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PERMANENT SOURCE BRACHYTHERAPY FOR PROSTATE CANCER

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Summary of Literature Review

Introduction/Background

Improvements in permanent prostate brachytherapy (PPB) utilizing transrectal ultrasound (TRUS) guidance via a perineal template resulted in this procedure becoming a major treatment option for localized prostate cancer by the mid-1990s [1]. PPB is an outpatient procedure with short treatment time, rapid patient recovery, and demonstrated long-term efficacy. For men with low-risk disease, treatment efficacy is comparable to other primary treatment options [2-5]. Similarly, short- and long-term toxicity and quality of life (QoL) outcomes with PPB compare favorably with alternative treatment methods [6-8]. For men with high-risk disease, dose escalation with brachytherapy combined with external-beam radiation therapy (EBRT) and androgen deprivation therapy (ADT) is associated with improved disease-free recurrence rates [9-11] as compared to EBRT and ADT alone. In the current study, we provide an update from our prior report in 2011 of appropriateness criteria for PPB [12], with consensus views on management strategies.

Patient Selection

Other consensus guidelines and recommendations on patient suitability and procedural aspects of PPB include those from the American Association of Physicists in Medicine [13], American Brachytherapy Society (ABS) [14-16], American College of Radiology (ACR)/American Society of Radiation Oncology [17], and the European Society of Therapeutic Radiation Oncology [18,19]. In general, a patient may be a suitable candidate for PPB if 1) the patient has clinically localized prostate cancer without evidence of regional or distant metastasis, 2) a high-quality implant is technically achievable, and 3) the patient is at low risk for significant morbidity as compared to alternative treatment approaches.

A common factor influencing whether a high-quality implant can be performed is pubic arch interference. Pubic arch (bone) interference remains a relative contraindication to PPB because of the difficulty of dosimetric optimization on the lateral and/or anterior extent of the prostate gland [20,21]. The TRUS volume study/simulation and/or pubic arch computed tomography (CT) study may identify those patients whose prostate is accessible to perform a high-quality implant. However, there is known variability in the ability of such studies to predict pubic arch interference [20,22]. Although large prostate volume has been considered a limiting factor, PPB for patients with prostate volume >100 cm^3 has been reported as performed by experienced practitioners [23]. For those patients with narrow pelvic anatomy or a large prostate, re-evaluation following cytoreductive ADT may be appropriate (see Variant 1).

Characteristics thought to place a patient at increased risk of morbidity with PPB have included poor baseline urinary function determined primarily by International Prostate Symptom Score (IPSS), history of prior transurethral resection of the prostate gland (TURP), large (>60 cm^3) or small (<20 cm^3) prostates, acute prostatitis, and inflammatory bowel disease (IBD) [24]. Currently, no reliable preimplant criteria can be used to

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predict prolonged urinary retention, but various risk factors have been identified. Predictive factors for acute urinary retention include preimplant obstructive symptoms, IPSS >15 to 20, postvoid residual volume >100 cm^3, and median lobe hyperplasia (the protrusion of hypertrophied prostate tissue into the bladder) [25]. The preimplant IPSS correlates with the duration of postimplant obstructive symptoms [26,27], but its impact on long-term urinary QoL is less clear [26,28]. The prophylactic use of alpha-blockers does not significantly affect retention rates but results in a significantly faster return of IPSS to baseline [29].

A prior history of TURP has been considered by some to be a relative contraindication for PPB. The risk of incontinence has been reported to be 6% or less if a peripheral source-loading technique is employed and adequate prostatic glandular tissue exists such that the radiation dose to the TURP defect can be limited to <110% of the prescription dose [30,31]. Using the Expanded Prostate Cancer Index instrument, patients with a preimplant TURP have been found to have urinary QoL approaching that of non-TURP brachytherapy patients [32].

