



Complete Summary

GUIDELINE TITLE

Permanent source brachytherapy for prostate cancer.

BIBLIOGRAPHIC SOURCE(S)

Merrick G, Roach M III, Anscher MS, Beyer DC, Lawton CA, Lee WR, Michalski JM, Pollack A, Vijayakumar S, Carroll PR, Higano CS, Mauch PM, Expert Panel on Radiation Oncology-Prostate Work Group. Permanent source brachytherapy for prostate cancer. [online publication]. Reston (VA): American College of Radiology (ACR); 2006. 16 p. [91 references]

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Potters L, Perez CA, Beyer DC, Blasko JC, Forman JD, Hussey DH, Lee WR, Paryani SB, Pollack A, Roach M, Scardino P, Schellhammer P, Leibel S. Permanent source brachytherapy for prostate cancer. American College of Radiology. ACR Appropriateness Criteria. Radiology 2000 Jun;215(Suppl):1383-400.

The appropriateness criteria are reviewed annually and updated by the panels as needed, depending on introduction of new and highly significant scientific evidence.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- [October 18, 2007, PDE5 inhibitors, Viagra \(sildenafil citrate\), Levitra \(vardenafil HCL\), Cialis \(tadalafil\)](#): The PRECAUTION and updated Adverse Reactions Sections of the approved product labeling for Viagra, Levitra, and Cialis were revised in response to reports of sudden decreases or loss of hearing.

COMPLETE SUMMARY CONTENT

** REGULATORY ALERT **

SCOPE

METHODOLOGY - including Rating Scheme and Cost Analysis

RECOMMENDATIONS
EVIDENCE SUPPORTING THE RECOMMENDATIONS
BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS
CONTRAINDICATIONS
QUALIFYING STATEMENTS
IMPLEMENTATION OF THE GUIDELINE
INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT
CATEGORIES
IDENTIFYING INFORMATION AND AVAILABILITY
DISCLAIMER

SCOPE

DISEASE/CONDITION(S)

Prostate cancer

GUIDELINE CATEGORY

Treatment

CLINICAL SPECIALTY

Internal Medicine
Oncology
Radiation Oncology
Radiology
Surgery

INTENDED USERS

Health Plans
Hospitals
Managed Care Organizations
Physicians
Utilization Management

GUIDELINE OBJECTIVE(S)

To summarize biochemical and quality of life (QOL) outcomes following permanent prostate brachytherapy, address areas of controversy, and provide guidelines for clinical management

TARGET POPULATION

Patients with prostate cancer undergoing permanent source brachytherapy

INTERVENTIONS AND PRACTICES CONSIDERED

1. Brachytherapy

- Iodine (I)-125 monotherapy
 - Palladium (Pd)-103 monotherapy
 - Iridium (Ir)-192 boost with external beam
 - I-125 boost with external beam
 - Pd-103 boost with external beam
2. Alternative treatments
- External beam prostate/seminal vesicle (SV) only
 - Observation only
 - Radical prostatectomy
 - External beam pelvis and prostate
 - Androgen ablation only
 - Temporary hormonal and external beam
 - Transurethral resection only
 - Permanent hormonal and external beam
3. Androgen ablation plus brachytherapy
- Temporary
 - Orchiectomy/permanent

MAJOR OUTCOMES CONSIDERED

- Quality of life
- Biochemical progression-free survival rates
- Adverse effects of permanent source brachytherapy

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The guideline developer performed literature searches of peer-reviewed medical journals and the major applicable articles were identified and collected.

NUMBER OF SOURCE DOCUMENTS

The total number of source documents identified as the result of the literature search is not known.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Not Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not stated

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

One or two topic leaders within a panel assume the responsibility of developing an evidence table for each clinical condition, based on analysis of the current literature. These tables serve as a basis for developing a narrative specific to each clinical condition.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus (Delphi)

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Since data available from existing scientific studies are usually insufficient for meta-analysis, broad-based consensus techniques are needed for reaching agreement in the formulation of the appropriateness criteria. The American College of Radiology (ACR) Appropriateness Criteria panels use a modified Delphi technique to arrive at consensus. Serial surveys are conducted by distributing questionnaires to consolidate expert opinions within each panel. These questionnaires are distributed to the participants along with the evidence table and narrative as developed by the topic leader(s). Questionnaires are completed by participants in their own professional setting without influence of the other members. Voting is conducted using a scoring system from 1-9, indicating the least to the most appropriate imaging examination or therapeutic procedure. The survey results are collected, tabulated in anonymous fashion, and redistributed after each round. A maximum of three rounds is conducted and opinions are unified to the highest degree possible. Eighty percent agreement is considered a consensus. This modified Delphi technique enables individual, unbiased expression, is economical, easy to understand, and relatively simple to conduct.

