

# Brachytherapy for Patients With Prostate Cancer: American Society of Clinical Oncology/Cancer Care Ontario Joint Guideline Update

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†The Update Panel and ASCO staff dedicate this guideline to the memory of Arthur Jacques, our dearly departed patient representative and Update Panel member.

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Editor's note: This American Society of Clinical Oncology (ASCO)/Cancer Care Ontario (CCO) Joint Guideline Update provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, which may include a Data Supplement, Methodology Supplement, slide sets, clinical tools and resources, and links to patient information at [www.cancer.net](http://www.cancer.net), is available at [www.asco.org/Brachytherapy-guideline](http://www.asco.org/Brachytherapy-guideline) and [www.asco.org/guidelineswiki](http://www.asco.org/guidelineswiki).

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## ASSOCIATED CONTENT

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## ABSTRACT

### Purpose

To jointly update the Cancer Care Ontario guideline on brachytherapy for patients with prostate cancer to account for new evidence.

### Methods

An Update Panel conducted a targeted systematic literature review and identified more recent randomized controlled trials comparing dose-escalated external beam radiation therapy (EBRT) with brachytherapy in men with prostate cancer.

### Results

Five randomized controlled trials provided the evidence for this update.

### Recommendations

For patients with low-risk prostate cancer who require or choose active treatment, low-dose rate brachytherapy (LDR) alone, EBRT alone, and/or radical prostatectomy (RP) should be offered to eligible patients. For patients with intermediate-risk prostate cancer choosing EBRT with or without androgen-deprivation therapy, brachytherapy boost (LDR or high-dose rate [HDR]) should be offered to eligible patients. For low-intermediate risk prostate cancer (Gleason 7, prostate-specific antigen < 10 ng/mL or Gleason 6, prostate-specific antigen, 10 to 20 ng/mL), LDR brachytherapy alone may be offered as monotherapy. For patients with high-risk prostate cancer receiving EBRT and androgen-deprivation therapy, brachytherapy boost (LDR or HDR) should be offered to eligible patients. Iodine-125 and palladium-103 are each reasonable isotope options for patients receiving LDR brachytherapy; no recommendation can be made for or against using cesium-131 or HDR monotherapy. Patients should be encouraged to participate in clinical trials to test novel or targeted approaches to this disease.

Additional information is available at [www.asco.org/Brachytherapy-guideline](http://www.asco.org/Brachytherapy-guideline) and [www.asco.org/guidelineswiki](http://www.asco.org/guidelineswiki).

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## INTRODUCTION

The goal of this update is to provide oncologists, other health care practitioners, patients, and caregivers with recommendations regarding the use of brachytherapy for patients with prostate cancer that includes the most recent evidence. Prostate cancer is the most commonly diagnosed cancer in men. In 2016, it is estimated that there will be 180,890 new cases, along with an estimated 26,120 deaths.<sup>1</sup> For this reason, there is great interest in finding optimum treatment strategies to reduce the burden of disease in this patient population.

The Cancer Care Ontario systematic review<sup>2</sup> and clinical practice guideline<sup>3</sup> on low-dose rate (LDR) brachytherapy for patients with low- or intermediate-risk prostate cancer were both published in 2013, and since then randomized evidence has been made available that might alter the original recommendations. The goal of this joint update is to consider this new evidence and determine if the original recommendations remain valid or if updates are warranted.

The scope of this guideline covers brachytherapy boost and monotherapy. Currently, the American Society for Radiation Oncology, ASCO, and the American Urologic Association

## THE BOTTOM LINE

**Brachytherapy for Patients With Prostate Cancer: American Society of Clinical Oncology/Cancer Care Ontario Joint Guideline Update****Guideline Questions**

1. In patients with newly diagnosed prostate cancer, what is the efficacy of brachytherapy alone for clinical outcomes compared with external beam radiation therapy (EBRT) alone or radical prostatectomy (RP) alone?
2. In patients with newly diagnosed prostate cancer, what is the efficacy of brachytherapy combined with EBRT for clinical outcomes compared with brachytherapy alone, EBRT alone, or RP alone?
3. Among the isotopes used for low-dose rate (LDR) brachytherapy (eg, iodine-125 [ $^{125}\text{I}$ ], palladium-103 [ $^{103}\text{Pd}$ ], and cesium-131 [ $^{131}\text{Cs}$ ]), which isotope maximizes clinical outcomes when used in patients with newly diagnosed prostate cancer?