Prostates that are large (typically considered to be >60 cm^3) or small (<20 cm^3) have historically been thought of as difficult to implant adequately, and these patients were often not offered PPB. Reports over the last decade, however, have demonstrated good dosimetric and treatment outcomes for men across a wide range of prostate sizes [33-36]. In regards to inflammatory conditions, it is still recommended that prostate implants be delayed in the setting of acute prostatitis. Inflammatory bowel disease (IBD) remains a relative contraindication to PPB, although acceptable outcomes in patients undergoing PPB with inactive disease have been reported [37,38]. In general, nonradiotherapeutic treatments for men with IBD should be considered or these patients should be referred to high-volume centers.

Quality of Life

Over the last decade, there has been increased emphasis and research on QoL in prostate cancer patients using validated patient-provided instruments. Two studies that examine toxicities associated with 3 main treatment modalities for localized prostate cancer—surgery, EBRT, and PPB—come from the prospective QoL studies of Prado et al and Sanda et al [7,8]. These studies allow for several generalizations. When comparing brachytherapy with EBRT, these studies report that short-term and long-term QoL from the patient perspective are similar along most dimensions [7,8]. Erectile function appears to be modestly better preserved with brachytherapy than with EBRT treatment [6], whereas resolution of urinary irritative symptoms is less after brachytherapy [7].

Comparing brachytherapy to surgery, sexual dysfunction and urinary incontinence were significantly more common with surgery than with brachytherapy. From the Prado et al [7] study, in men with no notable baseline sexual dysfunction, patients undergoing nerve-sparing radical prostatectomy had over double the rate of long-term severe sexual dysfunction compared to brachytherapy patients (64% versus 30%). Similarly, Sanda et al [8] reported 26% of prostatectomy patients versus 16% of brachytherapy patients had the most severe self-reported sexual function difficulties. Regarding urinary leakage, the Prado et al [7] study reported that men with no baseline incontinence undergoing nerve-sparing prostatectomy had double the rate of severe incontinence at 36 months post-treatment compared to brachytherapy patients (27% versus 13%). Sanda et al [8] reported a large deterioration in urinary continence scores after surgery compared to brachytherapy at 2 months, but they found less lingering severe incontinence than did the Prado et al study. Similar findings with respect to urinary and sexual QoL were also confirmed in the SPIRIT ACOSOG trial reported by Crook et al [39].

In contrast, surgery patients report fewer urinary and bowel irritative symptoms. The Prado et al [7] study found that the development of severe urinary irritative symptoms or bowel irritative symptoms were rare in men treated with prostatectomy, compared to 6% to 12% in brachytherapy patients. From the Sanda et al [8] study, 10% of brachytherapy patients reported moderate to severe bowel irritative symptoms at 1 year (versus 2% of surgery patients) and 18% of brachytherapy patients reported moderate to severe urinary irritation (versus 12% of surgery patients).

Simulation (Volume Study)

TRUS simulation for treatment-planning purposes can be performed prior to the day of the implant (preplanning approach) or immediately prior to the implant procedure (intraoperative approach) [16]. Advocates of the intraoperative approach point to consistent patient positioning for treatment planning and subsequent treatment, whereas advocates of the preplanning approach point to a decrease in operating room time and costs, as well as a decrease in stress on the implant team. In either case, proficiency in TRUS imaging of the prostate is essential to achieve consistent, high-quality TRUS-guided implants, and either approach is considered acceptable so long as a satisfactory seed distribution is obtained, as determined by postimplant dosimetry. Proficiency in ultrasound

interpretation, including identification of the base and apex of the prostate on sagittal and axial TRUS imaging, is crucial for optimal seed placement and TRUS-based treatment planning.