If consensus cannot be reached by the Delphi technique, the panel is convened and group consensus techniques are utilized. The strengths and weaknesses of each test or procedure are discussed and consensus reached whenever possible. If "No consensus" appears in the rating column, reasons for this decision are added to the comment sections.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Criteria developed by the Expert Panels are reviewed by the American College of Radiology (ACR) Committee on Appropriateness Criteria.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

ACR Appropriateness Criteria®

Clinical Condition: Permanent Source Brachytherapy for Prostate Cancer

Variant 1: 75-year-old, healthy, IPSS 4, 35 cm³ gland by TRUS. PSA 6.5. DRE negative. Biopsy, grade 3+2=5 adenocarcinoma in 2/6 cores. Negative work-up.

Treatment	Appropriateness Rating	Comments
Brachytherapy		
I-125 monotherapy	8	
Pd-103 monotherapy	8	
Ir-192 boost with external beam	3	
I-125 boost with external beam	2	
Pd-103 boost with external beam	2	
Alternative Treatments		
External beam prostate/seminal vesicle (SV) only	8	
Observation only	8	
Radical prostatectomy	4	Patient health and comorbidities must be taken into account.
External beam pelvis and prostate	2	
Androgen ablation only	2	
Temporary hormonal and external beam	2	

Treatment	Appropriateness Rating	Comments
Transurethral resection only	1	
Permanent hormonal and external beam	1	
Androgen Ablation+Brachytherapy		
Temporary (<6 months)	2	
Temporary (>6 months)	1	
Orchiectomy/permanent	1	
Appropriateness Criteria Scale 1 2 3 4 5 6 7 8 9 1 = Least appropriate 9 = Most appropriate		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 2: 65-year-old diabetic, IPSS 10, 50 cm³gland by TRUS. PSA 9.5. DRE, 1 cm mid-lobe nodule (T2a). Biopsy, grade 3+3=6 in 2/6 cores. Negative work-up.

Treatment	Appropriateness Rating	Comments
Brachytherapy		
I-125 monotherapy	8	
Pd-103 monotherapy	8	
Ir-192 boost with external beam	3	
I-125 boost with external beam	2	
Pd-103 boost with external beam	2	
Alternative Treatments		
External beam prostate/SV only	8	
Radical prostatectomy	8	

Treatment	Appropriateness Rating	Comments
Observation only	4	
External beam pelvis and prostate	3	
Androgen ablation only	2	
Temporary hormonal and external beam	2	
Transurethral resection only	1	
Permanent hormonal and external beam	1	
Androgen Ablation+Brachytherapy		
Temporary (<6 months)	7	To reduce the gland size
Temporary (>6 months)	2	
Orchiectomy/permanent	1	
Appropriateness Criteria Scale 1 2 3 4 5 6 7 8 9 1 = Least appropriate 9 = Most appropriate		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 3: 60-year-old mildly hypertensive, IPSS 3, 40 cm³ gland by TRUS. PSA 11.0. DRE, .5 cm right base nodule (T2b). Biopsy, grade 3+4=7 in 3/6 cores. Negative work-up.

Treatment	Appropriateness Rating	Comments
Brachytherapy		
I-125 monotherapy	7	Randomized control trials ongoing—addressing these modalities.
Pd-103 monotherapy	7	Randomized control trials ongoing—addressing these modalities.
I-125 boost with external beam	7	Randomized control trials ongoing—addressing these modalities.

Treatment	Appropriateness Rating	Comments
Pd-103 boost with external beam	7	Randomized control trials ongoing—addressing these modalities.
Ir-192 boost with external beam	7	Randomized control trials ongoing—addressing these modalities.
Alternative Treatments		
Temporary hormonal and external beam	8	
External beam prostate/SV only	7	
Radical prostatectomy	7	
External beam pelvis and prostate	7	
Observation only	2	
Androgen ablation only	2	
Transurethral resection only	1	
Permanent hormonal and external beam	1	
Androgen Ablation+Brachytherapy		
Temporary (<6 months)	5	Clinical trials ongoing.
Temporary (>6 months)	5	Clinical trials ongoing.
Orchiectomy/permanent	1	
Appropriateness Criteria Scale 1 2 3 4 5 6 7 8 9 1 = Least appropriate 9 = Most appropriate		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 4: 52-year-old, healthy, IPSS 0, 25 cm³ gland. Screening PSA 7.8. DRE negative. Biopsy, grade 3+3=6 in 1/6 cores. Negative work-up. Concerned about sexual potency.

