

# Low dose rate brachytherapy for primary treatment of localized prostate cancer: A systemic review and executive summary of an evidence-based consensus statement

Martin T. King<sup>1,\*</sup>, Mira Keyes<sup>2</sup>, Steven J Frank<sup>3</sup>, Juanita M. Crook<sup>4</sup>, Wayne M. Butler<sup>5</sup>, Peter J. Rossi<sup>6</sup>, Brett W. Cox<sup>7</sup>, Timothy N. Showalter<sup>8</sup>, Firas Mourtada<sup>9</sup>, Louis Potters<sup>10</sup>, Richard G. Stock<sup>11</sup>, Marisa A. Kollmeier<sup>12</sup>, Michael J. Zelefsky<sup>12</sup>, Brian J. Davis<sup>13</sup>, Gregory S. Merrick<sup>5</sup>, Peter F. Orio<sup>1</sup>

<sup>1</sup>Department of Radiation Oncology, Dana-Farber Cancer Institute, Boston, MA

<sup>2</sup>Department of Radiation Oncology, British Columbia Cancer Agency, University of British Columbia, Vancouver, Canada

<sup>3</sup>Department of Radiation Oncology, University of Texas MD Anderson Cancer Center, Houston, TX

<sup>4</sup>Department of Radiation Oncology, British Columbia Cancer Agency, University of British Columbia, Kelowna, Canada

<sup>5</sup>Department of Radiation Oncology, Schiffler Cancer Center, Wheeling Jesuit University, Wheeling, WV

<sup>6</sup>Calaway Young Cancer Center, Valley View Hospital, Glenwood Springs, CO

<sup>7</sup>Department of Radiation Oncology, Rush University Medical Center, Chicago, IL

<sup>8</sup>Department of Radiation Oncology, University of Virginia, Charlottesville, VA

<sup>9</sup>Helen F. Graham Cancer Center & Research Institute, Christiana Care Health System, Newark, DE

<sup>10</sup>Department of Radiation Oncology, Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY

<sup>11</sup>Department of Radiation Oncology, Mt. Sinai Medical Center, New York, NY

<sup>12</sup>Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY

<sup>13</sup>Department of Radiation Oncology, Mayo Clinic, Rochester, MN

## ABSTRACT

**PURPOSE:** The purpose of this guideline is to present evidence-based consensus recommendations for low dose rate (LDR) permanent seed brachytherapy for the primary treatment of prostate cancer.

**METHODS AND MATERIALS:** The American Brachytherapy Society convened a task force for addressing key questions concerning ultrasound-based LDR prostate brachytherapy for the primary treatment of prostate cancer. A comprehensive literature search was conducted to identify prospective and multi-institutional retrospective studies involving LDR brachytherapy as monotherapy or boost in combination with external beam radiation therapy with or without adjuvant androgen deprivation therapy. Outcomes included disease control, toxicity, and quality of life.

**RESULTS:** LDR prostate brachytherapy monotherapy is an appropriate treatment option for low risk and favorable intermediate risk disease. LDR brachytherapy boost in combination with external beam radiation therapy is appropriate for unfavorable intermediate risk and high-risk disease. Androgen deprivation therapy is recommended in unfavorable intermediate risk and high-risk disease. Acceptable radionuclides for LDR brachytherapy include iodine-125, palladium-103, and cesium-131. Although brachytherapy monotherapy is associated with increased urinary obstructive and irritative symptoms that peak within the first 3 months after treatment, the median time

Received 21 April 2021; received in revised form 28 June 2021; accepted 14 July 2021

**Abbreviations:** ABS, American brachytherapy society; AUA, American urological association; BED, biologically equivalent dose; bPFS, biochemical progression free survival; Cs-131, cesium-131; CTC/AE, Common Terminology Criteria for Adverse Events; CT, clinical target volume; EBRT, external beam radiation therapy; EPIC, Expanded Prostate Cancer Index Composite; FIR, favorable intermediate risk; HDR, high dose rate; I-125, iodine-125; IPSS, International Prostate Symptom Score; LDR, low dose rate; LENT-SOMA, Late Effects Normal Tissue Task Force (LENT)-Subjective, Objective, Management, Analytic; LHRH, luteinizing hormone releasing hormone; MCID, minimum clinically important differ-

ence; MFS, metastasis free survival; MRI, magnetic resonance imaging; NCCN, National Cancer Center Network; OS, overall survival; Pd-103, palladium-103; PDE-5, phosphodiesterase type 5; PSA, prostate specific antigen; PTV, planning target volume; RTOG, Radiation Therapy Oncology Group; SBRT, stereotactic body radiation therapy; TRUS, transrectal ultrasound; TURP, transurethral resection of the prostate; UIR, unfavorable intermediate risk.

\* Corresponding author. Brigham and Women's Hospital, ASB1-L2, 75 Francis St., Boston, MA 02115

E-mail address: [martin\\_king@dfci.harvard.edu](mailto:martin_king@dfci.harvard.edu) (M.T. King).

toward symptom resolution is approximately 1 year for iodine-125 and 6 months for palladium-103. Such symptoms can be mitigated with short-term use of alpha blockers. Combination therapy is associated with worse urinary, bowel, and sexual symptoms than monotherapy. A prostate specific antigen  $\leq 0.2$  ng/mL at 4 years after LDR brachytherapy may be considered a biochemical definition of cure.

**CONCLUSIONS:** LDR brachytherapy is a convenient, effective, and well-tolerated treatment for prostate cancer. © 2021 The Authors. Published by Elsevier Inc. on behalf of American Brachytherapy Society. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>)

**Keywords:** Brachytherapy; Low dose rate; Iodine-125; Palladium-125; Cesium-131; Prostate

## Introduction

Low dose rate (LDR) prostate brachytherapy is a standard treatment option for the primary treatment of localized prostate cancer. This treatment involves the insertion of radionuclides (e.g. iodine-125 [I-125], palladium-103 [Pd-103], or cesium-131 [Cs-131]) into the prostate gland under transrectal ultrasound (TRUS) guidance (Table 1). The delivered dose is determined by the half-life and strength of the radionuclide. LDR prostate brachytherapy can be given as monotherapy, or as a boost in combination with external beam radiation therapy (EBRT).

The American Brachytherapy Society (ABS) has previously published guidelines for LDR prostate brachytherapy in 1999 (1) and 2012 (2). The current consensus provides recommendations and statements for the primary treatment of localized prostate cancer based on key questions, while grading the quality of underlying evidence for each recommendation from a systemic review of the literature. Furthermore, these recommendations incorporate 4-tiered National Cancer Center Network (NCCN) guidelines (3), in which intermediate risk disease (clinical T2b-T2c, Gleason 7, prostate specific antigen (PSA) 10–20 ng/mL) is subdivided into favorable intermediate risk (FIR) and unfavorable intermediate risk (UIR) (e.g. primary Gleason 4,  $\geq 50\%$  positive biopsy cores, or two NCCN intermediate risk factors) categories (4). This guideline is endorsed by the ABS and the American Society for Radiation Oncology.

## Methods and materials

### Process

The ABS Board of Directors initiated a process to update the LDR prostate brachytherapy consensus in February 2019. The guidelines were developed utilizing the framework of a formal systemic review-based consensus methodology (5). Briefly, key questions that comprehensively addressed disease control, toxicity, and quality of life considerations for LDR brachytherapy were formulated. A draft of consensus recommendations were reviewed by a smaller panel (M King, P Orio, M Keyes,

G Merrick, M Zelefsky, and B Davis). Modified recommendations were then circulated to a larger consensus group. Members of this group rated their level of agreement with the recommendation, with a minimum threshold of 70% as required for consensus. The consensus recommendations were then reviewed and finalized (Table 2).

Key questions one through seven were based on systemic review. The outcomes of interest include disease control outcomes (biochemical progression free survival [bPFS], metastasis free survival [MFS], prostate cancer specific mortality [PCSM], and overall survival [OS]), physician-assigned toxicity, and patient reported quality-of-life. The patient population of interest included patients undergoing primary treatment for NCCN-defined low, intermediate, or high-risk prostate cancer. The intervention is LDR prostate brachytherapy. The comparator groups are alternative modalities (i.e. radical prostatectomy, EBRT, high dose rate [HDR] brachytherapy, and stereotactic body radiation therapy [SBRT]).

Regarding the systemic review, we (M King and P Orio) conducted a keyword search in MEDLINE, PubMed, and clinicaltrials.gov of all abstracts containing keywords of “prostate” and “brachytherapy” until June 2019. This yielded 5808 abstracts. We also identified 10 additional abstracts or publications not included in the initial search (Table A.1) that detailed randomized controlled trials (8), and recently published multi-institutional studies (2), that were deemed of high clinical importance for the practice of LDR brachytherapy. After reviewing abstracts, we included: (1) prospective randomized controlled trials involving LDR brachytherapy, (2) prospective or retrospective multi-institutional studies, with brachytherapy performed across multiple institutions, and (3) prospective single institutional studies involving Cs-131, due to the lack of published randomized data. All non-randomized studies must have contained  $\geq 100$  patients with  $\geq 1$  year followup for quality-of-life endpoints, or  $\geq 3$ -year followup for disease control outcome endpoints. We identified 123 publications for full-text review, and ultimately included 68 studies in this systemic review (see Fig. A.1). For each clinical question, the strength of recommendation (weak,

Table 1  
Radionuclides for permanent prostate brachytherapy

	Half-life (day)	Average energy (keV)	Year introduced	Typical monotherapy seed strength (U)	Suggested monotherapy dose (Gy)	Suggested combination therapy dose	
						Brachytherapy (Gy)	EBRT (Gy)
Iodine-125	59.4	28.4	1965	0.4–0.8	144–145	108–110	41.4–50.4
Palladium-103	17.0	20.7	1986	1.5–3.0	125	90–100	41.4–50.4
Cesium-131	9.7	30.4	2004	1.6–2.5	115	85	41.4–50.4

Abbreviations: EBRT = external beam radiation therapy

Table 2  
Guideline recommendations for key questions (KQ) based on systemic review

Guideline recommendation	Strength of recommendation	Strength of evidence
KQ1: Which patients are appropriate candidates for brachytherapy monotherapy?		
Low risk disease for patients declining active surveillance	Strong	High
Favorable intermediate risk disease	Strong	High
Select unfavorable intermediate risk disease (single unfavorable intermediate risk factor) and organ-confined disease on magnetic resonance imaging (MRI).	Weak	Moderate
KQ2: Which patients are appropriate candidates for brachytherapy boost in combination with external beam radiation therapy?		
Unfavorable intermediate risk disease	Strong	High
High risk disease	Strong	High
KQ3: What are the roles of androgen deprivation therapy with brachytherapy?		
Improving disease control outcomes for unfavorable intermediate risk and high-risk disease	Strong	High
Prostate cyoreduction for low or favorable intermediate risk disease	Weak	High
KQ4: Which radionuclides can be used for LDR brachytherapy?		
I-125	Strong	High
Pd-103	Strong	High
Cs-131	Strong	High
KQ5: What late toxicities are associated with brachytherapy?		
Brachytherapy monotherapy is associated with low rates of late Grade 3+ genitourinary and gastrointestinal toxicity.	Strong	High
Brachytherapy boost with EBRT is associated with greater risks of the late Grade 3+ genitourinary toxicity compared with brachytherapy or EBRT monotherapy.	Strong	High
KQ6: What are quality of life concerns for patients undergoing brachytherapy?		
Although brachytherapy is associated with increased urinary obstructive and irritative symptoms that peak within the first 3 months after treatment, the median time toward symptom resolution is approximately 1 year.	Strong	High
Brachytherapy boost with EBRT is associated with increased urinary, bowel, and sexual symptoms compared with brachytherapy or EBRT monotherapy.	Strong	High
KQ7: What are strategies for improving quality of life after implant?		
Alpha-blockers	Strong	High
KQ8: Which patients are appropriate candidates for prostate brachytherapy? <sup>a</sup>		
Sufficient life expectancy (>10 years for low or intermediate risk disease, >5 years for high-risk disease)	Strong	Low
Suitable prostate anatomy	Strong	Low
Adequate urinary function	Strong	Low
KQ9: How are brachytherapy plans evaluated? <sup>a</sup>		
Pre-implant dosimetry	Strong	Low
Post-implant dosimetry	Strong	Moderate
KQ10: What type of seeds should be utilized for brachytherapy? <sup>a</sup>		
Loose seeds	Strong	Low
Stranded seeds	Strong	Low

<sup>a</sup> refers to key questions not included in the systemic review

strong), and strength of evidence (low, moderate, high) were graded based on previously published guidelines (6).

