brachytherapy consisted of 3 implants of 5.5 Gy, 6.0 Gy, and 6.5 Gy each. Subsequently, the HDR brachytherapy dosages were changed to 2 implants using 8.25 Gy, 8.75 Gy, 9.5 Gy, 10.5 Gy, and 11.5 Gy to achieve dosages equivalent to the 3 implant dosages delivered initially in the study. EBRT was not delivered on the days the patients received HDR brachytherapy boost (eg, on days 5 and 15 when 2 implants were used). The authors reported the 10-year results were significantly better in the groups that received higher dose levels (ie, >268 Gy biologically equivalent dose), using the Phoenix definition for biochemical failure (43.1% vs 18.9%), clinical failure (23.4% vs 7.7%), and distant metastasis (12.4% vs 5.7%, all respectively). OS at 10 years was better in the higher dose group, but the difference was not statistically significant. Adverse events included grade 3 genitourinary (GU) and gastrointestinal (GI) tract complications of 2% to 3% and less than 5%, respectively.

In another series, outcomes were reported for 207 patients treated between 1991 and 2000. (15) All patients had poor prognostic factors, which included tumor stage T2B, a Gleason score of 7, or a PSA greater than 10 ng/mL. EBRT was alternated with HDR radiotherapy as a boost. At a mean follow-up of 4.7 years, overall biochemical control rate was 74%, but was 85% if 1 poor prognostic factor was present, 75% if 2 were present, and 50% if all 3 were present. Late toxicity was minimal.

Use of HDR brachytherapy as an adjunct to conformal EBRT with or without androgen-deprivation therapy was reported in a case series of 611 patients. (16) A total of 209 patients likely overlapped patients with the study previously reviewed. Although the results suggest that adjunctive HDR was associated with excellent long-term outcomes in terms of biochemical control, disease-free survival and cause-specific survival, interpretation of the findings is limited due to the absence of a control group.
Investigators reported on outcomes (median follow-up, ≥7 years) of 209 consecutive patients with localized prostate cancer treated with HDR brachytherapy combined with EBRT. (17) The PSA progression-free survival (PFS) rate was 90%, 87%, and 69% for the low-, intermediate-, and high-risk groups, respectively.

Phan et al reported on a case series of 309 patients treated with EBRT (40-45 Gy) and HDR brachytherapy (22-24 Gy). (18) At a median follow-up of 59 months, the 5-year biochemical control rate was 86%, and OS was 91%; rates were higher for those with lower risk disease.

Khor et al reported on a matched pair analysis of 344 patients who received EBRT (46 Gy in 23 fractions) plus HDR brachytherapy (19.5 Gy in 3 fractions) compared to 344 patients who received only EBRT (74 Gy in 37 fractions) for intermediate- or high-risk prostate cancer. (19) 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 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 EBRT (0.3% [p<.0001]).

In a retrospective analysis, Deutsch et al compared patients who had received HDR brachytherapy and IMRT to those who had received ultra-high dose IMRT alone for low- to high-risk prostate cancer. (20) In the HDR and IMRT treatment group, 160 patients received 3 fractions of HDR dosages of 5.5-7.0 Gy, delivered once on the day of implant and twice on the next day, followed with IMRT 1 month later at a dose of 45.0–50.4 Gy. The ultra-high dose IMRT group of 470 patients received 86.4 Gy delivered in 48 fractions with 5 to 7 beams of 15-MV photons. In the only outcome measured in this analysis, overall, the HDR and IMRT group had statistically significant improvement in the 5-year PSA RFS (PSA nadir + 2) compared to IMRT alone (97.7% vs 82%, respectively; p< 0.001). When the risk groups were separated out, the PSA-relapse survival for HDR plus IMRT over IMRT remained significant in the intermediate-risk group (98% vs 84%, respectively; p=0.001). However, improvement was not significant in the low-risk group (100% vs 98%) or the high-risk group (93% vs 71%, both respectively; p=0.23). Fewer patients in the low- and high-risk groups may have influenced results. Additionally, androgen-deprivation therapy may have confounded the outcomes in the high-risk group.

In another retrospective comparison of HDR brachytherapy and IMRT compared with IMRT alone, Wilder et al found no significant differences in 3-year biochemical disease-free (PSA nadir + 2) survival between treatment groups in low-, intermediate-, and high-risk patients (100% vs 100%, 98% vs 100%, and 93% vs 67%, all respectively). (21) The rates of toxicity incidence were reported to be similar in both treatment groups. In this study, 240 patients received HDR boost at 5.5 Gy twice on the day of implant and again 1 week later totaling 22 Gy followed by IMRT of up to 50.4 Gy administered 1 to 4 days later. The 44 patients in the IMRT-alone group received 79 to 81 Gy.