Isotope Selection

The 2 isotopes for PPB with the longest reported follow-up include iodine 125 (^{125}I) and palladium 103 (^{103}Pd). The half-life of ^{103}Pd is 17 days and the half-life of ^{125}I is 60 days. Because the dose is delivered in less time, prescription doses of ^{103}Pd are less than those of ^{125}I. Cesium 131 (^{131}Cs) is an alternative as an isotope for PPB, with a half-life of 9.7 days [40,41]. The choice of isotope generally depends on clinician preference and institutional experience.

Seed Deposition Technique and Seed Migration

Seed migration to the lungs and other locations is reported to occur following PPB in <1% of seeds implanted in 2.7% to 55% of patients who undergo loose-seed implantation [42,43]. In a randomized trial of PPB utilizing loose seeds versus a mixture of stranded seeds and 10 to 20 loose seeds per implant, the seed migration rate decreased from 47% to 23% (P=0.053) [44]. In a recent study by Merrell et al including 990 patients who underwent either loose-seed, combination loose-seed and stranded-seed, or exclusively stranded-seed implantation, the percentages of patients experiencing seed migration to the chest, as determined by chest radiography 3 to 5 months postimplant, were 43%, 13%, and 0.9%, respectively [45]. Nonetheless, reports of adverse clinical consequences of seed migration are rare [46,47]. In several studies examining changes in postimplant dosimetry that may occur post-PPB when stranded seeds are implanted [48-50], shifting of strands has been found to occur such that clinically significant changes in dosimetry may result. In contrast, other studies have shown improvement in postimplant dosimetry associated with stranded seeds [51,52]. Furthermore, loose or stranded seeds may migrate through the urinary tract [53]. Thus, given that loose-seed or stranded-seed deposition reported advantages and disadvantages compared to one another, the use of either technique is considered by both the ACR and the ABS to be an appropriate means of seed deposition [14].

Treatment Planning

Transaxial TRUS images of the prostate are imported into the treatment-planning system to facilitate treatment planning. The target volume includes the prostate and a 3- to 5-mm margin. All plans should be evaluated based on dose-volume histograms of the planning target volume, urethra, and rectum. Plans should attempt to minimize the number of needles and seeds as practically as possible, provide high-dose coverage to the target, and minimize high-dose volumes. A modified peripheral or uniform modified loading technique is recommended, which places the majority of sources in the prostate periphery. The Cesium Advisory Group recommends source placement further from the urethra and rectum than is practiced with ^{125}I or ^{103}Pd with a prostate V_{150} <45% [54].

Activity-per-volume nomograms can be incorporated into the treatment-planning process as a quality assurance metric [55]. Generally accepted dosimetric parameters include $V_{100/150/200}$ (volume of the target area receiving 100%, 150%, and 200% of the planned dose), D_{90} (maximum dose delivered to 90% of the target volume), urethral $V_{125/150/200}$ (volume of the urethra receiving 125%, 150%, and 200% of the prescribed dose), the average urethral dose, and the R_{100} (volume of the rectum receiving 100% of the prescribed dose). Common planning targets are V_{100} ≥90% and D_{90} ≥100% of the prescribed dose. To minimize the risk of urinary and rectal morbidity, treatment plans should be optimized to achieve urethral V_{150} <5% and rectal V_{100} <1 cc.

Postimplant Evaluation

The mainstay of quality assurance for prostate brachytherapy is postimplant dosimetric evaluation, which should be completed within 60 days following the implant [56,57], with most practices performing postimplant CT-based studies immediately after PPB or around day 30 [58]. This evaluation serves several quality assurance functions: 1) to verify that the target volume has received the prescribed dose, 2) to establish that normal tissues did not receive excessive dose, 3) to serve as a means of feedback to facilitate future improvement in the brachytherapy implant process, and 4) to assess dose within the target volume. If the target volume has not received the prescribed dose, considerations should be made to further optimize the implant. The advent of CT-based postoperative dosimetry provides the ability to evaluate implant quality associated with outcome and complications. The segmentation of prostate contours on postimplant CT scans may be affected by postoperative edema, degradation of the image due to implanted metallic seeds, and a tendency to overestimate prostate volume from CT compared to TRUS. Where available, incorporating magnetic resonance imaging (MRI) into the postimplant process has been shown to assist in improving postimplant dosimetry reproducibility [59].