Treatment	Appropriateness Rating	Comments
Brachytherapy		
I-125 monotherapy	8	
Pd-103 monotherapy	8	
Ir-192 boost with external beam	3	
I-125 boost with external beam	2	
Pd-103 boost with external beam	2	
Alternative Treatments		
External beam prostate/SV only	8	
Radical prostatectomy	8	
Observation only	2	
External beam pelvis and prostate	2	
Temporary hormonal and external beam	2	
Androgen ablation only	1	
Transurethral resection only	1	
Permanent hormonal and external beam	1	
Androgen Ablation+Brachytherapy		
Temporary (<6 months)	2	
Temporary (>6 months)	1	
Orchiectomy/permanent	1	
Appropriateness Criteria Scale 1 2 3 4 5 6 7 8 9 1 = Least appropriate 9 = Most appropriate		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 5: 61-year-old, healthy, IPSS 4, 30 cm³ gland by TRUS. PSA 10.0. DRE, 1 cm apical nodule (T2a). Sextant biopsy reveals grade 3+3=6 in 2 apical cores. Negative work-up.

Treatment	Appropriateness Rating	Comments
Brachytherapy		
I-125 monotherapy	8	
Pd-103 monotherapy	8	
I-125 boost with external beam	5	Clinical trials ongoing.
Pd-103 boost with external beam	5	Clinical trials ongoing.
Ir-192 boost with external beam	5	Clinical trials ongoing.
Alternative Treatments		
External beam prostate/SV only	8	
Radical prostatectomy	8	
Observation only	3	
External beam pelvis and prostate	3	
Temporary hormonal and external beam	3	
Androgen ablation only	2	
Permanent hormonal and external beam	2	
Transurethral resection only	1	
Androgen Ablation+Brachytherapy		
Temporary (<6 months)	2	
Temporary (>6 months)	2	

Treatment	Appropriateness Rating	Comments
Orchiectomy/permanent	1	
Appropriateness Criteria Scale 1 2 3 4 5 6 7 8 9 1 = Least appropriate 9 = Most appropriate		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 6: 60-year-old, healthy, IPSS 3, 35 cm³ gland by TRUS. PSA 13.5. DRE, 2.0 cm right base nodule (T2b). Biopsy, grade 4+4=8 in 3/6 cores. Negative work-up.

Treatment	Appropriateness Rating	Comments
Brachytherapy		
I-125 boost with external beam	7	
Pd-103 boost with external beam	7	
Ir-192 boost with external beam	7	
I-125 monotherapy	2	
Pd-103 monotherapy	2	
Alternative Treatments		
Temporary hormonal and external beam	8	
Radical prostatectomy	7	With adjuvant radiation or hormone therapy as indicated.
External beam pelvis and prostate	7	With adjuvant hormone therapy.
Permanent hormonal and external beam	5	Hormone therapy for ≤ 3 years.
External beam prostate/SV only	2	
Androgen ablation only	2	
Observation only	1	

Treatment	Appropriateness Rating	Comments
Transurethral resection only	1	
Androgen Ablation+Brachytherapy		
Temporary (<6 months)	5	
Temporary (>6 months)	5	
Orchiectomy/permanent	2	
Appropriateness Criteria Scale 1 2 3 4 5 6 7 8 9 1 = Least appropriate 9 = Most appropriate		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

VARIANT 7: 68-year-old, hypertensive, IPSS 18, post void residual (PVR) 20 cc, 92 cm³ gland by TRUS, PSA 12.0. DRE, vague induration entire right lobe. Sextant biopsy reveals grade 3+4=7 in 2 cores on the right. Negative work-up.

Treatment	Appropriateness Rating	Comments
Brachytherapy		
Ir-192 boost with external beam	5	Reevaluate after neoadjuvant ADT.
I-125 monotherapy	4	Reevaluate after neoadjuvant ADT.
Pd-103 monotherapy	4	Reevaluate after neoadjuvant ADT.
I-125 boost with external beam	4	Reevaluate after neoadjuvant ADT.
Pd-103 boost with external beam	4	Reevaluate after neoadjuvant ADT.
Alternative Treatments		
Radical prostatectomy	8	
Temporary hormonal and external beam	8	
External beam	7	

Treatment	Appropriateness Rating	Comments
prostate/SV only		
External beam pelvis and prostate	7	
Observation only	2	
Androgen ablation only	2	
Transurethral resection only	2	
Permanent hormonal and external beam	2	
Androgen Ablation+Brachytherapy		
Temporary (<6 months)	7	
Temporary (>6 months)	4	
Orchiectomy/permanent	1	
Appropriateness Criteria Scale 1 2 3 4 5 6 7 8 9 1 = Least appropriate 9 = Most appropriate		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 8: 70-year-old, excellent health, IPSS 18, PVR 125 cc, 80 cm³ gland by TRUS. PSA 9.8. DRE, 1 cm left mid lobe nodule (T2a). Biopsy reveals grade 3+3=6 in 1/6 cores. Negative work-up.