Key clinical questions eight through ten are concerned with patient eligibility and technical aspects of LDR brachytherapy. Literature for these questions did not meet criteria for the systemic review.

### **KQ1: Which patients are appropriate candidates for brachytherapy monotherapy?**

Brachytherapy monotherapy could be considered for patients with low-risk disease who decline active surveillance and FIR disease. These recommendations are based on randomized controlled trials and multi-institutional studies.

#### *Randomized controlled trials: low and intermediate risk*

Table A.2 lists randomized controlled trials involving brachytherapy. For low-risk disease, there have been two single institutional randomized trials authored by Giberti *et al.*, which reported no difference in bPFS between LDR brachytherapy and radical prostatectomy at 5-years (7) and 2-years (8), respectively.

For predominantly intermediate risk disease, two randomized trials compared brachytherapy monotherapy to combination therapy. Radiation Therapy Oncology Group (RTOG) 0232 randomized 588 patients with clinical T1c-T2b and either Gleason 6/PSA10–20 ng/dL or Gleason 7/PSA <10 ng/dL disease to either brachytherapy monotherapy (I-125 145 Gy or Pd-103 125 Gy) versus LDR (I-125 110 Gy or Pd-103 100 Gy) boost with EBRT (45 Gy). Androgen deprivation therapy (ADT) utilization was a stratification factor. The study was powered to observe a 10% increase in 5-year bPFS for combination therapy. As reported in abstract form, there was no difference in 5-year bPFS between the monotherapy and combination therapy (86% vs. 85%) at a median followup of 6.7 years (9).

The 20/0 trial compared brachytherapy monotherapy (Pd-103 125 Gy) versus EBRT (20 Gy) plus LDR boost (Pd-103 115 Gy) for Gleason 7–9 disease and/or a PSA of 10–20 ng/mL. The study was powered to observe a 15% difference in time-to-event survival, and 344 patients were required. Although 471 patients were enrolled, clinical outcomes could only be reported for 383 patients. Day 0 D90 was slightly greater in the EBRT 20 Gy arm (mean 122.0% vs. 118.2%,  $p < 0.001$ ). At a median followup of 5.0 years, there was no difference in 8-year biochemical failure (3.6% vs. 2.1%). ADT utilization (9.2% vs. 5.9%) and D90 were not associated with biochemical failure. There were no prostate cancer deaths in either arm (10).

These trials were developed before the NCCN subclassification of intermediate risk disease into FIR and UIR subgroups (3). A secondary analysis of the 20/0 trial in

combination with the 44/20 trial described below reported that the dose of supplemental EBRT (0 vs. 20 vs. 44 Gy) was not associated with biochemical failure or PCSM in either FIR or UIR cohorts (11).

#### *Multi-institutional outcomes: low and intermediate risk*

Table A.3 lists multi-institutional prospective series involving LDR brachytherapy. The single arm Phase II prospective RTOG 9805 study enrolled 101 patients with low-risk disease who were treated with I-125 monotherapy (145 Gy). No patients received ADT. At a median followup of 8.1 years among 94 eligible patients, the 8-year cumulative incidences of biochemical failure and metastasis were 8% and 1.1%, respectively (12).

J-POPS was a prospective multi-institutional registry study of 2354 patients with predominantly low and intermediate risk disease. Of the 1792 patients who received brachytherapy monotherapy (+/- ADT), the 5-year bPFS was 89.3% (13).

Table A.4 lists multiple multi-institutional retrospective studies for predominantly low and intermediate risk disease. The importance of post-implant dosimetry is highlighted by a multi-institutional analysis by Zelefsky *et al.* Of the 639 patients with available post-implant dosimetry, a higher prostate D90 > 130 Gy for I-125 was associated with improved 8-year bPFS (93% vs. 76%). Furthermore, a prostate D90 > 115 Gy for Pd-103 was associated with improved 5-year bPFS (92% vs. 83%)(14). Other studies have shown that LDR brachytherapy has similar outcomes compared to EBRT (15,16), SBRT (17) and radical prostatectomy(18). In a series of 1816 patients who received brachytherapy (93% monotherapy; 7% combination) without ADT, Frank *et al.* reported a 5-year bPFS of 90.9% that was better than nomogram-predicted outcomes (19). A recent multi-institutional study from Berlin *et al.* reported 10-year incidences of distant metastases for FIR and UIR prostate cancer of 3.5% versus 10.2% for brachytherapy ( $n=258$ ;  $p=0.063$ ), 0.2% versus 11.6% for radical prostatectomy ( $n=1149$ ;  $p < 0.001$ ), and 2.8% versus 13.5% for dose-escalated EBRT alone ( $n=1143$ ;  $p < 0.001$ ) (20).

Recently, Crook *et al.* conducted a multi-institutional analysis of 8746 patients (42.4% low, 49.2% intermediate, 8.4% high) who were treated with LDR brachytherapy and did not experience an early clinical failure (<3.5 years). A PSA  $\leq 0.2$  ng/mL was achieved in 77.1% of patients, and such patients exhibited a 98.7% freedom from recurrence at 10 years. High 10-year freedom from recurrence values (97–99%) were also observed in three independent validation cohorts. A PSA  $\leq 0.2$  ng/mL at 4 years after LDR brachytherapy has been proposed as a biochemical definition of cure (21).

In summary, present evidence supports using LDR brachytherapy monotherapy to provide excellent biochemical control outcomes for low, and FIR disease. Regarding UIR disease, LDR monotherapy was not associated with

inferior outcomes compared with combination therapy in a secondary analysis of the randomized 20/0 and 44/20 trials (11). Furthermore, patients with UIR disease were included on RTOG 0232 (9), but results for this unplanned subset have not been presented. Although more prospective evidence may be forthcoming, brachytherapy monotherapy may be considered for patients with a single unfavorable intermediate risk factor who have organ-confined disease (ie. no suspicion of radiographic extracapsular extension) on MRI. Shared decision-making of patient preferences for LDR monotherapy versus alternative approaches is advised.

### **KQ2: Which patients are appropriate candidates for brachytherapy boost in combination with external beam radiation therapy?**

Patients with UIR or high-risk disease could be considered for brachytherapy boost in combination with EBRT. The rationale for brachytherapy boost would be to provide further escalation of dose to the prostatic gland (22), whereas EBRT could be used to treat subclinical disease within the entire seminal vesicles with or without the pelvic lymph nodes. Below is a summary of evidence from randomized trials and multi-institutional studies.

#### *Randomized controlled trials: intermediate and high risk*

There were two randomized trials, which evaluated combination therapy for intermediate and high-risk disease. The Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy (ASCENDE-RT) trial randomized 398 patients to combination therapy (46 Gy EBRT to the pelvis and prostate plus LDR brachytherapy boost) versus dose-escalated EBRT alone (46 Gy EBRT to the pelvis and 78 Gy to the prostate) (Table A.2). All patients received 12 months of ADT. The study was powered to observe a 15% difference in biochemical failure events between both arms. At a median followup of 6.5 years, combination therapy was associated with improved bPFS (7-year bPFS 86% vs. 75%; HR 2.04;  $p = 0.004$ ). Benefits in bPFS were noted in both the intermediate ( $p = 0.03$ ) and high risk ( $p = 0.048$ ) stratifications. However, there was no improvement in MFS or OS (23). Of note the study was not powered for a survival benefit. Similar results were noted with a median followup of 10 years (24).

The 44/20 trial randomized patients with Gleason 7–9 disease and/or a PSA 10–20 ng/mL to two schedules of combination therapy (44 Gy EBRT + 90 Gy Pd-103 vs. 20 Gy EBRT + 115 Gy Pd-103). The study was powered to observe a 15% difference in time-to-event survival, and 344 patients were required. Although 566 patients were enrolled, data were only available for 247 patients due to administrative reasons. Day 0 D90 was slightly greater in the 44 Gy arm (mean 129.6% vs. 123.4%,  $p < 0.001$ ).

There was no difference in biochemical failure (13-year 8.2% vs. 8.0%) or prostate cancer-specific mortality (13-year 4.0% vs. 1.0%) (10).

#### *Multi-institutional outcomes: intermediate and high risk*

RTOG 0019 (Table A.3) was a multi-institutional single-arm Phase II trial of combination EBRT (45 Gy) with LDR brachytherapy boost (108 Gy I-125) that enrolled 138 patients (22% Gleason 6; 78% Gleason 7). In an analysis of 131 patients, of whom 27% received ADT, the 8-year biochemical failure rate was 18% (25).

Table A.5 shows multiple multi-institutional retrospective series of predominantly intermediate risk and high-risk prostate cancer. An analysis of 1078 patients with Gleason 7–10 disease (78.4% Gleason 7; 21.6% Gleason 8–10) by Stone et al. reported improved 5-year bPFS (biologically equivalent dose (BED) <200 Gy: 76.4%, BED 200–220 Gy: 83.5%; BED > 220 Gy: 88.3%) as well as 5-year MFS (92%; 94%; 99.5%) with increasing BED. A BED > 220 Gy could be achieved with 45 Gy EBRT and brachytherapy boost with D90 values of 130 Gy for I-125 or 120 Gy for Pd-103 (22).

For Gleason 9–10 prostate cancer, Kishan et al. reported that trimodality therapy (ADT, EBRT, and brachytherapy boost) was associated with better PCSM and longer time to distant metastasis compared with radical prostatectomy and ADT+EBRT. There was no difference in outcomes among patients who received LDR or HDR brachytherapy (26). A subsequent study by Sandler et al. reported a bPFS benefit of whole pelvis EBRT for combination EBRT plus brachytherapy boost, but not for EBRT alone (27).

In summary, the evidence from randomized controlled trials suggests that trimodality therapy with ADT, EBRT, and brachytherapy boost, can maximize biochemical control for UIR or high-risk disease. To date, there is no evidence in published randomized controlled trials that this treatment improves OS.

### **KQ3: What are the roles of androgen deprivation therapy with brachytherapy?**

ADT is recommended for UIR and high-risk disease. ADT can also be considered for prostate cytorreduction for patients with low and/or FIR disease with enlarged glands (>60 cc). These recommendations are consistent with those put forth by the American Brachytherapy Task Group Report entitled “Use of androgen deprivation therapy with prostate brachytherapy.” (28).