**Target Population**

Patients with newly diagnosed prostate cancer who require or choose active treatment and are not considering, or are not suitable for, active surveillance.

**Target Audience**

Radiation oncologists, urological surgeons, and other clinicians who provide care for patients defined by the target population.

**Methods**

A systematic review of the literature was performed and relevant evidence was evaluated for inclusion into this updated clinical practice guideline using the signals approach.

**Updated Recommendations**

- For patients with low-risk prostate cancer who require or choose active treatment, LDR alone, EBRT alone, or RP should be offered to eligible patients
- For patients with intermediate-risk prostate cancer choosing EBRT with or without androgen-deprivation therapy (ADT), brachytherapy boost (LDR or high-dose rate [HDR]) should be offered to eligible patients. For low-intermediate risk prostate cancer (Gleason 7, prostate-specific antigen < 10 ng/mL or Gleason 6, prostate-specific antigen, 10 to 20 ng/mL) LDR brachytherapy alone may be offered as monotherapy. For patients with high-risk prostate cancer receiving EBRT and ADT, brachytherapy boost (LDR or HDR) should be offered to eligible patients.
- $^{125}\text{I}$  and  $^{103}\text{Pd}$  are each reasonable isotope options for patients receiving LDR brachytherapy; no recommendation can be made for or against using  $^{131}\text{Cs}$  or HDR monotherapy.
- Patients should be encouraged to participate in clinical trials to test novel or targeted approaches to this disease.

**Qualifying Statements**

- Patients should be counseled about all their management options (surgery, EBRT, active surveillance, as applicable) in a balanced, objective manner, preferably from multiple disciplines.
- Recommendation for low-risk patients is unchanged from initial guideline, because no new randomized data informing this question have been presented or published since.
- Patients ineligible for brachytherapy may include: moderate to severe baseline urinary symptoms, large prostate volume, medically unfit, prior transurethral resection of the prostate, and contraindications to radiation treatment.
- ADT may be given in neoadjuvant, concurrent, and/or adjuvant settings at physician discretion. It is noted that neoadjuvant ADT may cytoreduce the prostate volume sufficiently to allow brachytherapy
- There may be increased genitourinary toxicity compared with EBRT alone.
- Brachytherapy should be performed at a center following strict quality-assurance standards.
- It cannot be determined whether there is an overall or cause-specific survival advantage for brachytherapy compared with EBRT alone, because none of the trials were designed or powered to detect a meaningful difference in survival outcomes.

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## THE BOTTOM LINE (CONTINUED)

**Additional Resources**

Additional information is available at [www.asco.org/Brachytherapy-guideline](http://www.asco.org/Brachytherapy-guideline) and [www.asco.org/guidelineswiki](http://www.asco.org/guidelineswiki). Patient information is available at [www.cancer.net](http://www.cancer.net).

**ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate**

are performing a joint review of hypofractionated radiotherapy (including stereotactic ablative body radiotherapy [SABR]).

## UPDATED GUIDELINE RESEARCH QUESTIONS

1. In patients with prostate cancer, what is the efficacy of brachytherapy alone for clinical outcomes compared with external beam radiation therapy (EBRT) alone or radical prostatectomy (RP) alone?
2. In patients with prostate cancer, what is the efficacy of brachytherapy combined with EBRT for clinical outcomes compared with brachytherapy alone, EBRT alone, or RP alone?
3. Among the isotopes used for low-dose rate brachytherapy (eg,  $^{125}\text{I}$ ,  $^{103}\text{Pd}$ , and  $^{131}\text{Cs}$ ), which isotope maximizes clinical outcomes when used in patients with newly diagnosed prostate cancer?