Treatment	Appropriateness Rating	Comments
Brachytherapy		
Ir-192 boost with external beam	3	
I-125 monotherapy	2	
Pd-103 monotherapy	2	
I-125 boost with external beam	2	

Treatment	Appropriateness Rating	Comments
Pd-103 boost with external beam	2	
Alternative Treatments		
External beam prostate/SV only	8	
Radical prostatectomy	7	
Temporary hormonal and external beam	7	
Observation only	5	Active surveillance.
External beam pelvis and prostate	3	
Androgen ablation only	2	
Transurethral resection only	2	
Permanent hormonal and external beam	2	
Androgen Ablation+Brachytherapy		
Temporary (<6 months)	3	
Temporary (>6 months)	2	
Orchiectomy/permanent	1	
Appropriateness Criteria Scale 1 2 3 4 5 6 7 8 9 1 = Least appropriate 9 = Most appropriate		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Permanent prostate brachytherapy has emerged as a highly efficacious treatment for clinically localized prostate cancer with biochemical outcomes and morbidity profiles that compare favorably with those of competing local modalities. The resurgence of interest in prostate brachytherapy is principally due to the evolution of transrectal ultrasonography, the development of a closed transperineal approach, and sophisticated treatment planning software. These imaging and planning advances dramatically improved the accuracy of seed placement. In addition, computerized tomography (CT) based postoperative dosimetry provided the ability to evaluate implant quality and proactively influence outcome. As

brachytherapy outcomes have matured, it has become increasingly apparent that efficacy and morbidity are dependent on implant quality. This review summarizes biochemical and quality of life (QOL) outcomes following permanent prostate brachytherapy, addresses areas of controversy, and provides guidelines for clinical management.

Patient Selection

With the assimilation of brachytherapy into the conventional uro-oncology armamentarium, a rapidly expanding body of literature regarding patient selection and treatment approach has been published. Although not all patients are acceptable candidates for brachytherapy, a reliable set of pretreatment criteria for predicting implant-related morbidity has not been formulated. While most alleged contraindications to brachytherapy have been propagated with little supporting data, an increasing number of evidence-based factors contributing to brachytherapy-related morbidity have accumulated.

Despite the fact that no clear relationship exists between prostate size and increased urinary morbidity, large prostate size remains a relative contraindication to brachytherapy due to technical concerns or the perception that patients with large prostate glands are at higher risk for acute and prolonged urinary morbidity. Patients with a prostate volume $>50 \text{ cm}^3$ are often counseled not to proceed with brachytherapy or to first receive neoadjuvant ADT for cytoreduction. But contrary to popular opinion, patients with large prostate glands can be implanted with acceptable morbidity. In a study using the patient-administered Expanded Prostate Cancer Index Composite (EPIC), long-term urinary function did not correlate with prostate size. On the other extreme, favorable dosimetry with minimal urinary morbidity has been reported for patients with prostate glands $<20 \text{ cm}^3$. In contrast to overall prostate size, transition zone volume has consistently correlated with brachytherapy-related urinary morbidity.

Currently, no reliable preimplant criteria can be used to predict prolonged urinary retention. The role of the IPSS in predicting urinary morbidity (including urinary retention) has been studied extensively with conflicting conclusions. Although almost all patients experience urinary irritation or obstructive symptomatology with 2%-34% developing acute urinary retention, only 2% -5% require a urinary catheter for more than one week. The preimplant IPSS does correlate with the duration of post-implant obstructive symptomatology, but it is not a predictor for long-term urinary QOL. The prophylactic and prolonged use of alpha blockers results in a return of IPSS to baseline significantly faster than in patients not receiving alpha blockers or receiving them after substantial exacerbation of urinary symptoms.

Pubic arch interference (the obstruction of anterior needle placement insertion by a narrow pubic arch) remains a relative contraindication to brachytherapy despite limited clinical information supporting such concerns.

Through the mid-1990s, urinary incontinence developed in approximately 50% of patients with a history of a preimplant transurethral resection of the prostate gland (TURP). In more contemporary series, however the risk of incontinence has been reported to be 6% or less due to the adoption of peripheral source loading and limitation of the radiation dose to the TURP defect to approximately 110% of

the prescription dose. Using the EPIC instrument, patients with a preimplant TURP were found to have urinary QOL approaching that of non-TURP brachytherapy patients.

After brachytherapy, approximately 2% of patients develop prolonged urinary retention, with the vast majority eventually spontaneously urinating without surgical intervention. Since significant urinary morbidity has been demonstrated in approximately 50% of patients undergoing a post-implant transurethral resection of the prostate gland (TURP), post-implant surgical intervention should be delayed for as long as possible. To minimize postbrachytherapy TURP-related incontinence, preservation of the bladder neck at the 5 and 7 o'clock positions with minimal cautery has been recommended to maintain sufficient prostatic urethral blood supply.