#### *Improved disease control outcomes*

Neoadjuvant ADT is recommended for patients with UIR and high-risk prostate cancer. The optimal duration of ADT for patients receiving LDR brachytherapy is not currently known, due to the lack of mature randomized

data specifically addressing the role of ADT for patients receiving LDR brachytherapy. However, the Trans-Tasman Radiation Oncology Group (TROG) 03.04 trial recently reported that patients treated with HDR brachytherapy boost had reduced distant progression with longer ADT duration (18 vs. 6 months) (29). Our current recommendation would be 4–6 months of ADT for UIR disease, and 12 (23)–36 months from high-risk disease. Below is a summary of multi-institutional studies that have explored the role of ADT for patients receiving brachytherapy.

For predominantly low risk patients (Table A.4), two retrospective studies by Fellin *et al.* (68% LR; 26% int) (30) and Martell *et al.* (74% low risk; 25% int risk) (31) reported that ADT was not associated with a bPFS benefit. However, a study of 1038 patients by Dickinson *et al.* (100% low risk) (32) concluded that neoadjuvant ADT was associated with a benefit in 5-year bPFS (96.8 vs. 93.4%;  $p = 0.033$ ).

For predominantly intermediate risk patients (Table A.4), studies by Tran *et al.* and Cosset *et al.* reported no benefit in bPFS with neoadjuvant ADT (33,34). The 44/20 (84.3% Gleason 6–7; 15.8% Gleason 8–9) and 20/0 (98.4% Gleason 6–7; 1.6% Gleason 8–9) trials each reported no benefit in bPFS with the addition of ADT (10). However, a series by Stone *et al.* (78.4% Gleason 7; 21.6% Gleason 8–10) reported that ADT was independently associated with improved bPFS, even after accounting for EBRT, and BED dose (Table A.5) (22). Furthermore, in a study by Rose *et al.* of 4550 patients (85% intermediate, 15% high), the addition of ADT to brachytherapy was associated with improved PCSM in patients with low (HR = 0.35;  $p = 0.02$ ), but not high (HR = 1.33;  $p = 0.30$ ) competing risk for death (defined as older age and presence of cardiac risk factors including diabetes, coronary artery disease, prior myocardial infarction, congestive heart failure) (35).

For high-risk cohorts, Shilkrut *et al.* reported that long-term ADT ( $\geq 24$  months) was associated with reduced biochemical failure but not PCSM for patients who received combination therapy (36). In an analysis of Gleason 9–10 cancer by Kishan *et al.*, ADT duration (12–23.9 or 24–35.9 months vs.  $\leq 12$  months) did not impact time to metastasis or PCSM for patients who received trimodality therapy (26).

### Cytoreduction

Neoadjuvant ADT can be utilized for prostate volume cytoreduction for patients with low or intermediate risk disease who have a large gland ( $>60$  cc gland). For such patients, 2–3 months of neoadjuvant ADT may reduce the gland size, and decrease the risk of pubic arch interference at the time of prostate implant. However, because patients with low or favorable intermediate risk disease are unlikely to receive a long-term benefit from ADT (4,37), patients, especially those with a history of major cardiovascular events (e.g. myocardial infarction or stroke), should

be counseled on the potential risks of cardiovascular events after leuprolide (38). Degarelix and relugolix may offer comparable prostate down-sizing (39,40) with less cardiovascular side effects (38,41).

Neoadjuvant ADT for cytoreduction has been evaluated in a randomized trial. To avoid toxicity of luteinizing hormone releasing hormone (LHRH) agonists, Gaudet *et al.* randomized 60 patients with low or intermediate risk disease to 3 months of LHRH agonist versus dutasteride 0.5 mg, bicalutamide 50 mg, and tamoxifen 10 mg before I-125 implant. Tamoxifen was administered to prevent gynecomastia. Dutasteride with bicalutamide was non-inferior to LHRH agonist for volume reduction of prostate gland size from  $\geq 50$  mL to  $<50$  mL. Relative volume reductions for respective groups were 31.7% and 35.5%, respectively. 17% of patients who received dutasteride with bicalutamide required a longer duration of treatment (additional 2–3 months) for adequate volume reduction. Patients who received dutasteride and bicalutamide had improved EPIC sexual summary scores at 6 weeks and 3 months compared with LHRH agonist (42).

In summary, ADT is recommended for UIR and high-risk disease. ADT can also be considered for cytoreduction in patients with low and favorable intermediate risk disease who have enlarged glands.

### Q4: Which radionuclide can be used for ldr brachytherapy?

I-125, Pd-103, and Cs-131 are all acceptable radionuclides for LDR brachytherapy. Table 1 shows the energy, half-lives, as well as the recommended prescription doses.

For Pd-103, a multi-institutional open-label randomized controlled trial compared I-125 (144 Gy) versus Pd-103 (125 Gy) for low-risk disease (Table A.2). The trial was initially powered to enroll 380 patients with a time-to-survival endpoint, but the sample size was subsequently increased to 600 patients. A preliminary analysis of 115 patients reported no difference in 3-year bPFS (defined as PSA  $\leq 0.5$  ng/mL at last followup) between I-125 (91%) and Pd-103 (89%) ( $p = 0.76$ ). Patients with V100  $> 90\%$  or a D90  $> 100\%$  had improved 3-year bPFS (43). A subsequent analysis of 352 patients (baseline American Urological Association (AUA) score of 7.6 for I-125 and 8.2 for Pd-103) reported that Pd-103 was associated with a higher AUA score at 1 month (18.5 vs. 14.8), but a lower AUA score at 6 months (9.9 vs. 12.0). The time for the mean AUA score to return within three points of baseline was 6 months for Pd-103 compared with 12 months for I-125 (44). No further reports from this trial were found in the literature. In addition, a multi-institutional analysis by Zelefsky *et al.* reported that radionuclide (I-125 vs. Pd-103) was not associated with biochemical failure on multivariable analysis in a subset of 602 patients with available post-implant dosimetry and clinical features (14).

For Cs-131, a single institutional randomized controlled trial compared I-125 (144 Gy) with Cs-131 (115 Gy) in 140 patients with low (81.4%) or intermediate (18.6%) risk disease. No patients received ADT. A preliminary analysis of 52 patients, published in abstract form, reported no differences in Expanded Prostate Cancer Index Composite (EPIC) urinary quality of life scores at 0, 3 months, and 1 year between the two arms (45). Long-term data among all randomized patients, also published in abstract form, reported no difference in 9-year bPFS (89% vs. 86%) at a median followup of 7.9 years (46).

A single institutional Phase II trial of LDR monotherapy enrolled 300 patients with intermediate-risk localized disease. Cohorts of 100 patients were treated with I-125 to 145 Gy, Pd-103 to 125 Gy, or Cs-131 to 115 Gy. No patients received ADT and the 5-year freedom from biochemical failure was 97.3% with no difference between radionuclides (47). The three radionuclides had similar quality of life profiles with no clinically significant differences between them. However, patients reported statistically higher overall satisfaction at 2-years when treated with Pd-103 (48). Other single institutional series reported that Cs-131 was associated with excellent oncologic outcomes at 5 years (49) with minimal long-term changes in EPIC urinary or bowel quality of life (50). The prevalence of late rectal bleeding after Cs-131 also remained low (4.0%), despite a slightly elevated incidence (12.4%) at a median followup of 4 years (51).

In summary, randomized evidence suggest that Pd-103, and Cs-131 can provide long-term biochemical progression free survival similar to that reported with I-125.

#### **KQ5: What late toxicities are associated with brachytherapy?**

Brachytherapy monotherapy is associated with low rates of late Grade 2–3+ genitourinary and gastrointestinal toxicity. In the RTOG 0232 randomized controlled trial, patients who underwent brachytherapy monotherapy had a 3% rate of RTOG late Grade 3+ genitourinary toxicity as well as a 2% rate of Grade 3+ gastrointestinal toxicity (9). In the single arm prospective RTOG 9805 trial, rates of maximal RTOG late Grade 2 and Grade 3 genitourinary toxicities were 21% and 3%, respectively. Respective rates of gastrointestinal toxicities were 5% and 0%, respectively (12). 10% of patients developed erectile dysfunction (moderate or severe impotence). Regarding the impact of dosimetry on toxicity outcomes, the J-POPS study reported that urethra D5 was associated with late Common Terminology Criteria for Adverse Events (CTCAE) version 2.0 Grade 2+ urinary toxicity (mean urethra D5 164.98% for Grade 2+ versus 156.84% for Grade 0–1 toxicity). The cumulative incidence of late Grade 2+ gastrointestinal toxicity was also elevated for rectal V100 (RV100)  $\geq 1$  mL (10.94%) versus RV100  $< 1$  mL (4.22%) (52).

Brachytherapy boost in combination with EBRT may be associated with greater risks of late Grade 3+ genitourinary toxicity compared with brachytherapy or EBRT monotherapy. In RTOG 0232, combination therapy was associated with a 7% rate of late Grade 3+ genitourinary toxicity compared with a 3% rate for brachytherapy monotherapy. Respective rates for late Grade 3+ gastrointestinal toxicity were 3% and 2%, respectively (9). In the ASCENDE-RT randomized controlled trial, combination therapy was associated with a greater 5-year cumulative incidence of Late Effects of Normal Tissue-Somatic, Objective, Management, Analytic (LENT-SOMA) Grade 3+ genitourinary toxicity (18.4% vs. 5.2%;  $p < 0.001$ ), although the 5-year prevalence was much lower in both arms (8.6% vs. 2.2%;  $p = 0.058$ ). Of the 31 patients who developed a late Grade 3 genitourinary event after brachytherapy boost, 16 developed urethral strictures requiring urethral dilatation. There was no significant difference in the cumulative incidence of Grade 3+ gastrointestinal toxicity (8.1% vs. 3.2%;  $p = 0.124$ ) (53). Of the 12 patients who developed a late Grade 3 gastrointestinal event after brachytherapy boost, seven developed rectal bleeding requiring  $\geq 2$  endoscopic plasma-argon coagulation procedures.

In summary, combination therapy has been associated with greater toxicity compared with brachytherapy or EBRT monotherapy. However, combination therapy may be an acceptable treatment option for patients with long life expectancy and minimal comorbidity who are willing to accept higher risk of toxicity for the chance of minimizing the risk of subsequent biochemical failure. Biochemical failure often leads to long-term ADT and other systemic therapies, resulting in significant lifelong downstream toxicities (54).

#### **KQ6: What are quality of life concerns for patients undergoing brachytherapy?**

##### *Brachytherapy monotherapy and quality of life*

Brachytherapy monotherapy is a well-tolerated treatment compared with alternative modalities. Although brachytherapy is associated with increased urinary irritative symptoms that peak within the first 3 months after treatment, the median time toward symptom resolution is 1 year for I-125, and 6 months for Pd-103.

As noted in KQ4, a report of the I-125 versus Pd-103 randomized controlled trial reported that the time for the mean AUA score to return within three points of baseline was 12 months for I-125 versus 6 months for Pd-103 (44). In a preliminary analysis of 52 of 140 patients who were randomized to I-125 (144 Gy) versus Cs-131 (115 Gy), there were no differences in EPIC urinary quality of life scores at 0, 3 months, and 1 year between the two arms (45). In a prospective Phase II trial reported by Blanchard *et al.*, I-125, Pd-103, and Cs-131 had similar quality of life

profiles with no clinically significant differences between them (48).