Standard dosimetric parameters used to evaluate implant quality include the prostate V_{100} and D_{90}. In 1998, Stock et al [60] reported a dose response for patients undergoing ^{125}I brachytherapy alone, with superior biochemical results in patients with a Day 30 D_{90} ≥140 Gy. Urethral and rectal dosimetry is predictive of long-term QoL outcomes and complication rates and should be determined for each patient [56,61].

Monotherapy for Low-Risk and Some Intermediate-Risk Patients

In contemporary series, brachytherapy as a monotherapeutic approach for patients with low-risk features (defined by the American Joint Commission on Cancer 7th edition [62] as prostate-specific antigen [PSA] <10 ng/mL, Gleason score [GS] ≤6, and clinical stage ≤T2a) has resulted in high rates of biochemical control. Biochemical progression-free survival (bPFS) rates of 86% to 98% have been reported [3,63,64]. Consequently, the routine addition of supplemental EBRT to men with low-risk disease being treated with a brachytherapy implant has not been associated with improved outcomes.

Whether supplemental EBRT is necessary for men with intermediate-risk disease is a subject of continued investigation and is being addressed by the RTOG 02-32 randomized trial, which has completed accrual. The rationale for supplemental EBRT in conjunction with PPB includes the enhancement of radiation dose to the periprostatic region, intraprostatic dose escalation, dose modification of a technically inadequate implant, and/or irradiation of the seminal vesicles. In particular, dose to periprostatic areas to cover for potential extraprostatic extension (EPE) is considered an important issue in men with intermediate-risk disease. However, detailed pathology studies indicate that the radial extent of extraprostatic cancer extension is almost always ≤5 mm, which is within the confines of a monotherapeutic brachytherapy dose distribution [56,65]. In addition, with improved contemporary MR imaging, determination of the presence of T3a/b may also be established. In a study by Pugh et al [66], it was determined that endorectal MRI (erMRI) was helpful in determining the presence and extent of EPE. An EPE-negative erMRI was highly predictive of EPE limited to a radial distance of 5 mm or less from the prostatic capsule (negative predictive value, 95.6%). It should be noted that several of the earlier published studies of monotherapy for intermediate-risk patients reported suboptimal results, raising concern about the adequacy of monotherapy in these men [67-69]. However, it should also be noted many of these studies are limited in that they predate the routine use of CT-based postimplant dosimetry (see Variant 2 and Variant 3).

Other studies have shown favorable outcomes with a monotherapeutic approach for intermediate-risk patients. Blasko et al [70] reported a 9-year freedom-from-biochemical-progression rate of 82%, with a plateau on the curve for a ^{103}Pd monotherapeutic approach. Supplemental RT did not improve the 5-year biochemical outcome for intermediate-risk patients (84% versus 85%) [71]. Taira et al [72] reported a 12-year bPFS rate of 96% for hormone-naïve, monotherapeutic intermediate-risk patients. Munro et al [73] reported 82% 10-year bPFS for monotherapeutic intermediate-risk patients, with significantly higher bPFS for men receiving D_{90} >140 Gy. Potter et al published a series with 12-year results that did not demonstrate superior biochemical control rates in patients receiving supplemental RT [64]. When these data are taken together along with the results of the Prostate Cancer Results Study Group [58] (see below), there appears to be at least a subset of men with intermediate-risk disease for whom brachytherapy without supplemental RT is an effective treatment option [64,74,75] (see Variant 4).