**HDR Brachytherapy as Monotherapy**

Publications on use of HDR as monotherapy for treatment of prostate cancer are fewer than those that report its use as combined modality therapy (CMT) with EBRT. In 2013, Tsellis et al reported on short-term outcomes of 351 patients with clinically localized prostate cancer treated with HDR brachytherapy as monotherapy. (22) At 36 and 60 months, biochemical control rates were 98% and
94% and metastasis-free survival rates were 99% and 98%, respectively. No acute Grade 3 gastrointestinal toxicity occurred and acute Grade 3 genitourinary events were 4.8%. Late Grade 3 genitourinary toxicity events were 3.4% and gastrointestinal toxicity events were 1.4%. There were no Grade 4 or greater acute or late adverse events reported.

Demanes et al reported on a prospective case series of 298 patients with previously untreated low- to intermediate-risk localized prostate cancer (median value PSA of 6.0 ng/mL) treated with HDR brachytherapy as monotherapy between 1996 and 2005, with different treatment protocols. (23) A total of 42 Gy in 6 fractions of 7 Gy were delivered using computed tomography images for treatment planning in 1 protocol; the other used a total of 38 Gy delivered in 4 fractions of 9.5 Gy with US images used for treatment planning. At 8-year follow-up, outcomes included 99% local control, 97% biochemical control (using the Phoenix definition defined as PSA nadir + 2), 99% distant metastasis-free survival, 99% cause-specific survival, and 95% OS. Grade 2 urinary frequency or urgency was transient in 10% of patients, whereas grade 3 urinary retention was experienced in 3% of patients. GI tract toxicity was reported to be less than 1%.

Martinez et al reported on a nonrandomized study comparing 454 patients treated with either palladium-103 seed LDR brachytherapy (206 patients) or HDR brachytherapy as monotherapy (171 patients) during the period of 1993 through 2004. (24) The patients selected which treatment option they received. Also included in the study analysis were 77 patients who received HDR brachytherapy as monotherapy during the period of 1996 through 2002. All of the patients selected for this study were low-to-intermediate risk and had PSA levels equal to or less than 12 ng/mL, Gleason scores of equal to or less than 7, and clinical stage T1c to T2a disease. The HDR brachytherapy dosages were the same as in the previously discussed Demanes et al study (9.5 Gy x 4 and 7 Gy x 6). Treatment outcomes at 5 years included biochemical control rates (PSA nadir + 2) of 89% in the LDR group, 91% in the HDR group, and 88% in the second HDR group. Overall and cause-specific survival rates at 5 years did not differ statistically between groups. The HDR groups experienced statistically significant lower rates of dysuria, urinary frequency/urgency, and acute rectal pain. Rates of diarrhea, rectal bleeding, and acute urinary incontinence and retention were similar. Most toxicities were grade 1 in both groups, but more grade 3 acute GU toxicities were seen in the LDR group. Potency was 30% in the LDR group and 20% in the HDR groups.

Corner et al published results of a phase 2 study of HDR brachytherapy as monotherapy in 110 patients treated with 3 regimens: 34 Gy in 4 fractions, 36 Gy in 4 fractions, and 31.5 Gy in 3 fractions. (25) At 6 months, 2 patients had grade 3 bladder toxicity, and 1 patient had grade 2 gastrointestinal (GI) tract toxicity. No PSA relapses have been detected, although the median follow-up was just 12 months among the 55 patients who received 31.5 Gy.

Grills et al reported on a series of 149 patients with early-stage prostate cancer who were treated with either permanent or temporary (HDR) brachytherapy monotherapy at 1 center. (26) In this series, patients selected which of the 2 treatments they would receive. Treatments were given between 1999 and 2001. The authors note lower acute grade 1 to 3 symptoms in the HDR group, but many of these symptoms were grade 1. The reported rates of grade 2 and 4 chronic genitourinary (GU) toxicity did not vary and were 23%. The impotence rate was 16% in the HDR group and 45% in the LDR group. Levels of biochemical control were similar in the 2 groups with median follow-up of 35 months.
Salvage HDR brachytherapy

Data on using HDR in the salvage treatment following failed prior radiation therapy are limited. Chen et al reported on a retrospective analysis of 52 men with locally recurrent prostate cancer treated consecutively with salvage HDR (36 Gy in 6 fractions). (27) Median follow-up was 59.6 months. Median survival was not yet reached, but estimated 5-year OS was 92% (95% CI, 80% to 97%) and 5-year biochemical control using the Phoenix definition was 51% (95% CI, 34% to 66%). Acute GI tract events of grade 2 or higher did not occur. Late grade 2 GI events occurred in 4%. Acute grade 3 genitourinary toxicity occurred in 2%. Late grade 3 genitourinary toxicity occurred in 2%.

Jo et al reported on 11 patients with radiorecurrent local prostate cancer who received salvage HDR brachytherapy with EBRT (n=10) or proton beam (n=1). (28) During mean follow-up of 29 months (range 18-41 months), PSA levels remained low in 7 patients but rose in 4 patients. No grade 3 adverse events were reported.

Ongoing Clinical Trials

Some currently unpublished trials that might influence this policy are listed in Table 1.

Table 1. Summary of Key Trials

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<td>NCT00604526</td>
<td>Pilot Study of High Dose Rate Prostate Brachytherapy as Salvage Therapy for Locally Recurrent Prostate Cancer Previously Treated With External Beam Radiotherapy</td>
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NCT: national clinical trial.