Table A.6 shows multiple prospective studies comparing brachytherapy with competing modalities with respect to quality of life. There are two large multi-institutional prospective studies, which analyzed functional outcomes in patients who were treated for prostate cancer within the past decade. A multi-institutional study from the North Carolina Central Cancer Registry (*Chen et al.*) enrolled 1141 patients who subsequently underwent active surveillance, EBRT (94% intensity-modulated radiation therapy), brachytherapy (I-125), or radical prostatectomy between 2011 and 2013 (55). Patients who underwent brachytherapy reported worse urinary obstruction and/or irritation, and sexual dysfunction (Prostate Cancer Symptom Index) at 3 months compared to active surveillance. For both domains, there were smaller differences at 1 year, but no differences at 2 years compared with active surveillance. Radical prostatectomy was associated with worse urinary incontinence, urinary obstruction and/or irritation, and sexual dysfunction at 3 months compared to active surveillance. At 2 years, there was persistent urinary incontinence and sexual dysfunction, but improved urinary irritative symptoms. EBRT, on the other hand, was associated with worse urinary obstruction and/or irritation, bowel symptoms, and sexual dysfunction compared to active surveillance at 3 months. There were no differences in urinary obstruction and/or irritation at 1 year and sexual dysfunction at 2 years. However, differences in bowel symptoms persisted at 2 years.

More recently, *Hoffman et al.* reported on a prospective cohort (Comparative Effectiveness Analysis of Surgery and Radiation: CAESAR) of 2005 patients with favorable and unfavorable risk disease, who received treatment between 2011 and 2012 (56). 1386 patients had favorable risk disease. Compared with active surveillance, brachytherapy (I-125) was associated with worse urinary irritative, urinary incontinence, bowel, and sexual symptoms per EPIC scores that exceeded the minimum clinically important difference (MCID) thresholds (57) at 6 months. At 1 year, there were persistent differences in urinary irritative, bowel, and sexual symptoms. There were no differences in any domain that exceeded the MCID thresholds at 3 or 5 years. Compared with EBRT, brachytherapy was associated with worse urinary incontinence and urinary irritative scores at 6 months and 1 year, but these differences subsided at 3, and 5 years. Sexual and bowel symptoms were similar. Compared with nerve-sparing radical prostatectomy, brachytherapy was associated with improved urinary incontinence, but worse urinary irritative scores and bowel scores at 6 months, 1, 3, and 5 years. Sexual function was better at 6 months, 1, 3, and 5 years.

Two randomized controlled trials compared urinary quality of life between I-125 brachytherapy and single fraction HDR monotherapy (19–21 Gy x 1) (Table A.7). In a trial of 31 patients (*Hathout et al.*), LDR monotherapy

was associated with greater International Prostate Symptom Score (IPSS) at 3 months, along with a longer time to IPSS resolution (58). In another trial of 100 patients from *Agoston et al.*, LDR brachytherapy was associated with greater IPSS scores at 3 months, but not at 12 months (59). However, a randomized controlled trial reported significantly worse bPFS with single fraction (19 Gy x 1) compared with two fraction HDR monotherapy (13.5 Gy x 2) (60).

In summary, brachytherapy monotherapy is associated with transient urinary irritative symptoms that peak within the first 3 months of treatment, and tend to resolve toward baseline at 1 year for I-125 and 6 months for Pd-103.

### *Brachytherapy boost and quality of life*

Urinary, bowel, and sexual symptoms may be more severe for combination brachytherapy boost with EBRT compared with brachytherapy monotherapy or EBRT alone. This observation is supported by two randomized controlled trials as well as a large prospective multi-institutional cohort study.

In the RTOG 0232 randomized controlled trial, brachytherapy boost was associated with significantly worse declines in EPIC urinary, urinary-irritative, and bowel function compared with brachytherapy monotherapy at 4 months and 24 months. Brachytherapy boost was also associated with worse sexual function declines at 24 months. However, none of these differences met the pre-defined clinically significant threshold (effect sizes  $\geq 0.5$  standard deviation) (61).

In the ASCENDE-RT randomized controlled trial, brachytherapy boost was associated with worse bowel and sexual function compared with EBRT at 12 months. At 6 years, brachytherapy boost was associated with worse urinary function compared with EBRT. Sexual function was similar in both arms at 6 years (62).

A recent report from the CAESAR study also reported worse EPIC urinary irritative and bowel function at 1-year, as well as urinary irritative function at 3 years for combination therapy compared with EBRT alone (63).

In summary, brachytherapy boost is associated with worse urinary irritative, bowel, and sexual symptoms compared with brachytherapy or EBRT monotherapy.

## **KQ7: What are strategies for improving quality of life after implant?**

### *Urinary quality of life*

Alpha-adrenergic blockers could be considered for improving short-term urinary quality of life in patients undergoing brachytherapy. This is based on review of multiple randomized controlled trials evaluating alpha-adrenergic blockers, anti-inflammatory medications, and intraoperative steroids (Table A.8).



Regarding alpha-adrenergic medications, two randomized controlled trials compared an alpha-adrenergic blocker to no further therapy. In the first trial (*Elshaiikh et al.*), two months of tamsulosin 0.8 mg daily resulted in a significant improvement in AUA score at 5 weeks compared to placebo in a randomized trial of 118 patients (64). Another randomized trial (*Shimizu et al.*) involving 105 patients revealed that the addition of silodosin 8 mg daily for 6 months' improved IPSS at 1, 3, and 6, months, but not 12 months (65).

Regarding anti-inflammatory medications, *Tanaka et al.* reported that the addition of 200 mg celecoxib for 3 months to 0.2 mg tamsulosin for 6 months did not improve IPSS scores (66). *Crook et al.* reported no difference in urinary retention (7%) or IPSS scores up to 6 months with meloxicam 7.5 mg BID starting on the day of implant or 1 week before implant in a study of 300 patients (67).

Intraoperative dexamethasone (6 mg) was not effective in decreasing the rate of urinary retention for patients undergoing I-125 prostate seed implant in a randomized trial of 196 patients by *Mierzwa et al.* However, the rates of urinary retention (2% vs. 1%) were exceptionally low in both arms (68).

In summary, randomized trials show a benefit of alpha-adrenergic blockers for improving short-term urinary quality of life.

### Sexual quality of life

Oral phosphodiesterase type V (PDE-5) inhibitors have not consistently improved sexual function for patients undergoing radiation therapy including brachytherapy in randomized controlled trials. RTOG 0831 randomized 242 patients to radiation therapy (63% EBRT/37% brachytherapy) with 5 mg tadalafil versus placebo for 24 weeks. The study was powered to detect a 20% increase in spontaneous erectile function at 28–30 weeks after the start of radiation therapy. There was no difference in spontaneous off-drug erectile function between the two arms at 28 (79% vs. 74%) or 52-weeks (72% vs. 71%). On multivariable analysis, radiation therapy type (EBRT vs. brachytherapy) was not associated with worse erectile function (69). A trial reported by *Zelevsky et al.* randomized 279 patients with intent to undergo radiation therapy (EBRT, brachytherapy, or combination with or without ADT) to sildenafil citrate (50 mg daily) versus placebo for 6 months in a 2:1 ratio. Of the 180 patients who did not receive ADT, a greater percentage of patients who received sildenafil citrate reported improved erectile function (73% vs. 50%;  $p = 0.024$ ) at 12-months. The type of radiation therapy was not associated with erectile function (70).

In the randomized controlled trial for prostate cytoreduction by *Gaudet et al.* (KQ3), dutasteride 0.5 mg daily, and bicalutamide 50 mg daily with tamoxifen 10 mg daily for 3 months were associated with improved EPIC sexual

summary scores at 6 weeks and 3 months compared with LHRH agonist for 3 months (42).

In summary, it is unclear whether sexual function preservation may be enhanced with use of PDE-5 inhibitors in the postoperative period. Dutasteride and Bicalutamide, when used for cytoreduction, allow for improved sexual function preservation compared with LHRH agonists.

### KQ8: Which patients are appropriate candidates for prostate brachytherapy?

Patients should have a prostate anatomy suitable for implant, as assessed utilizing transrectal ultrasound (TRUS), computed tomography (CT), or MRI. Special consideration should be made for patients with large prostate glands, large median lobes, or prior history of transurethral resection of the prostate (TURP). Patients with large prostate volumes (>60 cc) may benefit from a TRUS (71,72), CT (73), or MRI-guided (74) volume study to ensure minimal pubic arch interference. Such patients may also be at greater risk of urinary retention (75) and late urinary toxicity (76). Patients with large median lobes (e.g. prostate protrusion into the bladder) may also be at greater risk for acute urinary retention after implant (77), but median lobe resection with a limited TURP could be safely performed more than 4 months' before implant (78). Patients with prior TURP defects may be candidates for prostate brachytherapy if there are sufficient prostatic margins (e.g. 1 cm) around the defect, and with careful attention to urethral-sparing dosimetry (79,80).

Patients should have adequate urinary function, without significant irritative or obstructive symptoms. Medications for improving urinary function (alpha-adrenergic blockers, anti-muscarinic agents, 5-alpha reductase inhibitors) may be considered. Furthermore, patient-reported outcomes, such the IPSS, should be utilized for quantifying urinary function. Studies have reported that patients with higher baseline IPSS scores ( $\geq 15$ –18) may be at greater risk of acute urinary retention after implant (81,82). Urodynamic testing can be helpful in patients with a higher IPSS score, as those with worse peak flow rate (83,84) and significant post-void residual (85) are at higher risk of postimplant urinary retention and late urinary morbidity. Optimizing urinary function with medications before implant is recommended.

Brachytherapy could be considered in those with well controlled inflammatory bowel disease (86). However, patients should be counseled on the potential increased risks of acute, and late toxicity in this setting (87).

Absolute contraindications for TRUS-guided prostate brachytherapy include inability to tolerate general, spinal, or local anesthesia in the dorsal lithotomy position, absence of a rectum, active inflammatory bowel disease, or unacceptable operative risks.

Table 3  
Recommended metrics for pre-implant and post-implant dosimetry for day 0–60

	Pre-implant dosimetry			Post-implant dosimetry	Acceptable post-implant dosimetry
	I-125	Pd-103	Cs-131		
PTV	V100 $\geq$ 95% V150 $\leq$ 65% V200 $\leq$ 30%	V100 $\geq$ 95% V150 $\leq$ 75% V200 $\leq$ 45%	V100 $\geq$ 95% V150 $\leq$ 55% V200 $\leq$ 20%		
Prostate				D90, V100, V150	D90 $\geq$ 90% V100 $\geq$ 85%
Urethra	D5 < 150%			D5	
Rectum	RV100 < 1 cc	RV100 < 1 cc	RV100 < 0.5 cc	RV100	RV100 < 1 cc for I-125/Pd-103 RV100 < 0.5 cc for Cs-131

Abbreviations: DX = minimum dose received by X% of the structure; PTV = planning target volume; VX = volume of the structure receiving X% of the prescription dose. RV = rectal volume.

## KQ9: How are brachytherapy plans evaluated?

### Pre-implant dosimetry

Prostate brachytherapy plans are evaluated before (e.g. pre-implant) and after (post-implant) seed implantation. Regarding pre-implant dosimetry, LDR brachytherapy implants are performed either with a pre-plan, in which ultrasound or MRI images(88) are obtained within 6 weeks before the actual implant, or intraoperative planning during the same procedure as the actual seed implant (89). The clinical target volume (CTV) represents the prostate and up to 5 mm of subclinical disease in all directions, except posteriorly toward the rectum and cranially into the bladder neck. The CTV can be more generous around regions of clinical or radiographic extracapsular extension. The planning target volume (PTV) represents the CTV (90,91). Organs at risk include the urethra and the rectum (contoured 0.5–1 cm above and below the prostate) (92).

Recommended pre-implant dose constraints are provided in Table 3. Specific pre-implant metrics are provided for different radionuclides due to their differing energies (Table 2)(93). For all radionuclides, each institution should formally evaluate such metrics against their institutional practice and experience, given significant differences in planning algorithms as well as little shared experience in pre-implant and post-implant dosimetry across different institutions. When transitioning to a new radionuclide, it is highly recommended to seek guidance from an experienced practitioner to appreciate the nuances of treatment planning and delivery.