Supplemental External-Beam Radiation Therapy for Higher-Risk Patients

Brachytherapy alone has been perceived to be inadequate therapy in most men with high-risk disease. Examining a cohort of 1342 high-risk men treated with brachytherapy, D'Amico et al [76] found a significant increase in the risk of prostate cancer–specific mortality in high-risk men treated with brachytherapy alone, compared to those treated with brachytherapy plus EBRT and androgen suppression. In general, the few studies of men with high-risk disease treated with monotherapy have tended to report suboptimal outcomes [68,77].

In contrast, when combined with EBRT, brachytherapy is an effective therapy for men with higher-risk disease [9]. The ASCENDE-RT trial is a prospective randomized study that completed accrual in 2011 and compared intermediate- and high-risk patients treated with EBRT alone to 78 Gy in 39 fractions to 46 Gy in 23 fractions with a brachytherapy boost, and both arms receiving 12 months of ADT, with 8 of the 12 months given in neoadjuvant form. For these patients, initial reports with a median follow-up of 6.5 years demonstrate that a brachytherapy implant with supplemental EBRT and ADT provides superior PSA relapse–free survival (hazard ratio, 0.47) when compared to EBRT and ADT alone in men with intermediate- and high-risk disease. However, there has not yet been a difference in metastasis or survival endpoints. Also, there was an increase in late genitourinary toxicity in the combination arm [10]. While further reports on the outcomes of patients treated on the ASCENDE-RT trial are awaited, the results thus far indicate that adding brachytherapy to the treatment of

prostate cancer appears to be an important consideration for men with higher-risk disease. Gleason pattern 5 may be the greatest risk factor for clinical failure and prostate cancer death in men undergoing definitive treatment for presumed local disease [78]. In this subset of very high-risk men, Taira et al [79] recently reported a 10-year cause-specific survival rate of 90% for men treated with low-dose-rate brachytherapy, EBRT, and ADT. Looking at men with somewhat different very high-risk features (GS 10, GS 8-9 with PSA >20 or >50% cores positive, clinical T3, or any PSA >40), another analysis reported that those treated with brachytherapy-based combined therapy had cause-specific survival at 12 years of 87%, also very favorable compared to other treatment modalities (see Variant 5 and Variant 6).

Androgen Deprivation Therapy for High-Risk Patients

For low-risk patients, no clearly defined role for ADT has been demonstrated [75], although neoadjuvant ADT can be used in men with large prostates prior to implant for the purpose of prostate cytoreduction. The use of ADT in intermediate-risk patients may vary and may be dependent on many factors [80]. High-risk patients are believed to harbor a more aggressive local tumor burden, likely EPE, and possible micrometastatic disease. As a result, high-risk brachytherapy patients usually receive ADT combined with EBRT [14,81].

Supplemental External-Beam Radiation Therapy to Pelvic Nodes

The benefit of including pelvic lymph nodes in supplemental EBRT fields when delivered with brachytherapy has yet to be definitively determined. All patients in the ASCENDE-RT trial, which demonstrated a benefit to a brachytherapy boost in higher-risk patients, received initial whole-pelvic RT. However, for patients in the D'Amico series, which found improved cause-specific survival when supplemental EBRT and ADT were added to brachytherapy for high-risk men, pelvic lymph nodes were not included in the EBRT volume [76]. RTOG trial 0924 was established in part to specifically address this issue [82], which remains unresolved until definitive trial results are available (see Variant 7).

Salvage Brachytherapy Following External-Beam Failure

Brachytherapy is occasionally performed in men with prior pelvic RT, particularly in a salvage setting [83]. Nonetheless, prior pelvic RT remains a relative contraindication to brachytherapy. Men with prior pelvic radiation are at a higher risk of complications following salvage PPB [83] and should also be considered for referral to a high-volume center. Low-dose-rate brachytherapy and high-dose-rate brachytherapy have been utilized for men treated in the salvage setting [84,85] (see Variant 8).