Median lobe hyperplasia (the protrusion of hypertrophied prostate tissue into the bladder) has been reported to be a relative contraindication to brachytherapy because of concerns for an increased risk of post-implant urinary morbidity and technical difficulties encountered while implanting intravesical tissue. In a small contemporary series, 25% of patients with median lobe hyperplasia developed prolonged post-implant urinary retention. It is conceivable that preimplant resection of the intravesical component could reduce the incidence of brachytherapy-related morbidity.

In addition, other often-quoted contraindications to brachytherapy including prostatitis, patient age, obesity, diabetes mellitus, and inflammatory bowel disease have been propagated without clinical or dosimetric support.

Brachytherapy Planning

Favorable brachytherapy results have been obtained with various planning and intraoperative techniques. It is universally accepted that an adequate implant should encompass the prostate, but there is no consensus on what represents the optimal target volume. In addition, urethral and rectal tolerances are still being defined, while the significance and degree of dose homogeneity throughout the implant region remains unclear.

Brachytherapy planning entails preplanning (in which a transrectal ultrasound volumetric study of the prostate gland is obtained before the day of implantation) or intraoperative planning. All plans should be evaluated based on dose volume histograms of the planning target volume, urethra, and rectum. 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} (dose delivered to 90% of the target volume), urethral $V_{125/150}$ (the volume of the urethra receiving 125% and 150% of the prescribed dose), the average urethral dose, and the R_{100} (volume of the rectum receiving 100% of the prescribed dose). Plans should attempt to minimize the number of needles and seeds, provide high-dose coverage to the target, and minimize high dose volumes.

Post-Implant Evaluation

The advent of CT-based postoperative dosimetry provided a unique opportunity to evaluate quality and proactively predict outcome and complications. Postoperative

CT-based dosimetric analysis provides detailed information regarding the coverage and uniformity of an implant, affords the ability to compare various intraoperative techniques, and provides a sound basis for future improvement. Although CT determination of prostate volume is widely accepted for external beam planning, the use of CT for brachytherapy purposes remains controversial. The accurate delineation of prostate contours on post-implant CT scans may be difficult because of postoperative edema, degradation of the image due to implanted metallic seeds, and a tendency to overestimate prostate volume from CT compared to transrectal ultrasound. However, if the levator ani muscles are not included in the CT-determined prostate volume, a close correlation has been demonstrated for CT and ultrasound-determined prostate volumes. In addition, if implants are designed and executed with generous periprostatic treatment margins, the determination of post-implant prostate volume by CT does not significantly influence dosimetric outcome.

The timing of post-implant CT remains controversial. Some groups recommend a day 30 CT scan to allow for the resolution of edema, while others propose day zero dosimetry to provide information about edema at its maximum extent and for prompt closure of the learning loop. For intraoperative dosimetric evaluation, knowledge of day 0 threshold dosimetric parameters is essential to evaluate the advisability of corrective seed placement.

In 1998, a dose response curve was reported for patients undergoing monotherapeutic I-125 brachytherapy with superior biochemical results in patients with a day 30 $D_{90} \geq 140$ Gy. Subsequently, day 30 D_{90} cut points of 140 Gy and 100 Gy for I-125 and Pd-103, respectively, were reported. Urethral and rectal dosimetry is predictive of long-term QOL outcomes and complication rates and should be determined for each patient. No significant differences in dosimetric quality have been reported when stratified by isotope.

Biochemical Outcomes

In contemporary series, brachytherapy as a monotherapeutic approach for patients with low-risk features (defined by the American Joint Commission on Cancer [AJCC] in 2002 as PSA ≤ 10 ng/mL, Gleason score ≤ 6 , and clinical stage $\leq T2b$) has resulted in high rates of biochemical control without further improvement following the addition of supplemental radiation therapy. Biochemical progression-free survival rates of 87%-98% have been reported.

For patients with intermediate-risk disease as defined by the AJCC (PSA ≥ 10 ng/mL or Gleason score ≥ 7 or clinical stage $\geq T2c$), one study reported a 9-year freedom from biochemical progression rate of 82% with a plateau on the curve for a Pd-103 monotherapeutic approach. Supplemental radiation therapy (RT) did not improve the 5-year biochemical outcome for intermediate-risk patients (84% vs 85%). Another study reported an 8-year biochemical progression-free survival rate of 95% for hormone-naïve monotherapeutic intermediate-risk patients with a median post-treatment PSA < 0.1 ng/mL. In addition, a large, recently published series with 12-year results failed to demonstrate superior biochemical control rates in patients receiving supplemental RT. When these data are taken together, no biochemical advantage has been reported for the addition of supplemental RT in hormone-naïve intermediate risk brachytherapy patients. Brachytherapy is

relatively resilient to extraprostatic cancer extension because of its ability to aggressively irradiate the periprostatic region.