### Post-implant dosimetry

Post-implant dosimetry is essential for the evaluation of every prostate seed implant, given the association between post-implant dosimetry and biochemical control (14,94,95). Day 0 dosimetry performed on the same day as the implant provides patient convenience, as well as immediate information regarding implant quality to improve the learning curve. Day 0 dosimetry is recommended for early practitioners of LDR prostate brachytherapy. Dosimetry at later

timepoints (Day 30 – Day 60) accounts for resolution of prostate edema, and may be more reflective of the deposited dose for I-125 due to its prolonged half-life (96). CT-based dosimetry remains the standard method for identifying seed locations. However, MR and/or CT fusion is highly recommended as it provides the best anatomic delineation of the prostate and surrounding organs-at-risk (97,98). A Foley catheter is recommended if the patient can tolerate to clearly define the urethra for the purpose of post-implant dosimetry.

Recommended post-implant dosimetry metrics, defined broadly to encompass dosimetry at any timepoint between Days 0 and 60, are included in Table 3. Acceptable prostate coverage is signified by a prostate D90  $\geq$  90%, given the increased risk of biochemical recurrence if this constraint is not met (14,94,95), as well as a V100  $\geq$  85% (99). If these constraints are not met on Day 0 dosimetry, post-implant dosimetry could be repeated at a later timepoint to evaluate if prostate coverage may improve with edema resolution (100). If these constraints are not met on later postimplant dosimetry, additional treatment with radionuclides (101), external beam radiation therapy, or ADT (28), could be considered. Acceptable rectal dosimetry is indicated by a rectal V100 (RV100) < 1 cc, given the increased risk of late Grade 2+ rectal toxicity if this constraint is not met (52,102). If this constraint is not met, a rectal spacer could be considered to increase the distance between the prostate and rectum (103). The urethra D5 has been suggested as a reportable metric in prior brachytherapy guidelines (2,92). Although the urethra D5 has been associated with Grade 2+ late urinary toxicity(52), there is insufficient data to recommend a dosimetric threshold. Dosimetric constraints that have been associated with urinary toxicity include the bladder neck (104) (D2cc < 50%) and external urethral sphincter (V200 < 0.04 cm<sup>3</sup>) (105).

## KQ10: What type of seeds should be utilized for brachytherapy?

Both loose and stranded seeds can be utilized for the prostate seed implant. Loose seeds are loaded in sterile

cartridges. Stranded seeds can be delivered with pre-loaded needles, or constructed intraoperatively. A randomized controlled trial reported less seed migration with stranded seeds compared with loose seeds (106). However, bioabsorbable polymer coated seeds have been shown to reduce migration (107).

Seeds (loose or stranded) should be delivered under real-time TRUS guidance with specialized treatment planning software. Because the needle insertion process may distort the gland, the physician must continuously compare the actual position of the prostate and urethra with respect to their relative positions from the treatment planning image. If deviations are noted, an effort should be made to align needles with the actual prostate and urethral anatomy to ensure that the seeds are deposited in their intended locations. Care must be taken to ensure that seeds are not deposited too close to the urethra or rectum. Interactive planning, in which real-time dosimetry is updated based on needle positions, may aid physicians in making manual adjustments (89). Additional seeds could also be deposited before anesthesia reversal if real-time dosimetric assessment with TRUS and/or cone-beam CT fusion is available (108,109).

## Discussion

This consensus statement is intended to provide a comprehensive update of the clinical benefits and risks of prostate LDR brachytherapy based on a systemic review of the literature. Recommendations have been made based on the new 4-tiered NCCN risk stratification system and completion of practice-changing randomized controlled trials. These guidelines are consistent with those from the NCCN (3), American Society of Clinical Oncology and/or Cancer Care Ontario (110), and European Association of Urology and/or European Society for Radiotherapy and Oncology and/or International Society of Geriatric Oncology (111).

The practice of brachytherapy will continue to evolve as results from multiple ongoing randomized controlled trials are published. Current trials are evaluating:

- whether HDR monotherapy is associated with different PSA control (NCT02960087), toxicity (NCT02258087; PROMOBRA), or urinary quality of life (NCT03426748) outcomes compared with LDR monotherapy in favorable risk prostate cancer;
- whether SBRT is associated with different acute toxicity profile (NCT02895854; BRAVEROBO) or cost utility (NCT03830788) compared with LDR brachytherapy;
- whether quality of life differs between HDR brachytherapy boost and LDR brachytherapy boost (NCT01936883; BrachyQOL) in conjunction with EBRT for unfavorable risk prostate cancer;
- whether LDR or HDR brachytherapy boost with EBRT can improve 5-year bPFS compared with dose-escalated

EBRT (NCT02271659; GETUGP05) in unfavorable risk prostate cancer;

- whether longer durations of ADT for LDR brachytherapy can improve bPFS in intermediate (NCT00664456: SHIP 0804) (112) and high risk (UMIN000003992: SHIP 36B) (113) prostate cancer. Of note, a recent analysis of the TROG RADAR trial reported that patients who received HDR brachytherapy boost had reduced distant progression with 18-months versus 6 months of ADT (29);
- whether the presence of ADT can improve OS for patients within the EBRT + LDR brachytherapy boost stratification (NCT00936390; RTOG 0815).

However, critical challenges surrounding LDR brachytherapy remain. First, strategies need to be developed for mitigating toxicities associated with LDR brachytherapy boost. Imaging technologies, such as multiparametric magnetic resonance imaging (mpMRI), may play an important role in dose escalation of dominant intraprostatic lesions (114), while safely sparing organs at risk associated with toxicity and/or adverse quality of life after brachytherapy such as the bladder neck (104), external urethral sphincter (105,115), and rectum (116). Second, brachytherapy boost should be offered only to selected group of patients with UIR and HR disease. Only those with long life expectancy, absence of significant comorbidities, and good baseline urinary function are likely to benefit from this treatment over the long term, by avoiding biochemical failure and subsequent toxic systemic salvage therapy such as long-term ADT (54). The final treatment decision should be an individualized shared decision-making between the physician and patient, with consideration of patient's preference on the improved disease control with the potential of increased urinary toxicity with brachytherapy boost.

In addition, predictive biomarkers, and novel functional imaging may improve patient selection. This is especially important, given the emergence of potential competing modalities including androgen receptor signaling inhibitors to the radiotherapeutic (NCT02446444; ENZARAD) and surgical management (NCT03767244; PROTEUS) of high-risk prostate cancer. Candidate biomarkers include mpMRI (117), prostate PET (118,119), or genomic classifiers (120,121). Third, LDR brachytherapy is heavily user-dependent, such that clinical outcomes may vary across providers and institutions due to pronounced dosimetric heterogeneity associated this technique. Standardization of brachytherapy treatment planning using activity per volume nomograms (122,123), autosegmentation of pelvic anatomy (124), and knowledge-based planning (125) may reduce such variabilities, and ensure that brachytherapy outcomes are generalizable across institutions. This could also be helpful in training the new generation of brachytherapists (126). Fourth, the role of brachytherapy for focal therapy in combination with mpMRI, while out-

side the scope of this guideline, needs to be further defined as this may be an acceptable oncologic treatment for patients with low or favorable intermediate risk disease who desire to preserve quality of life (127). Finally, alternative payment models may have important implications for the utilization of LDR brachytherapy as monotherapy and boost treatment, given unique cost savings, and cost effectiveness of LDR brachytherapy with respect to competing modalities (128,129).

The most promising strategies should be incorporated into randomized controlled trials with primary endpoints involving long-term disease control, late toxicity, quality of life, and cost effectiveness so that the value of LDR brachytherapy in the rapidly changing clinical environment can be enhanced.

## Disclosures

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.brachy.2021.07.006](https://doi.org/10.1016/j.brachy.2021.07.006).

## References

- [1] Nag S, Beyer D, Friedland J, et al. American brachytherapy society (ABS) recommendations for transperineal permanent brachytherapy of prostate cancer. *Int J Radiat Oncol* 1999;44(4):789–799. doi:10.1016/S0360-3016(99)00069-3.
- [2] Davis BJ, Horwitz EM, Lee WR, et al. American Brachytherapy Society consensus guidelines for transrectal ultrasound-guided permanent prostate brachytherapy. *Brachytherapy* 2012;11(1):6–19. doi:10.1016/j.brachy.2011.07.005.
- [3] Mohler JL, Horwitz EM, Richey S. NCCN guidelines prostate cancer. *Prostate Cancer* 2019;165.
- [4] Zumsteg ZS, Spratt DE, Pei I, et al. A new risk classification system for therapeutic decision making with intermediate-risk prostate cancer patients undergoing dose-escalated external-beam radiation therapy. *Eur Urol* 2013;64(6):895–902. doi:10.1016/j.eururo.2013.03.033.
- [5] Loblaw DA, Prestrud AA, Somerfield MR, et al. American society of clinical oncology clinical practice guidelines: formal systematic review-based consensus methodology. *J Clin Oncol* 2012;30(25):3136–3140. doi:10.1200/JCO.2012.42.0489.
- [6] Guyatt G, Gutterman D, Baumann MH, et al. Grading strength of recommendations and quality of evidence in clinical guidelines: report from an american college of chest physicians task force. *Chest* 2006;129(1):174–181. doi:10.1378/chest.129.1.174.
- [7] Giberti C, Chiono L, Gallo F, et al. Radical retropubic prostatectomy versus brachytherapy for low-risk prostatic cancer: a prospective study. *World J Urol* 2009;27(5):607–612. doi:10.1007/s00345-009-0418-9.
- [8] Giberti C, Gallo F, Schenone M, et al. Robotic prostatectomy versus brachytherapy for the treatment of low risk prostate cancer. *Can J Urol* 2017;6.
- [9] Prestidge BR, Winter K, Sanda MG, et al. Initial report of NRG oncology/RTOG 0232: a phase 3 study comparing combined external beam radiation and transperineal interstitial permanent brachytherapy with brachytherapy alone for selected patients with intermediate-risk prostatic carcinoma. *Int J Radiat Oncol Biol Phys* 2016;96(2S):S4.
- [10] Merrick GS, Wallner KE, Galbreath RW, et al. Is supplemental external beam radiation therapy necessary for patients with higher risk prostate cancer treated with 103Pd? Results of two prospective randomized trials. *Brachytherapy* 2015;14(5):677–685. doi:10.1016/j.brachy.2015.05.001.
- [11] Merrick GS, Wallner KE, Galbreath RW, et al. Is supplemental external beam radiation radiation therapy essential to maximize brachytherapy outcomes in patients with unfavorable intermediate-risk disease? *Brachytherapy* 2016;15(1):79–84. doi:10.1016/j.brachy.2015.09.011.
- [12] Lawton CA, Hunt D, Lee WR, et al. Long-term results of a phase II trial of ultrasound-guided radioactive implantation of the prostate for definitive management of localized adenocarcinoma of the prostate (RTOG 98-05). *Int J Radiat Oncol* 2011;81(1):1–7. doi:10.1016/j.ijrobp.2010.05.056.
- [13] Ito K, Saito S, Yorozu A, et al. Nationwide Japanese prostate cancer outcome study of permanent Iodine-125 seed implantation (J-POPS): first analysis on survival. *Int J Clin Oncol* 2018;23(6):1148–1159. doi:10.1007/s10147-018-1309-0.
- [14] Zelefsky MJ, Kuban DA, Levy LB, et al. Multi-institutional analysis of long-term outcome for stages T1–T2 prostate cancer treated with permanent seed implantation. *Int J Radiat Oncol* 2007;67(2):327–333. doi:10.1016/j.ijrobp.2006.08.056.
- [15] Kupelian PA, Potters L, Khuntia D, et al. Radical prostatectomy, external beam radiotherapy <72 Gy, external beam radiotherapy ≥72 Gy, permanent seed implantation, or combined seeds/external beam radiotherapy for stage T1–T2 prostate cancer. *Int J Radiat Oncol* 2004;58(1):25–33. doi:10.1016/S0360-3016(03)00784-3.
- [16] Smith GD, Pickles T, Crook J, et al. Brachytherapy improves biochemical failure-free survival in low- and intermediate-risk prostate cancer compared with conventionally fractionated external beam radiation therapy: a propensity score matched analysis. *Int J Radiat Oncol* 2015;91(3):505–516. doi:10.1016/j.ijrobp.2014.11.018.
- [17] Loblaw A, Pickles T, Crook J, et al. Stereotactic ablative radiotherapy versus low dose rate brachytherapy or external beam radiotherapy: propensity score matched analyses of canadian data. *Clin Oncol* 2017;29(3):161–170. doi:10.1016/j.clon.2016.10.001.
- [18] Kibel AS, Ciezki JP, Klein EA, et al. Survival among men with clinically localized prostate cancer treated with radical prostatectomy or radiation therapy in the prostate specific antigen era. *J Urol* 2012;187(4):1259–1265. doi:10.1016/j.juro.2011.11.084.
- [19] Frank SJ, Levy LB, Vulpen M van, et al. Outcomes after prostate brachytherapy are even better than predicted. *Cancer* 2012;118(3):839–847. doi:10.1002/ncr.26307.
- [20] Berlin A, Moraes FY, Sanmamed N, et al. International multicenter validation of an intermediate risk subclassification of prostate cancer managed with radical treatment without hormone therapy. *J Urol* 2019;201(2):284–291. doi:10.1016/j.juro.2018.08.044.
- [21] Crook JM, Tang C, Thames H, et al. A biochemical definition of cure after brachytherapy for prostate cancer. *Radiother Oncol* 2020;149:64–69. doi:10.1016/j.radonc.2020.04.038.
- [22] Stone NN, Potters L, Davis BJ, et al. Multicenter analysis of effect of high biologic effective dose on biochemical failure and survival outcomes in patients with gleason score 7–10 prostate cancer treated with permanent prostate brachytherapy. *Int J Radiat Oncol* 2009;73(2):341–346. doi:10.1016/j.ijrobp.2008.04.038.
- [23] Morris WJ, Tyldesley S, Rodda S, et al. Androgen suppression combined with elective nodal and dose escalated radiation therapy