## METHODS

**Guideline Update Process**

ASCO uses a “signals”<sup>4</sup> approach to facilitate guideline updating. This approach is intended to identify new, potentially practice-changing data—signals—that might translate into revised practice recommendations. The approach relies on routine literature searching and the expertise of ASCO guideline panel members to identify signals. The Methodology Supplement (available at: [www.asco.org/Brachytherapy-guideline](http://www.asco.org/Brachytherapy-guideline)) provides additional information about the signals approach.

For this update, the signal was the presentation of a randomized controlled trial (RCT) reported by Morris et al,<sup>5,6</sup> comparing dose-escalated (DE)-EBRT with LDR brachytherapy boost (LDR-B) that could potentially expand the patient population to whom the original recommendations would apply. The full Update Committee was then convened to review the evidence.

Prognostication for nonmetastatic prostate cancer is strongly associated with risk category. Localized prostate cancer is divided into low-, intermediate-, and high-risk disease.<sup>7,8</sup> Intermediate-risk prostate cancer is known to have heterogeneous outcomes, and recently there are subclassifications that refine this category into low-intermediate and high-intermediate risk categories. Two classifications commonly referred to are the Memorial Sloan Kettering group modification of the National Comprehensive Cancer Network<sup>9</sup> and the Prostate Cancer Risk Stratification (ProCaRS).<sup>10</sup> Where reported, these classifications are summarized.

Androgen-deprivation therapy (ADT) is a standard for patients with high-risk prostate cancer treated with radiotherapy and can be considered for those with intermediate-risk disease.<sup>11</sup> Where reported, use and duration of ADT was also summarized.

Evidence was also collected through a systematic review of the medical literature. Publications were included if they were phase III randomized clinical trials of brachytherapy compared with either EBRT or RP in men with prostate cancer. These publications were identified by rerunning the original strategy in MEDLINE, EMBASE, and the Cochrane database of systematic reviews, for the period from the original search in 2011 through to the end of August 2015. A final search for important papers was made in December 2016. Of the 32 publications identified, six<sup>3,6,12-15</sup> publications (addressing five RCTs) met the eligibility criteria and form the evidence base for this update.

The Update Committee contributed to the development of the guideline, provided critical review, and finalized the guideline recommendations. All ASCO guidelines are reviewed and approved by the ASCO Clinical Practice Guidelines Committee.

**Guideline Disclaimers**

The Clinical Practice Guidelines and other guidance published herein are provided by the American Society of Clinical Oncology, Inc (ASCO) to assist providers in clinical decision making. The information herein should not be relied upon as being complete or accurate, nor should it be considered as inclusive of all proper treatments or methods of care or as a statement of the standard of care. With the rapid development of scientific knowledge, new evidence may emerge between the time information is developed and when it is published or read. The information is not continually updated and may not reflect the most recent evidence. The information addresses only the topics specifically identified therein and is not applicable to other interventions, diseases, or stages of diseases. This information does not mandate any particular course of medical care. Further, the information is not intended to substitute for the independent professional judgment of the treating provider, as the information does not account for individual variation among patients. Recommendations reflect high, moderate, or low confidence that the recommendation reflects the net effect of a given course of action. The use of words like “must,” “must not,” “should,” and “should not” indicates that a course of action is recommended or not recommended for either most or many patients, but there is latitude for the treating physician to select other courses of action in individual cases. In all cases, the selected course of action should be considered by the treating provider in the context of treating the individual patient. Use of the information is voluntary. ASCO provides this information on an “as is” basis and makes no warranty, express or implied, regarding the information. ASCO specifically disclaims any warranties of merchantability or fitness for a particular use or purpose. ASCO assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this information or for any errors or omissions.

This is the most recent information as of the publication date. For the most recent information, and to submit new evidence, please visit [www.asco.org/Brachytherapy-guideline](http://www.asco.org/Brachytherapy-guideline) and the ASCO Guidelines Wiki ([www.asco.org/guidelineswiki](http://www.asco.org/guidelineswiki)).