For high-risk patients as defined by the AJCC (2 or 3 of the following risk factors: PSA ≥ 10 ng/mL, Gleason score ≥ 7 , and/or clinical stage $\geq T2c$), one study reported a 79% 10-year biochemical progression-free survival (PSA ≤ 0.2 ng/mL) for patients receiving supplemental RT followed by a Pd-103 boost with a plateau on the biochemical freedom-from-failure curves within 3 years of implantation. For hormone-naïve high-risk patients undergoing brachytherapy and supplemental RT, another study reported an approximate 80% 8-year freedom from biochemical failure rate with a median post-treatment PSA < 0.1 ng/mL.

Two studies have reported favorable results for high-risk patients undergoing monotherapeutic brachytherapy. The first reported a 65% 9-year freedom from biochemical progression rate for Pd-103 monotherapy patients with a pretreatment PSA > 20 ng/mL. The other study stratified hormone-naïve high-risk patients undergoing brachytherapy without supplemental RT into day 30 low-dose ($D_{90} < 140$ Gy for I-125 and < 100 Gy for Pd-103) versus high-dose implants with an 80% 5-year freedom from biochemical failure in the high dose arm.

Almost all studies of intermediate- and high-risk patients receiving combined brachytherapy and supplemental RT have reported favorable biochemical outcomes. However, biochemical progression-free survival in intermediate- and high-risk patients undergoing monotherapeutic brachytherapy remains controversial. Three monotherapeutic studies have reported suboptimal results. None of these studies implanted patients with generous periprostatic treatment margins or presented post-implant dosimetric outcomes. Because patients with higher risk features have at least a 50% chance of extraprostatic cancer extension and the dose gradient at the periphery of the target volume is as great as 20 Gy/mm, these patients may not have received adequate doses to sterilize intraprostatic or extracapsular disease. It is likely that cancer eradication in intermediate- and high-risk patients treated with a monotherapeutic approach requires patients with a minimal risk of pelvic lymph node involvement, limited seminal vesicle extension, and post-implant dosimetric confirmation of radiation dose to the intraprostatic and extracapsular regions.

Adjuvant Androgen Deprivation Therapy

Despite recent reports detailing favorable biochemical outcomes for hormone-naïve brachytherapy patients with higher risk features, intermediate- and high-risk brachytherapy patients often receive ADT as an extrapolation from the conventional external beam radiation therapy dose (65-70 Gy) literature. In a matched-pair analysis, no biochemical benefits for ADT combined with brachytherapy were discerned for any risk group, Gleason score, pretreatment PSA level, or clinical stage. In addition, ADT has been implicated in brachytherapy-related morbidity.

Other than its proven role as a cytoreductive therapy, no defined role for ADT has been demonstrated in brachytherapy patients. Following high quality brachytherapy, one study reported that ADT did not alter biochemical outcome for high-risk patients. In contrast, another study reported a statistically significant improvement in 8-year biochemical progression-free survival for high-risk (but not

low- or intermediate-risk) patients with the addition of ADT. Although the results of these two studies appear contradictory, patients in the first study were treated without supplemental RT while patients in the second series received pelvic nodal external beam RT. It is possible that the beneficial effects of ADT are maximized when combined with pelvic nodal irradiation.

Supplemental External Beam Radiation Therapy

The rationale for supplemental external beam RT in conjunction with permanent prostate brachytherapy 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 entirety of the seminal vesicles and/or pelvic lymph nodes. Initially there was agreement that patients with a Gleason score ≥ 7 , a pretreatment PSA > 10 ng/mL, and/or $\geq T2c$ prostate cancer should receive supplemental RT. However, the utility of supplemental RT has been questioned by favorable results with an implant alone in patients with higher PSA and/or Gleason scores. 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. If the prostate gland is implanted with generous periprostatic treatment margins, supplemental RT is unlikely to improve the biochemical outcome in low-, intermediate-, and selected high-risk cases. A prospective randomized trial evaluating 20 Gy of supplemental RT versus 44 Gy in Pd-103 patients with higher risk features demonstrated no difference in biochemical control.

PSA Spikes

Following brachytherapy, PSA spikes are noted in up to a third of all hormone-naïve patients. This phenomenon typically occurs 12-30 months following implantation and most importantly does not adversely impact long-term biochemical outcome. PSA spikes are least common in patients with a post-treatment PSA ≤ 0.2 ng/mL.

Post-treatment prostate biopsies to differentiate viable cancer from a benign PSA spike can be misleading. A recent publication 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.

Morbidity

Urinary Morbidity

An enlarging body of data demonstrates that brachytherapy-related urinary morbidity can be lessened with refinements in patient selection, medical intervention, and intraoperative technique. Following brachytherapy, almost all patients develop urinary irritation or obstructive symptomatology, with acute urinary retention in up to 34% of patients. To ameliorate brachytherapy-related urinary symptoms, alpha blockers are widely used, and the timing of their initiation may substantially influence their effect. The initiation of alpha blockers 2-3 weeks prior to implantation with continuation at least until normalization of the IPSS maximizes the alpha blocker beneficial effect. Dysuria is common

following brachytherapy. Although dysuria is a relatively common event during the first few years following brachytherapy, only rarely is it severe in frequency or intensity.