Practice Guidelines and Position Statements

The National Comprehensive Cancer Network (NCCN) guidelines (v.1.2015) for the treatment of prostate cancer indicate HDR brachytherapy alone or combined with EBRT (45-50 Gy) may be used instead of LDR brachytherapy to increase the dose of radiation for intermediate- to high-risk patients. (29) Boost regimens commonly used include 9.5 to 10.5 Gy x 2 fractions, 5.5 to 7.5 Gy x 3 fractions, and 4.0 to 6.0 Gy x 4 fractions. For HDR brachytherapy alone, 13.5 x 2 fractions is a commonly used regimen. HDR brachytherapy may also be considered to treat local recurrence after EBRT or primary...
brachytherapy. HDR dosages for recurrence range from 9 to 12 Gy x 2 fractions, depending on the primary radiation dosage delivered.

The American Brachytherapy Society (ABS) Prostate High-Dose Rate Task Group (26) suggests patients selected for monotherapy should be clinical stage T1b to T2b and Gleason score ≤ 7, and/or prostate-specific antigen (PSA) ≤ 10 ng/mL (11, 30) For HDR boost, ABS patient selection criteria include: patients with high-risk features such as T3 to T4, Gleason score 7 to 10, and/or PSA greater than 10 ng/mL or patients with bulky T1 to 2b tumor. ABS recommends HDR brachytherapy with or without EBRT for various risk levels of localized prostate cancer especially for intermediate- or high-risk patients as a boost with EBRT. ABS guidelines note HDR brachytherapy is contraindicated in patients, who have a preexisting rectal fistula, are unable to tolerate anesthesia and/or have no proof of malignancy. HDR monotherapy is considered investigational for high-risk patients by ABS. HDR monotherapy as salvage treatment is only recommended for use in specialty centers or institutional review board–approved protocols.

American College of Radiology (ACR) Appropriateness Criteria for high-dose-rate brachytherapy for prostate cancer were issued in 2014. (31) The ACR indicates HDR monotherapy, HDR with EBRT and HDR as salvage treatment may be appropriate treatment options.

U.S. Preventive Services Task Force Recommendations

Not applicable

Summary of Evidence

The evidence for HDR temporary brachytherapy plus external beam radiotherapy (EBRT) for treatment in patients who have primary localized prostate cancer consists of 2 randomized controlled trials (RCTs) that compare HDR brachytherapy with surgery (eg, radical prostatectomy [RP]) or EBRT alone, plus nonrandomized comparative studies. Clinical outcomes of interest include overall survival (OS) and treatment-related morbidity. The evidence shows similar OS and treatment-related morbidity achieved in the RCTs with HDR brachytherapy plus EBRT compared with RP. Limitations of the RCT evidence include some heterogeneity in patient populations and treatment protocols, and the timeframe of the studies, generally encompassing the period 1995 to 2005, during which treatment protocols and patient selection have evolved. Nonetheless, the body of evidence is sufficient to support a conclusion that use of HDR temporary brachytherapy plus EBRT improves health outcomes in patients with primary localized prostate cancer.

The evidence for HDR temporary brachytherapy alone for treatment in patients who have primary localized prostate cancer comprises a series of large observational studies. Clinical outcomes of interest include OS and treatment-related morbidity. Similarity of survival and adverse event rates achieved across studies, plus indirect comparison with outcomes of the RCTs using HDR brachytherapy with or without EBRT, suggest that the beneficial effects of HDR brachytherapy alone are real and sustainable. Additional limitations of the evidence include some heterogeneity in patient populations and treatment protocols, and the timeframe of the studies, generally encompassing the period 1993 to 2005, during which treatment protocols and patient selection have evolved.
Nonetheless, the body of evidence is sufficient to support a conclusion that use of HDR temporary brachytherapy alone improves health outcomes in patients with primary localized prostate cancer. The evidence for HDR temporary brachytherapy alone or with EBRT for salvage treatment in patients who have recurrent prostate cancer comprises 2 observational studies. Clinical outcomes of interest include OS and treatment-related morbidity. The body of evidence is insufficient to support a conclusion that use of HDR temporary brachytherapy alone or with EBRT improves health outcomes in patients with primary localized prostate cancer.

Medicare National Coverage

Brachytherapy sources and services for administration and delivery of brachytherapy are covered by Medicare.

References


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<td>New Policy</td>
<td>Policy updated with literature search; reference numbers 2, 7-8, 20 added; references removed. Policy statements unchanged.</td>
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<tr>
<td>September 2014</td>
<td>Update Policy</td>
<td>Policy updated with literature review; references 7-8 and 12 added; reference 29 updated. Policy statements unchanged.</td>
</tr>
</tbody>
</table>
Brachytherapy, High-Dose Rate, Prostate Cancer
High-Dose Rate Brachytherapy, Prostate Cancer
Prostate Cancer, High-Dose Rate Brachytherapy

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on September 18, 2015 and is effective October 15, 2015.

Signature on file
Deborah M. Smith, MD, MPH