- (the ASCENDE-RT Trial): an analysis of survival endpoints for a randomized trial comparing a low-dose-rate brachytherapy boost to a dose-escalated external beam boost for high- and intermediate-risk prostate cancer. *Int J Radiat Oncol* 2017;98(2):275–285. doi:10.1016/j.ijrobp.2016.11.026.
- [24] Oh J, Tyldesley S, Pai HH, et al. An updated analysis of survival endpoints for ASCENDE-RT, a randomized trial comparing a low-dose-rate brachytherapy boost to a dose-escalated external beam boost for high- and intermediate-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2020;108(3):S62. doi:10.1016/j.ijrobp.2020.07.2194.
- [25] Lawton CA, Yan Y, Lee WR, et al. Long-term results of an RTOG phase II trial (00-19) of external-beam radiation Therapy combined with permanent source brachytherapy for intermediate-risk clinically localized adenocarcinoma of the prostate. *Int J Radiat Oncol* 2012;82(5):e795–e801. doi:10.1016/j.ijrobp.2011.11.040.
- [26] Kishan AU, Cook RR, Ciezki JP, et al. Radical prostatectomy, external beam radiotherapy, or external beam radiotherapy with brachytherapy boost and disease progression and mortality in patients with gleason score 9-10 prostate cancer. *JAMA* 2018;319(9):896–905. doi:10.1001/jama.2018.0587.
- [27] Sandler KA, Cook RR, Ciezki JP, et al. Prostate-only Versus Whole-pelvis Radiation with or Without a Brachytherapy Boost for Gleason Grade Group 5 Prostate Cancer: a Retrospective Analysis. *Eur Urol* 2019. doi:10.1016/j.eururo.2019.03.022.
- [28] Keyes M, Merrick G, Frank SJ, et al. American brachytherapy society task group report: use of androgen deprivation therapy with prostate brachytherapy? a systematic literature review. *Brachytherapy* 2017;16(2):245–265. doi:10.1016/j.brachy.2016.11.017.
- [29] Joseph D, Denham JW, Steigler A, et al. Radiation dose escalation or longer androgen suppression to prevent distant progression in men with locally advanced prostate cancer: 10-year data from the TROG 03.04 RADAR trial. *Int J Radiat Oncol Biol Phys* 2020;106(4):693–702. doi:10.1016/j.ijrobp.2019.11.415.
- [30] Fellin G., Mirri M.A., Santoro L., et al. Low dose rate brachytherapy (LDR-BT) as monotherapy for early stage prostate cancer in Italy: practice and outcome analysis in a series of 2237 patients from 11 institutions. *Br J Radiol* 2016;89(1065). doi:10.1259/bjr.20150981.
- [31] Martell K, Husain S, Taussky D, et al. Multicenter evaluation of biochemical relapse-free survival outcomes for intraoperatively planned prostate brachytherapy using an automated delivery system. *Int J Radiat Oncol* 2017;99(4):895–903. doi:10.1016/j.ijrobp.2017.05.045.
- [32] Dickinson PD, Malik J, Mandall P, et al. Five-year outcomes after iodine-125 seed brachytherapy for low-risk prostate cancer at three cancer centres in the UK. *BJU Int* 2014;113(5):748–753. doi:10.1111/bju.12358.
- [33] Tran ATH, Mandall P, Swindell R, et al. Biochemical outcomes for patients with intermediate risk prostate cancer treated with I-125 interstitial brachytherapy monotherapy. *Radiother Oncol* 2013;109(2):235–240. doi:10.1016/j.radonc.2013.05.030.
- [34] Cosset J-M, Flam T, Thiounn N, et al. Selecting patients for exclusive permanent implant prostate brachytherapy: the experience of the paris institut curie/cochin hospital/neckar hospital group on 809 patients. *Int J Radiat Oncol* 2008;71(4):1042–1048. doi:10.1016/j.ijrobp.2007.11.056.
- [35] Rose BS, Chen M-H, Wu J, et al. Androgen deprivation therapy use in the setting of high-dose radiation therapy and the risk of prostate cancer-specific mortality stratified by the extent of competing mortality. *Int J Radiat Oncol* 2016;96(4):778–784. doi:10.1016/j.ijrobp.2016.08.014.
- [36] Shilkrut M, Merrick GS, McLaughlin PW, et al. The addition of low-dose-rate brachytherapy and androgen-deprivation therapy decreases biochemical failure and prostate cancer death compared with dose-escalated external-beam radiation therapy for high-risk prostate cancer. *Cancer* 2013;119(3):681–690. doi:10.1002/cncr.27784.
- [37] Zumsteg ZS, Spratt DE, Daskivich TJ, et al. Effect of androgen deprivation on long-term outcomes of intermediate-risk prostate cancer stratified as favorable or unfavorable: a secondary analysis of the RTOG 9408 randomized clinical trial. *JAMA Netw Open* 2020;3(9):e2015083. doi:10.1001/jamanetworkopen.2020.15083.
- [38] Shore ND, Saad F, Cookson MS, et al. Oral relugolix for androgen-deprivation therapy in advanced prostate cancer. *N Engl J Med* 2020;382(23):2187–2196. doi:10.1056/NEJMoa2004325.
- [39] Korzeniowski MA, Crook JM, Bowes D, et al. A phase II trial of 8 weeks of degarelix for prostate volume reduction: efficacy and hormonal recovery. *Brachytherapy* 2018;17(3):530–536. doi:10.1016/j.brachy.2017.12.005.
- [40] Dearnaley DP, Saltzstein DR, Sylvester JE, et al. The oral gonadotropin-releasing hormone receptor antagonist relugolix as neoadjuvant/adjuvant androgen deprivation therapy to external beam radiotherapy in patients with localised intermediate-risk prostate cancer: a randomised, open-label, parallel-group phase 2 trial. *Eur Urol* 2020;78(2):184–192. doi:10.1016/j.eururo.2020.03.001.
- [41] Margel D, Peer A, Ber Y, et al. Cardiovascular morbidity in a randomized trial comparing GnRH agonist and GnRH antagonist among patients with advanced prostate cancer and preexisting cardiovascular disease. *J Urol* 2019;202(6):1199–1208. doi:10.1097/JU.0000000000000384.
- [42] Gaudet M, Vigneault É, Foster W, et al. Randomized non-inferiority trial of bicalutamide and dutasteride versus LHRH agonists for prostate volume reduction prior to I-125 permanent implant brachytherapy for prostate cancer. *Radiother Oncol* 2016;118(1):141–147. doi:10.1016/j.radonc.2015.11.022.
- [43] Wallner K, Merrick G, True L, et al. 125I versus 103Pd for low-risk prostate cancer: preliminary PSA outcomes from a prospective randomized multicenter trial. *Int J Radiat Oncol* 2003;57(5):1297–1303. doi:10.1016/S0360-3016(03)01448-2.
- [44] Herstein A, Wallner K, Merrick G, et al. I-125 versus Pd-103 for low-risk prostate cancer: long-term morbidity outcomes from a prospective randomized multicenter controlled trial. *Cancer J* 2005;11(5):385.
- [45] Moran BJ, Braccioforte MH. One-year results of 125I vs. 131Cs prospective randomized trial on urinary function following prostate brachytherapy. *Brachytherapy* 2009;8(2):109–110.
- [46] Moran BJ, Braccioforte MH. Long-term PSA outcomes in a single institution, prospective randomized 131Cs /125I permanent prostate brachytherapy trial. *Int J Radiat Oncol Biol Phys* 2017;99(2):E255. doi:10.1016/j.ijrobp.2017.06.1212.
- [47] Frank SJ, Pugh TJ, Blanchard P, et al. Prospective phase 2 trial of permanent seed implantation prostate brachytherapy for intermediate-risk localized prostate cancer: efficacy, toxicity, and quality of life outcomes. *Int J Radiat Oncol* 2018;100(2):374–382. doi:10.1016/j.ijrobp.2017.09.050.
- [48] Blanchard P, Pugh TJ, Swanson DA, et al. Patient-reported health-related quality of life for men treated with low-dose-rate prostate brachytherapy as monotherapy with 125-iodine, 103-palladium, or 131-cesium: results of a prospective phase II study. *Brachytherapy* 2018;17(2):265–276. doi:10.1016/j.brachy.2017.11.007.
- [49] Benoit RM, Smith RP, Beriwal S. Five year prostate-specific antigen outcomes after caesium prostate brachytherapy. *Clin Oncol* 2014;26(12):776–780. doi:10.1016/j.clon.2014.08.002.
- [50] Glaser SM, Chen KS, Benoit RM, et al. Long-term quality of life in prostate cancer patients treated with cesium-131. *Int J Radiat Oncol* 2017;98(5):1053–1058. doi:10.1016/j.ijrobp.2017.03.046.
- [51] Ling DC, Chen KS, Benoit RM, et al. Long-term patient-reported rectal bleeding and bowel-related quality of life after Cs-131 prostate brachytherapy. *Int J Radiat Oncol* 2019;104(3):622–630. doi:10.1016/j.ijrobp.2019.02.056.