Care has been taken in the preparation of the information contained herein. Nevertheless, any person seeking to consult the report or apply its recommendations is expected to use independent medical judgment in the context of individual clinical circumstances or to seek out the supervision

of a qualified clinician. CCO makes no representations or guarantees of any kind whatsoever regarding the report content or its use or application and disclaims any responsibility for its use or application in any way.

### Guideline and Conflicts of Interest

The Update Panel (Appendix Table A1, online only) was assembled in accordance with ASCO's Conflict of Interest Management Procedures for Clinical Practice Guidelines ("Procedures," summarized at <http://www.asco.org/rwc>). Members of the Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests that are relevant to the subject matter of the guideline, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Procedures, the majority of the members of the Panel did not disclose any such relationships.

## RESULTS

Five<sup>5,6,12-15</sup> RCT reports were obtained for this targeted update. All five of these trials were randomized; three<sup>12-14</sup> were available in fully published form, one<sup>6</sup> was available as both a fully published paper that reported on efficacy outcomes and an abstract<sup>5</sup> that reported on the toxicity outcomes, and one<sup>15</sup> was available in abstract form only. Four<sup>5,12,13,15</sup> of these trials were phase III, and the trial reported by Morton et al<sup>14</sup> was described as being a phase II trial. All efficacy outcomes for the four trials<sup>5,12,13,15</sup> that compared EBRT with brachytherapy are reported in Table 1; adverse effects are reported in Table 2. The earliest trial, the fully published phase III trial reported by Sathya et al<sup>13</sup> in 2005, randomly assigned 104 patients with T2 to 3 nonmetastatic prostate cancer to either EBRT (four-field box radiation to the prostate and seminal vesicles with a 2-cm margin at 66 Gy total dose given in 33 fractions over 6.5 weeks; n = 53) or brachytherapy boost (iridium implant, 35 Gy over 48 hours) with EBRT (40 Gy, 20 fractions over 4 weeks; n = 51). Use of concurrent ADT was not reported. Patients were stratified by age, prostate-specific antigen (PSA) levels, Gleason score, tumor stage (T2 v T3), and risk status (intermediate v high). The primary outcome for this trial was biochemical or clinical failure (which was defined as biochemical failure, clinical failure, or death resulting from prostate cancer), and a statistically significant benefit in favor of the EBRT with brachytherapy arm was detected (hazard ratio [HR], 0.42;  $P = .0024$ ) after a median reported follow-up of 98 months.<sup>16</sup> While the authors report that the treatment effect was greater in the intermediate-risk group compared with the high-risk group, the difference between the HR for biochemical or clinical failure was not significant; however, when adjusted for age, baseline PSA, Gleason score, and tumor stage, the treatment effect (brachytherapy boost v EBRT alone) was more pronounced (HR, 0.31; 95% CI, 0.17 to 0.58;  $P = .0002$ ). No differences in the toxicity profile between the two arms were detected.

The second trial, the fully published phase III trial first reported by Hoskin et al<sup>12</sup> in 2007, randomly assigned 220 patients with histologically confirmed T1 to 3 prostate cancer, no evidence of metastases, PSA < 50, no previous transurethral resection of the

prostate, and fitness for general anesthesia to either EBRT (given as either three-field without shaped blocks [54% of patients] or three-dimensional volumetric planning and conformal three-field plans [46% of patients] at 55 Gy given in 20 fractions; n = 111) or EBRT (35.75 Gy, 13 fractions) with high-dose rate brachytherapy boost (HDR-B; iridium implant delivering a total of 17 Gy in two fractions over 24 hours; n = 109). Patients were stratified according to tumor stage, PSA levels, and Gleason scores. Neoadjuvant and concurrent ADT (duration not specified) were used in 76% of patients. The primary outcome of interest was biochemical disease-free survival (bDFS), and a statistically significant benefit in favor of the EBRT/HDR-B was detected (HR, 0.76;  $P = .03$ ) after a median follow-up of 30 months. This benefit in favor of the addition of brachytherapy to EBRT was also shown in the comparisons between the tumor stage, PSA levels, and Gleason score groups. No difference was detected in acute toxicity scores between the two arms for grade 2 or higher late bowel or bladder reactions. Health-related quality-of-life scores between the two arms detected a benefit in favor of EBRT/HDR-B ( $P = .025$ ) as assessed by the Functional Assessment of Cancer Therapy-Prostate instrument. A second report with a median follow-up of 85 months continued to show superiority of EBRT/HDR-B over EBRT (HR, 0.69;  $P = .04$ ).<sup>17</sup>