Following brachytherapy, the incidence of urethral strictures ranges from 1%-12%. Strictures typically involve the bulbomembranous urethra and are usually easily managed by dilatation. Brachytherapy and supplemental RT doses to the bulbomembranous urethra represent the primary risk factors for the development of brachytherapy-related stricture disease.

Supplemental RT can result in a deleterious effect on long-term urinary function, including hematuria and incontinence (determined by EPIC).

Rectal Morbidity

Rectal complications consist primarily of mild, self-limited proctitis and have been correlated with rectal dose. The onset of bleeding peaks at 8 months with an incidence of 4%-12% and usually resolves spontaneously. Rectal ulceration and fistula formation occasionally have been reported.

Bowel function assessments by patient-administered questionnaires illustrate that long-term dysfunction following brachytherapy is relatively uncommon. Only 12% of patients report bowel function to be worse after implantation, with the number of preimplant bowel movements, history of tobacco consumption, median rectal dose, and the use of supplemental RT predictive for deterioration in bowel habits.

Intraoperatively, careful attention to implant technique and ultrasound anatomy will reduce the dose to the anterior rectal wall and minimize bowel dysfunction. Extensive use of both transverse and sagittal ultrasonography to confirm appropriate needle placement and the use of multiple ultrasound frequencies helps ensure proper seed placement.

Erectile Dysfunction

Although it has been widely asserted that preservation of erectile function (ED) is more likely after brachytherapy, the incidence of brachytherapy-induced ED is substantially greater than initially reported, with rates ranging from 6%-90%. The wide range likely reflects differences in follow-up, patient selection, implant technique, and mode of data collection. In general, series with the longest follow-up and the use of patient-administered questionnaires report lower rates of potency preservation. Fortunately, most patients with brachytherapy-induced ED respond to erectogenic agents such as sildenafil citrate.

Although the etiology of brachytherapy-induced ED is likely multifactorial, the available data strongly support the proximal penis as an important site-specific structure. Suboptimal seed placement (either due to poor planning and/or poor implementation) of periapical radiation sources results in excessive radiation doses to the bulb of the penis. As such, refinements in implant technique should result in lower radiation doses to the proximal penis with increased rates of potency preservation. To date, no relationship has been established between brachytherapy-related ED and the dose to the neurovascular bundles.

From a clinical perspective, potency preservation following brachytherapy is most closely related to preimplant erectile function. The presence of preimplant nocturnal erections also predicts for post-treatment erectile function. Initially, the addition of supplemental RT was reported to result in a deleterious effect on erectile function. However, the results of a prospective randomized trial that limited radiation dose to the proximal penis from both the supplemental RT and brachytherapy components reported no adverse effect of RT on potency preservation. The role of neoadjuvant ADT in potency preservation has also been mixed.

Conclusions

The majority of brachytherapy series have demonstrated favorable morbidity profiles and durable biochemical control rates for patients with low, intermediate, and high risk features. As brachytherapy follow-ups have matured, it has become increasingly apparent that efficacy and morbidity are highly dependent on implant quality. Continued attempts to refine patient selection, brachytherapy treatment planning philosophy, intraoperative technique, and post-implant management should result in further improvements in biochemical outcome and decreased brachytherapy-related morbidity.

Abbreviations

- ADT, androgen deprivation therapy
- DRE, digital rectal examination
- I, iodine
- IPSS, International Prostate Symptom Score
- Ir, iridium
- Pd, palladium
- PSA, prostate-specific antigen
- SV, seminal vesicle
- TRUS, transrectal ultrasound

CLINICAL ALGORITHM(S)

Algorithms were not developed from criteria guidelines.

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are based on analysis of the current literature and expert panel consensus.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Selection of appropriate radiologic procedures for patients undergoing permanent source brachytherapy in the management of prostate cancer

POTENTIAL HARMS

See the "Major Recommendations" field for a complete list of harms associated with urinary morbidity, rectal morbidity, and erectile dysfunction.