- [52] Ohashi T, Yorozu A, Saito S, et al. Urinary and Rectal toxicity profiles after permanent iodine-125 implant brachytherapy in Japanese men: nationwide J-POPS multi-institutional prospective cohort study. *Int J Radiat Oncol* 2015;93(1):141–149. doi:10.1016/j.ijrobp.2015.05.014.
- [53] Rodda S, Tyldesley S, Morris WJ, et al. An analysis of treatment-related morbidity for a randomized trial comparing a low-dose-rate brachytherapy boost with a dose-escalated external beam boost for high- and intermediate-risk prostate cancer. *Int J Radiat Oncol* 2017;98(2):286–295. doi:10.1016/j.ijrobp.2017.01.008.
- [54] Crook JM, O’Callaghan CJ, Duncan G, et al. Intermittent androgen suppression for rising PSA level after radiotherapy. *N Engl J Med* 2012;367(10):895–903. doi:10.1056/NEJMoa1201546.
- [55] Chen RC, Basak R, Meyer AM, et al. Association between choice of radical prostatectomy, external beam radiotherapy, brachytherapy, or active surveillance and patient-reported quality of life among men with localized prostate cancer. *JAMA* 2017;317(11):1141–1150. doi:10.1001/jama.2017.1652.
- [56] Hoffman KE, Penson DF, Zhao Z, et al. Patient-reported outcomes through 5 years for active surveillance, surgery, brachytherapy, or external beam radiation with or without androgen deprivation therapy for localized prostate cancer. *JAMA* 2020;323(2):149–163. doi:10.1001/jama.2019.20675.
- [57] Skolarus TA, Dunn RL, Sanda MG, et al. Minimally important difference for the expanded prostate cancer index composite short form. *Urology* 2015;85(1):101–106. doi:10.1016/j.urology.2014.08.044.
- [58] Hathout L, Mahmoud O, Wang Y, et al. A phase 2 randomized pilot study comparing high-dose-rate brachytherapy and low-dose-rate brachytherapy as monotherapy in localized prostate cancer. *Adv Radiat Oncol* 2019;4(4):631–640. doi:10.1016/j.adro.2019.04.003.
- [59] Agoston P, Major T, Jorgo K, et al. SP-0350: HDR brachytherapy in one fraction vs LDR brachytherapy in the treatment of localized prostate cancer. Early results. *Radiother Oncol* 2018;127:S182–S183. doi:10.1016/S0167-8140(18)30660-1.
- [60] Morton G, McGuffin M, Chung HT, et al. Prostate high dose-rate brachytherapy as monotherapy for low and intermediate risk prostate cancer: efficacy results from a randomized phase II clinical trial of one fraction of 19 Gy or two fractions of 13.5 Gy. *Radiother Oncol* 2020;146:90–96. doi:10.1016/j.radonc.2020.02.009.
- [61] Bruner DW, Moughan J, Prestidge BR, et al. Patient reported outcomes of NRG oncology/RTOG 0232: a phase III study comparing combined external beam radiation and transperineal interstitial permanent brachytherapy with brachytherapy alone in intermediate risk prostate Cancer. *Int J Radiat Oncol Biol Phys* 2018;102(3):S2–S3. doi:10.1016/j.ijrobp.2018.06.103.
- [62] Rodda S, Morris WJ, Hamm J, Duncan G. ASCENDE-RT: an analysis of health-related quality of life for a randomized trial comparing low-dose-rate brachytherapy boost with dose-escalated external beam boost for high- and intermediate-risk prostate cancer. *Int J Radiat Oncol* 2017;98(3):581–589. doi:10.1016/j.ijrobp.2017.02.027.
- [63] Lee DJ, Barocas DA, Zhao Z, et al. Comparison of patient-reported outcomes after external beam radiation therapy and combined external beam with low-dose-rate brachytherapy boost in men with localized prostate cancer. *Int J Radiat Oncol* 2018;102(1):116–126. doi:10.1016/j.ijrobp.2018.05.043.
- [64] Elshaikh MA, Ulchaker JC, Reddy CA, et al. Prophylactic tamsulosin (Flomax) in patients undergoing prostate 125I brachytherapy for prostate carcinoma: final report of a double-blind placebo-controlled randomized study. *Int J Radiat Oncol* 2005;62(1):164–169. doi:10.1016/j.ijrobp.2004.09.036.
- [65] Shimizu N, Minami T, Sugimoto K, et al. Efficacy of silodosin in patients undergoing brachytherapy: a randomized trial involving a pressure flow study. *World J Urol* 2014;32(6):1423–1432. doi:10.1007/s00345-014-1239-z.
- [66] Tanaka N, Torimoto K, Asakawa I, et al. Comparison of chronological changes in urinary function in patients who underwent low-dose-rate brachytherapy for prostate cancer—A randomized controlled trial of alpha-1 adrenoceptor antagonist alone versus combination with cyclooxygenase-2 inhibitor—. *Brachytherapy* 2018;17(3):537–543. doi:10.1016/j.brachy.2017.12.004.
- [67] Crook J, Patil N, Wallace K, et al. A phase III randomized trial of the timing of meloxicam with iodine-125 prostate brachytherapy. *Int J Radiat Oncol* 2010;77(2):496–501. doi:10.1016/j.ijrobp.2009.04.078.
- [68] Mierzwa ML, Barrett WL, Redmond K, et al. Randomized trial to assess the efficacy of intraoperative steroid use in decreasing acute urinary retention after transperineal radioactive iodine-125 implantation for prostate cancer. *Cancer* 2008;113(9):2605–2609. doi:10.1002/cncr.23905.
- [69] Pisansky TM, Pugh SL, Greenberg RE, et al. Tadalafil for prevention of erectile dysfunction after radiotherapy for prostate cancer: the radiation therapy oncology group [R831] randomized clinical trial. *JAMA* 2014;311(13):1300. doi:10.1001/jama.2014.2626.
- [70] Zelefsky MJ, Shasha D, Branco RD, et al. Prophylactic Sildenafil Citrate Improves Select Aspects of Sexual Function in Men Treated with Radiotherapy for Prostate Cancer. *J Urol* 2014;192(3):868–874. doi:10.1016/j.juro.2014.02.097.
- [71] Wallner K, Ellis W, Russell K, et al. Use of TRUS to predict pubic arch interference of prostate brachytherapy. *Int J Radiat Oncol* 1999;43(3):583–585. doi:10.1016/S0360-3016(98)00459-3.
- [72] Henderson A, Laing RW, Langley SEM. Identification of pubic arch interference in prostate brachytherapy: Simplifying the transrectal ultrasound technique. *Brachytherapy* 2003;2(4):240–245. doi:10.1016/j.brachy.2003.11.001.
- [73] Bellon J, Wallner K, Ellis W, et al. Use of pelvic CT scanning to evaluate pubic arch interference of transperineal prostate brachytherapy. *Int J Radiat Oncol* 1999;43(3):579–581. doi:10.1016/S0360-3016(98)00466-0.
- [74] Martin GV, Pugh TJ, Mahmood U, et al. Permanent prostate brachytherapy pubic arch evaluation with diagnostic magnetic resonance imaging. *Brachytherapy* 2017;16(4):728–733. doi:10.1016/j.brachy.2017.02.001.
- [75] Crook J, McLean M, Catton C, et al. Factors influencing risk of acute urinary retention after TRUS-guided permanent prostate seed implantation. *Int J Radiat Oncol* 2002;52(2):453–460. doi:10.1016/S0360-3016(01)02658-X.
- [76] Keyes M, Miller S, Moravan V, et al. Predictive factors for acute and late urinary toxicity after permanent prostate brachytherapy: long-term outcome in 712 consecutive patients. *Int J Radiat Oncol Biol Phys* 2009;73(4):1023–1032. doi:10.1016/j.ijrobp.2008.05.022.
- [77] Roeloffzen EM, van Vulpen M, Battermann JJ, et al. Pretreatment nomogram to predict the risk of acute urinary retention after I-125 prostate brachytherapy. *Int J Radiat Oncol* 2011;81(3):737–744. doi:10.1016/j.ijrobp.2010.06.009.
- [78] Ivanowicz AN, Wakeman CM, Hubbard RT, et al. Two-step transurethral surgery of the prostate and permanent implant brachytherapy for patients with lower urinary tract symptoms and low- to intermediate-risk prostate cancer. *Brachytherapy* 2012;11(6):483–488. doi:10.1016/j.brachy.2011.08.006.
- [79] Moran BJ, Stutz MA, Gurel MH. Prostate brachytherapy can be performed in selected patients after transurethral resection of the prostate. *Int J Radiat Oncol* 2004;59(2):392–396. doi:10.1016/j.ijrobp.2003.10.013.
- [80] Brousil P, Hussain M, Lynch M, et al. Modified transurethral resection of the prostate (TURP) for men with moderate lower urinary tract symptoms (LUTS) before brachytherapy is safe and feasible. *BJU Int* 2015;115(4):580–586. doi:10.1111/bju.12798.
- [81] Locke J, Ellis W, Wallner K, et al. Risk factors for acute urinary retention requiring temporary intermittent catheterization after prostate brachytherapy: a prospective study. *Int J Radiat Oncol* 2002;52(3):712–719. doi:10.1016/S0360-3016(01)02657-8.