Post-treatment Prostate-Specific Antigen Bounce

Following brachytherapy, PSA bounces, sometimes referred to as "spikes," are noted in up to 40% to 50% of all hormone-naïve patients and more commonly among younger men [86-88]. This phenomenon typically occurs 12 to 30 months following PPB and does not appear to adversely impact long-term biochemical outcome [89]. The time of the PSA rise after nadir occurs far sooner for a PSA bounce than for biochemical failure [90]. Crook et al [91] have shown that an increase of >2 ng/mL above the nadir can be seen in 15% of patients, and the magnitude of increase does not distinguish bounce from failure. Post-treatment prostate biopsies performed to differentiate viable cancer from a benign PSA spike can be misleading. Reed et al [90] reported that despite an increasing PSA and a biopsy positive for recurrent cancer, patients may experience subsequent normalization of serum PSA without additional therapeutic intervention. In the first 30 months after brachytherapy in favorable-risk patients, caution is advised in interpreting early increasing PSA levels, and consideration of forgoing or delaying prostate biopsies should be given [91].

Summary of Recommendations

- PPB 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 may be useful in selecting such patients.
- Neoadjuvant total androgen blockade is a useful means by which to facilitate prostate volume cytoreduction and avoid potential pubic arch interference.
- ^{125}I and ^{103}Pd are appropriate isotopes for PPB. ^{131}Cs has comparable short- and intermediate-term outcomes that support its use as an effective isotope.

- High-risk localized prostate cancer treated with PPB should be managed in conjunction with EBRT and ADT. Recent reports confirm excellent cancer control with this combination therapy.
- PPB can be considered in patients experiencing local recurrence following primary EBRT but is associated with increased toxicity as compared to primary PPB. Such patients are ideally referred to high-volume centers.
- Brachytherapy can be considered as a boost treatment in prostate cancer patients with involvement of pelvic lymph nodes in conjunction with EBRT and ADT, but long-term clinical data with this option are limited.

Summary of Evidence

Of the 91 references cited in the *ACR Appropriateness Criteria® Permanent Source Brachytherapy for Prostate Cancer* document, 86 are categorized as therapeutic references including 10 well designed studies, 46 good quality studies, and 7 quality studies that may have design limitations. Additionally, 5 references are categorized as diagnostic references including 3 quality studies that may have design limitations. There are 25 references that may not be useful as primary evidence.

The 91 references cited in the *ACR Appropriateness Criteria® Permanent Source Brachytherapy for Prostate Cancer* document were published from 1997-2015.

While there are references that report on studies with design limitations, 56 well designed or good quality studies provide good evidence.

Supporting Documents

For additional information on the Appropriateness Criteria methodology and other supporting documents go to www.acr.org/ac.

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Clinical Condition: **Permanent Source Brachytherapy for Prostate Cancer**

Variant 1: **65-year-old man, diabetic (Type II), with adenocarcinoma of the prostate. Clinical T1c, PSA 6.5 ng/mL, and GS =6 (3+3) in 3/10 cores. IPSS 9, 65-cm^3 gland by TRUS, postvoid residual volume =5 cc. No history of TURP and no pubic arch interference.**

Treatment	Rating	Comments
Brachytherapy		
Monotherapy	8	One may wish to check for technical feasibility given the potential for pubic arch interference.
Supplemental External Beam		
Prostate + seminal vesicles only	3	This option is generally not considered useful because this is a low-risk case. This option is helpful only in very rare situations.
Prostate + seminal vesicles + pelvic nodes	3	
Androgen Ablation		
No androgen deprivation therapy	8	
Cytoreduction/short duration (≤6 months)	7	One can consider antiandrogen therapy alone instead of luteinizing hormone-releasing hormone agonist or total androgen blockade.
Long duration (>6 months)	2	
Isotope		
Iodine 125	8	
Palladium 103	8	
Cesium 131	7	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: **Permanent Source Brachytherapy for Prostate Cancer**