CONTRAINDICATIONS

CONTRAINDICATIONS

- Despite the fact that no clear relationship exists between prostate size and increased urinary morbidity, large prostate size remains a relative contraindication to brachytherapy due to technical concerns or the perception that patients with large prostate glands are at higher risk for acute and prolonged urinary morbidity.
- Pubic arch interference (the obstruction of anterior needle placement insertion by a narrow pubic arch) remains a relative contraindication to brachytherapy despite limited clinical information supporting such concerns.
- Median lobe hyperplasia (the protrusion of hypertrophied prostate tissue into the bladder) has been reported to be a relative contraindication to brachytherapy because of concerns for an increased risk of post-implant urinary morbidity and technical difficulties encountered while implanting intravesical tissue.
- Other often-quoted contraindications to brachytherapy including prostatitis, patient age, obesity, diabetes mellitus, and inflammatory bowel disease have been propagated without clinical or dosimetric support.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

An American College of Radiology (ACR) Committee on Appropriateness Criteria and its expert panels have developed criteria for determining appropriate imaging examinations for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide radiologists, radiation oncologists, and referring physicians in making decisions regarding radiologic imaging and treatment. Generally, the complexity and severity of a patient's clinical condition should dictate the selection of appropriate imaging procedures or treatments. Only those exams generally used for evaluation of the patient's condition are ranked. Other imaging studies necessary to evaluate other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate imaging procedures or treatments. Imaging techniques classified as investigational by the U.S. Food and Drug Administration (FDA) have not been considered in developing these criteria; however, study of new equipment and applications should be encouraged. The ultimate decision regarding the appropriateness of any specific radiologic examination or treatment must be made by the referring physician and radiologist in light of all the circumstances presented in an individual examination.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Personal Digital Assistant (PDA) Downloads

For information about [availability](#), see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Merrick G, Roach M III, Anscher MS, Beyer DC, Lawton CA, Lee WR, Michalski JM, Pollack A, Vijayakumar S, Carroll PR, Higano CS, Mauch PM, Expert Panel on Radiation Oncology-Prostate Work Group. Permanent source brachytherapy for prostate cancer. [online publication]. Reston (VA): American College of Radiology (ACR); 2006. 16 p. [91 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1996 (revised 2006)

GUIDELINE DEVELOPER(S)

American College of Radiology - Medical Specialty Society

SOURCE(S) OF FUNDING

The American College of Radiology (ACR) provided the funding and the resources for these ACR Appropriateness Criteria®.

GUIDELINE COMMITTEE

Committee on Appropriateness Criteria, Expert Panel on Radiation Oncology–Prostate Work Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Panel Members: Gregory Merrick, MD; Mack Roach III, MD; Mitchell S. Anscher, MD; David C. Beyer, MD; Colleen A. Lawton, MD; W. Robert Lee, MD; Jeff M. Michalski, MD, MBA; Alan Pollack, MD, PhD; Srinivasan Vijayakumar, MD; Peter R. Carroll, MD; Celestia S. Higano, MD; Peter M. Mauch, MD

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Potters L, Perez CA, Beyer DC, Blasko JC, Forman JD, Hussey DH, Lee WR, Paryani SB, Pollack A, Roach M, Scardino P, Schellhammer P, Leibel S. Permanent source brachytherapy for prostate cancer. American College of Radiology. ACR Appropriateness Criteria. Radiology 2000 Jun;215(Suppl):1383-400.

The appropriateness criteria are reviewed annually and updated by the panels as needed, depending on introduction of new and highly significant scientific evidence.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the [American College of Radiology \(ACR\) Web site](#).

ACR Appropriateness Criteria® *Anytime, Anywhere*™ (PDA application). Available from the [ACR Web site](#).

Print copies: Available from the American College of Radiology, 1891 Preston White Drive, Reston, VA 20191. Telephone: (703) 648-8900.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- ACR Appropriateness Criteria®. Background and development. Reston (VA): American College of Radiology; 2 p. Electronic copies: Available in Portable

Document Format (PDF) from the [American College of Radiology \(ACR\) Web site](#).

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on September 5, 2006. This summary was updated by ECRI Institute on November 6, 2007, following the updated U.S. Food and Drug Administration advisory on Viagra, Cialis, Levitra, and Revatio.

COPYRIGHT STATEMENT

Instructions for downloading, use, and reproduction of the American College of Radiology (ACR) Appropriateness Criteria® may be found on the [ACR Web site](#).

DISCLAIMER

NGC DISCLAIMER

The National Guideline Clearinghouse™ (NGC) does not develop, produce, approve, or endorse the guidelines represented on this site.

All guidelines summarized by NGC and hosted on our site are produced under the auspices of medical specialty societies, relevant professional associations, public or private organizations, other government agencies, health care organizations or plans, and similar entities.

Guidelines represented on the NGC Web site are submitted by guideline developers, and are screened solely to determine that they meet the NGC Inclusion Criteria which may be found at <http://www.guideline.gov/about/inclusion.aspx>.

NGC, AHRQ, and its contractor ECRI Institute make no warranties concerning the content or clinical efficacy or effectiveness of the clinical practice guidelines and related materials represented on this site. Moreover, the views and opinions of developers or authors of guidelines represented on this site do not necessarily state or reflect those of NGC, AHRQ, or its contractor ECRI Institute, and inclusion or hosting of guidelines in NGC may not be used for advertising or commercial endorsement purposes.

Readers with questions regarding guideline content are directed to contact the guideline developer.

Date Modified: 11/3/2008