- [82] Bucci J, Morris WJ, Keyes M, et al. Predictive factors of urinary retention following prostate brachytherapy. *Int J Radiat Oncol* 2002;53(1):91–98. doi:10.1016/S0360-3016(01)02812-7.
- [83] Williams SG, Millar JL, Duchesne GM, et al. Factors predicting for urinary morbidity following 125iodine transperineal prostate brachytherapy. *Radiother Oncol* 2004;73(1):33–38. doi:10.1016/j.radonc.2004.07.026.
- [84] Martens C, Pond G, Webster D, et al. Relationship of the International Prostate Symptom score with urinary flow studies, and catheterization rates following 125I prostate brachytherapy. *Brachytherapy* 2006;5(1):9–13. doi:10.1016/j.brachy.2005.12.002.
- [85] Beekman M, Merrick GS, Butler WM, et al. Selecting patients with pretreatment postvoid residual urine volume less than 100 mL may favorably influence brachytherapy-related urinary morbidity. *Urology* 2005;66(6):1266–1270. doi:10.1016/j.urology.2005.06.109.
- [86] Peters CA, Cesaretti JA, Stone NN, Stock RG. Low-dose rate prostate brachytherapy is well tolerated in patients with a history of inflammatory bowel disease. *Int J Radiat Oncol* 2006;66(2):424–429. doi:10.1016/j.ijrobp.2006.05.027.
- [87] Pai HH, Keyes M, Morris WJ, Christie J. Toxicity after 125I prostate brachytherapy in patients with inflammatory bowel disease. *Brachytherapy* 2013;12(2):126–133. doi:10.1016/j.brachy.2012.04.008.
- [88] Albert JM, Swanson DA, Pugh TJ, et al. Magnetic resonance imaging-based treatment planning for prostate brachytherapy. *Brachytherapy* 2013;12(1):30–37. doi:10.1016/j.brachy.2012.03.009.
- [89] Nag S, Ciezki JP, Cormack R, et al. Intraoperative planning and evaluation of permanent prostate brachytherapy: report of the American brachytherapy society. *Int J Radiat Oncol* 2001;51(5):1422–1430. doi:10.1016/S0360-3016(01)01616-9.
- [90] Salembier C, Lavagnini P, Nickers P, et al. Tumour and target volumes in permanent prostate brachytherapy: a supplement to the ESTRO/EAU/EORTC recommendations on prostate brachytherapy. *Radiother Oncol* 2007;83(1):3–10. doi:10.1016/j.radonc.2007.01.014.
- [91] Nath R, Bice WS, Butler WM, et al. AAPM recommendations on dose prescription and reporting methods for permanent interstitial brachytherapy for prostate cancer: report of task group 137. *Med Phys* 2009;36(11):5310–5322. doi:10.1118/1.3246613.
- [92] Crook JM, Potters L, Stock RG, Zelefsky MJ. Critical organ dosimetry in permanent seed prostate brachytherapy: defining the organs at risk. *Brachytherapy* 2005;4(3):186–194. doi:10.1016/j.brachy.2005.01.002.
- [93] Bice WS, Prestidge BR, Kurtzman SM, et al. Recommendations for permanent prostate brachytherapy with 131Cs: a consensus report from the Cesium Advisory Group. *Brachytherapy* 2008;7(4):290–296. doi:10.1016/j.brachy.2008.05.004.
- [94] Potters L, Cao Y, Calugaru E, et al. A comprehensive review of CT-based dosimetry parameters and biochemical control in patients treated with permanent prostate brachytherapy. *Int J Radiat Oncol* 2001;50(3):605–614. doi:10.1016/S0360-3016(01)01473-0.
- [95] Morris WJ, Spadinger I, Keyes M, et al. Whole prostate D90 and V100: a dose–response analysis of 2000 consecutive 125I monotherapy patients. *Brachytherapy* 2014;13(1):32–41. doi:10.1016/j.brachy.2013.08.006.
- [96] Tanaka O, Hayashi S, Matsuo M, et al. Effect of edema on postimplant dosimetry in prostate brachytherapy using CT/MRI fusion. *Int J Radiat Oncol* 2007;69(2):614–618. doi:10.1016/j.ijrobp.2007.05.082.
- [97] Crook J, McLean M, Yeung I, et al. MRI-CT fusion to assess postbrachytherapy prostate volume and the effects of prolonged edema on dosimetry following transperineal interstitial permanent prostate brachytherapy. *Brachytherapy* 2004;3(2):55–60. doi:10.1016/j.brachy.2004.05.001.
- [98] Martin GV, Pugh TJ, Mahmood U, et al. Permanent prostate brachytherapy postimplant magnetic resonance imaging dosimetry using positive contrast magnetic resonance imaging markers. *Brachytherapy* 2017;16(4):761–769. doi:10.1016/j.brachy.2017.04.004.
- [99] Morris WJ, Keyes M, Palma D, et al. Evaluation of dosimetric parameters and disease response after 125iodine transperineal brachytherapy for low- and intermediate-risk prostate cancer. *Int J Radiat Oncol* 2009;73(5):1432–1438. doi:10.1016/j.ijrobp.2008.07.042.
- [100] Taussky D, Austen L, Toi A, et al. Sequential evaluation of prostate edema after permanent seed prostate brachytherapy using CT-MRI fusion. *Int J Radiat Oncol* 2005;62(4):974–980. doi:10.1016/j.ijrobp.2004.12.012.
- [101] Keyes M, Pickles T, Agranovich A, et al. 125I reimplantation in patients with poor initial dosimetry after prostate brachytherapy. *Int J Radiat Oncol* 2004;60(1):40–50. doi:10.1016/j.ijrobp.2004.02.011.
- [102] Price JG, Stone NN, Stock RG. Predictive factors and management of rectal bleeding side effects following prostate cancer brachytherapy. *Int J Radiat Oncol* 2013;86(5):842–847. doi:10.1016/j.ijrobp.2013.04.033.
- [103] Beydoun N, Bucci JA, Chin YS, et al. First report of transperineal polyethylene glycol hydrogel spacer use to curtail rectal radiation dose after permanent iodine-125 prostate brachytherapy. *Brachytherapy* 2013;12(4):368–374. doi:10.1016/j.brachy.2013.01.164.
- [104] Hathout L, Folkert MR, Kollmeier MA, et al. Dose to the bladder neck is the most important predictor for acute and late toxicity after low-dose-rate prostate brachytherapy: implications for establishing new dose constraints for treatment planning. *Int J Radiat Oncol* 2014;90(2):312–319. doi:10.1016/j.ijrobp.2014.06.031.
- [105] Boyce-Fappiano D, Bathala TK, Ye R, et al. Predictors of urinary toxicity with MRI-assisted radiosurgery for low-dose-rate prostate brachytherapy. *Brachytherapy* 2020;19(5):574–583. doi:10.1016/j.brachy.2020.06.011.
- [106] Reed DR, Wallner KE, Merrick GS, et al. A prospective randomized comparison of stranded vs. loose 125I seeds for prostate brachytherapy. *Brachytherapy* 2007;6(2):129–134. doi:10.1016/j.brachy.2007.01.003.
- [107] Sarkar A, Donavanik V, Zhang I, et al. Prostate implant dosimetric outcomes and migration patterns between bio-absorbable coated and uncoated brachytherapy seeds. *Brachytherapy* 2013;12(4):356–361. doi:10.1016/j.brachy.2013.01.163.
- [108] Zelefsky MJ, Cohen GN, Taggar AS, et al. Real-time intraoperative evaluation of implant quality and dose correction during prostate brachytherapy consistently improves target coverage using a novel image fusion and optimization program. *Pract Radiat Oncol* 2017;7(5):319–324. doi:10.1016/j.proro.2017.01.009.
- [109] Westendorp H, Hoekstra CJ, Immerzeel JJ, et al. Cone-beam CT-based adaptive planning improves permanent prostate brachytherapy dosimetry: an analysis of 1266 patients. *Med Phys* 2017;44(4):1257–1267. doi:10.1002/mp.12156.
- [110] Chin J, Rumble RB, Kollmeier M, et al. Brachytherapy for patients with prostate cancer: American society of clinical oncology/cancer care ontario joint guideline update. *J Clin Oncol* 2017. doi:10.1200/JCO.2016.72.0466.
- [111] Mottet N, Bellmunt J, Bolla M, et al. EAU-ESTRO-SIOG guidelines on prostate cancer. part I: screening, diagnosis, and local treatment with curative intent. *Eur Urol* 2017;71(4):618–629. doi:10.1016/j.eururo.2016.08.003.
- [112] Miki K, Kiba T, Sasaki H, et al. Transperineal prostate brachytherapy, using I-125 seed with or without adjuvant androgen deprivation, in patients with intermediate-risk prostate cancer: study protocol for a phase III, multicenter, randomized, controlled trial. *BMC Cancer* 2010;10:572. doi:10.1186/1471-2407-10-572.
- [113] Konaka H, Egawa S, Saito S, et al. Tri-modality therapy with I-125 brachytherapy, external beam radiation therapy, and short- or

- long-term hormone therapy for high-risk localized prostate cancer (TRIP): study protocol for a phase III, multicenter, randomized, controlled trial. *BMC Cancer* 2012;12(1):110. doi:10.1186/1471-2407-12-110.
- [114] Tissaverasinghe S, Crook J, Bachand F, et al. Dose to the dominant intraprostatic lesion using HDR vs. LDR monotherapy: a phase II randomized trial. *Brachytherapy* 2019;18(3):299–305. doi:10.1016/j.brachy.2019.01.006.
- [115] Register SP, Kudchadker RJ, Levy LB, et al. An MRI-based dose-response analysis of urinary sphincter dose and urinary morbidity after brachytherapy for prostate cancer in a phase II prospective trial. *Brachytherapy* 2013;12(3):210–216. doi:10.1016/j.brachy.2012.10.006.
- [116] Orio PF, Merrick GS, Galbreath RW, et al. Patient-reported long-term rectal function after permanent interstitial brachytherapy for clinically localized prostate cancer. *Brachytherapy* 2012;11(5):341–347. doi:10.1016/j.brachy.2012.02.005.
- [117] Liauw SL, Kropp LM, Dess RT, Oto A. Endorectal MRI for risk classification of localized prostate cancer: radiographic findings and influence on treatment decisions. *Urol Oncol* 2016;34(9):416.e15–416.e21. doi:10.1016/j.urolonc.2016.04.014.
- [118] Perera M, Papa N, Roberts M, et al. Gallium-68 prostate-specific membrane antigen positron emission tomography in advanced prostate cancer—updated diagnostic utility, sensitivity, specificity, and distribution of prostate-specific membrane antigen-avid lesions: a systematic review and meta-analysis. *Eur Urol* 2020;77(4):403–417. doi:10.1016/j.eururo.2019.01.049.
- [119] Hofman MS, Lawrentschuk N, Francis RJ, et al. Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study. *The Lancet* 2020;395(10231):1208–1216. doi:10.1016/S0140-6736(20)30314-7.
- [120] Nguyen PL, Haddad Z, Ross AE, et al. Ability of a genomic classifier to predict metastasis and prostate cancer-specific mortality after radiation or surgery based on needle biopsy specimens. *Eur Urol* 2017;72(5):845–852. doi:10.1016/j.eururo.2017.05.009.
- [121] Spratt DE, Zhang J, Santiago-Jiménez M, et al. Development and validation of a novel integrated clinical-genomic risk group classification for localized prostate cancer. *J Clin Oncol* 2018;36(6):581–590. doi:10.1200/JCO.2017.74.2940.
- [122] Kudchadker RJ, Swanson DA, Kuban DA, et al. Is a loose-seed nomogram still valid for prostate brachytherapy in a stranded-seed era? *Int J Radiat Oncol* 2008;72(2):623–627. doi:10.1016/j.ijrobp.2008.03.001.
- [123] Hanania AN, Kudchadker RJ, Bruno TL, et al. MRI-assisted radiosurgery: a quality assurance nomogram for palladium-103 and iodine-125 prostate brachytherapy. *Brachytherapy* 2020;19(1):38–42. doi:10.1016/j.brachy.2019.10.002.
- [124] Sanders JW, Lewis GD, Thames HD, et al. Machine segmentation of pelvic anatomy in MRI-assisted radiosurgery (MARS) for prostate cancer brachytherapy. *Int J Radiat Oncol* 2020. doi:10.1016/j.ijrobp.2020.06.076.
- [125] Nicolae A, Semple M, Lu L, et al. Conventional vs machine learning-based treatment planning in prostate brachytherapy: results of a phase I randomized controlled trial. *Brachytherapy* 2020. doi:10.1016/j.brachy.2020.03.004.
- [126] Orio PF, Nguyen PL, Buzurovic I, et al. Prostate brachytherapy case volumes by academic and nonacademic practices: implications for future residency training. *Int J Radiat Oncol* 2016;96(3):624–628. doi:10.1016/j.ijrobp.2016.07.013.
- [127] Ferro A, Bae HJ, Yenokyan G, et al. Reductions in prostatic doses are associated with less acute morbidity in patients undergoing Pd-103 brachytherapy: substantiation of the rationale for focal therapy. *Brachytherapy* 2018;17(2):313–318. doi:10.1016/j.brachy.2017.10.008.
- [128] Dutta SW, Bauer-Nilsen K, Sanders JC, et al. Time-driven activity-based cost comparison of prostate cancer brachytherapy and intensity-modulated radiation therapy. *Brachytherapy* 2018;17(3):556–563. doi:10.1016/j.brachy.2018.01.013.
- [129] Vu CC, Jawad MS, Krauss DJ. The Cost-effectiveness and value proposition of brachytherapy. *Semin Radiat Oncol* 2020;30(1):87–93. doi:10.1016/j.semradonc.2019.08.007.