Variant 2: **52-year-old healthy man, IPSS 5, 35-cm^3 gland. Screening PSA 7.8 ng/mL. Digital rectal examination (DRE) finding of 1-cm apical nodule (T2a) confirmed by MRI of the prostate. Biopsy grade 3+4=7 in 4/12 cores. Negative metastatic workup. Concerned about sexual potency. No pubic arch interference.**

Treatment	Rating	Comments
Brachytherapy		
Monotherapy	7	
Supplemental External Beam		
Prostate + seminal vesicles only	7	
Prostate + seminal vesicles + pelvic nodes	4	
Androgen Ablation		
No androgen deprivation therapy	7	
Cytoreduction/short duration (≤6 months)	4	The role of short-term androgen deprivation is unclear in this patient being managed with primary brachytherapy.
Long duration (>6 months)	3	
Isotope		
Iodine 125	8	
Palladium 103	8	
Cesium 131	7	
Rating Scale: **1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate**		

Clinical Condition: **Permanent Source Brachytherapy for Prostate Cancer**

Variant 3: **52-year-old healthy man, IPSS 5, 35-cm^3 gland. Screening PSA 7.8 ng/mL. DRE normal. MRI of the prostate shows no evidence of T3a/b prostate cancer. Biopsy grade 3+4=7 in 7/12 cores. Negative metastatic workup. Concerned about sexual potency. No pubic arch interference.**

Treatment	Rating	Comments
Brachytherapy		
Monotherapy	7	
Supplemental External Beam		
Prostate + seminal vesicles only	7	
Prostate + seminal vesicles + pelvic nodes	4	Pelvic nodal radiation therapy is generally not used if there is no evidence of T3a/b disease, as stated in the variant.
Androgen Ablation		
No androgen deprivation therapy	7	
Cytoreduction/short duration (≤6 months)	5	The role of short-term androgen deprivation is unclear. Nonetheless, it is not inappropriate. There is wide variation in acceptable practice.
Long duration (>6 months)	4	
Isotope		
Iodine 125	8	
Palladium 103	8	
Cesium 131	6	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: **Permanent Source Brachytherapy for Prostate Cancer**

Variant 4: **62-year-old man, mildly hypertensive, IPSS 3, 50-cm^3 gland by TRUS. PSA 15.0 ng/mL. DRE, 0.5-cm right base nodule (T2a). Biopsy, grade 3+3=6 in 5/12 cores. MR of the prostate reveals no evidence of EPE or seminal vesicle invasion.**

Treatment	Rating	Comments
Brachytherapy		
Monotherapy	7	
Supplemental External Beam		
Prostate + seminal vesicles only	6	
Prostate + seminal vesicles + pelvic nodes	4	
Androgen Ablation		
No androgen deprivation therapy	7	
Cytoreduction/short duration (≤6 months)	5	The role of short-term androgen deprivation remains unclear. It is not inappropriate to give it, particularly if the goal is to achieve cytoreduction in this 50-cm^3 gland. There is wide variation in acceptable practice.
Long duration (>6 months)	3	
Isotope		
Iodine 125	8	
Palladium 103	8	
Cesium 131	7	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: **Permanent Source Brachytherapy for Prostate Cancer**

Variant 5: **64-year-old healthy man, IPSS 6, 35-cm^3 gland by TRUS. PSA 6.5 ng/mL. DRE, (T1c). Biopsy, grade 4+4=8 in 2/12 cores. Negative workup. MR of the prostate is suspicious for possible EPE but no seminal vesicle invasion.**

Treatment	Rating	Comments
Brachytherapy		
Monotherapy	3	High-risk patients generally do not undergo prostate brachytherapy monotherapy. Per the ASCENDE trial, high-risk patients did well with all 3 treatments.
Supplemental External Beam		
Prostate + seminal vesicles only	7	There is ongoing debate about the inclusion of pelvic nodes in radiotherapeutic management of localized high-risk patients. It is a generally acceptable approach to not include nodes. It is unclear if inclusion of nodes improves outcomes.
Prostate + seminal vesicles + pelvic nodes	7	
Androgen Ablation		
No androgen deprivation therapy	4	Per the ASCENDE trial and other retrospective data, ADT would generally be given because of the GS of 8.
Cytoreduction/short duration (≤6 months)	6	Per the EBRT data in the ASCENDE trial, >6 months ADT would generally be given because of the GS of 8. Nonetheless, this may be appropriate since there are no specific studies comparing 6 months or less in high-risk patients with brachytherapy as a component of treatment.
Long duration (>6 months)	7	
Isotope		
Iodine 125	8	
Palladium 103	8	
Cesium 131	7	
Rating Scale: **1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate**		

Clinical Condition: **Permanent Source Brachytherapy for Prostate Cancer**

Variant 6: **67-year-old healthy man, IPSS 9, 55-cm^3 gland by TRUS. PSA 18 ng/mL. DRE, right EPE (T3a). Biopsy, grade 4+4=8 in 8/12 cores. Negative workup.**

Treatment	Rating	Comments
Brachytherapy		
Monotherapy	3	
Supplemental External Beam		
Prostate + seminal vesicles only	7	There is ongoing debate about the inclusion of pelvic nodes. It is a generally acceptable approach to not include the nodes in the treatment fields. It is unclear if inclusion of nodes improves outcomes.
Prostate + seminal vesicles + pelvic nodes	7	
Androgen Ablation		
No androgen deprivation therapy	3	
Cytoreduction/short duration (≤6 months)	5	The role of short-term hormones remains unclear. It is not inappropriate to give it. There is a wide variation in practice.
Long duration (>6 months)	8	
Isotope		
Iodine 125	8	
Palladium 103	8	
Cesium 131	6	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: **Permanent Source Brachytherapy for Prostate Cancer**

Variant 7: **63-year-old healthy man, IPSS 6, 40-cm^3 gland by TRUS. PSA 35 ng/mL. DRE, EPE (T3a). Biopsy, grade 4+4=8 in 5/12 cores. Imaging demonstrates probable left seminal vesicle invasion, 2 suspicious lymph nodes. No distant metastases.**

Treatment	Rating	Comments
Additional Workup		
CT-guided lymph node biopsy	7	The potential for CT-guided biopsy may strongly depend on the location and feasibility of safe biopsy of the node.
Initial Management (Lymph Node Positive)		
ADT alone	4	
ADT + EBRT	7	
ADT + EBRT + brachytherapy	7	If lymph node biopsy is negative and possible left seminal vesicle invasion is close enough to implant, then trimodality therapy may be reasonable.
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Variant 8: **69-year-old healthy man, IPSS 11, 42-cm^3 gland by TRUS. Initially presented with grade 3+4=7 in 3/12 cores, PSA 6, T1c prostate cancer. EBRT to 75.6 Gy 3 years ago to prostate and base of seminal vesicles only. Biopsy-proven recurrence with current PSA of 4.2 ng/mL with doubling time of 14 months. MRI shows single 2-cm lesion in right peripheral zone without EPE. Negative metastatic workup.**

Treatment	Rating	Comments
Brachytherapy		
Monotherapy	7	Refer to experienced center.
Supplemental External Beam		
Prostate + seminal vesicles only	3	
Prostate + seminal vesicles + pelvic nodes	3	
Androgen Ablation		
No androgen deprivation therapy	5	For the RTOG trial, patients could be put on hormones, but it was not necessary. There are no strong data to support either using or not using ADT.
Cytoreduction/short duration (≤6 months)	6	For the RTOG trial, patients could be put on hormones, but it was not necessary. There are no strong data to support either using or not using ADT.
Long duration (>6 months)	6	
Isotope		
Iodine 125	8	
Palladium 103	8	
Cesium 131	6	
High-dose-rate iodine 192	7	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		