The third trial, a phase III trial, reported in both fully published<sup>6</sup> and abstract form<sup>5</sup> by Morris et al,<sup>5,6</sup> randomly assigned 398 patients with intermediate- and high-risk prostate cancer to either DE-EBRT (whole pelvis EBRT: 46 Gy, 23 fractions followed by conformal EBRT to prostate: 32 Gy, 16 fractions; n = 200) or LDR-B (whole pelvis EBRT: 46 Gy, 23 fractions followed by an <sup>125</sup>I boost to a minimum dose of 115 Gy to prostate; n = 198). Patients were stratified by risk category (intermediate v high risk). Twelve months (8 months neoadjuvant, 2 months concurrent, 2 months adjuvant) of ADT was used in all patients. The primary outcome was bDFS as defined by biochemical criteria using the Phoenix (nadir + 2 ng/mL) threshold. After a median follow-up of 78 months, a statistically significant benefit in favor of EBRT/LDR-B was detected (log-rank  $P < .001$ ). Multivariate analysis confirmed brachytherapy boost (but not risk category) as an independent predictor of bDFS. Assessment of the 5-year cumulative incidence of late grade 3 or higher toxicity detected a significant benefit in grade 3 genitourinary (GU) effects in favor of treatment with DE-EBRT ( $P < .001$ ) but not in grade 4 GU or in grade 3 or higher GI effects.<sup>5</sup> Quality of life was prospectively collected using the Short Form-36 instrument, which assessed physical function, role physical, bodily pain, general health, vitality, social functioning, and emotional and mental health. Additional items to gather data on urinary function, bowel function, and sexual function were added. All items were scored on a scale from 0 to 100. Baseline scores were balanced between treatment arms, but area under the curve differences were detected for bodily pain ( $P = .04$ ), general health ( $P = .01$ ), sexual function ( $P = .02$ ), and urinary function ( $P = .006$ ) in favor of treatment with DE-EBRT over LDR-PB.<sup>18</sup> No health-related quality-of-life differences were detected for any other domains.

The fourth trial, a phase III trial reported in abstract form only by Prestidge et al<sup>15</sup> in 2016, randomly assigned 588 patients with low-intermediate risk prostate cancer (Gleason 6, PSA 10 to 20 ng/mL or Gleason 7, PSA < 10 ng/mL) 1:1 to EBRT (45 Gy, 25 fractions mini-pelvis) with LDR boost (110 Gy <sup>125</sup>I or 100 Gy <sup>103</sup>Pd) or LDR alone (145 Gy or 125 Gy, respectively). The primary outcome

Table 1. Results

RCT	Treatment (dose)	No. Patients, Risk Group if Reported	Median Age (years)	Median Follow-Up Time (months)	Primary Outcome	OS Rate	PCSM (No., %)	MFSR (No., %)
Prestidge <sup>15</sup> RTOG 0232 2003-2012 (abstract)	EBRT LDR-B	287 292 Low-intermediate: 588		80.4	5-yr PFS: 85% (95% CI, 80% to 89%)† 5-yr PFS: 86% (95% CI, 81% to 90%)† HR, 1.02; <i>P</i> < .001 for fertility			
Morris <sup>5,6</sup> ASCENDE-RT 2002-2011*	LDR-B  DE-EBRT	198  200  Low-intermediate: 2; high-intermediate: 120; high: 276	68	78†	bDFS: 3-yr, 94% 5-yr, 89% 7-yr, 86% 9-yr, 83%  bDFS: 3-yr, 94%; 5-yr, 84%; 7-yr, 75%; 9-yr, 62% Log-rank <i>P</i> < .001	3-yr, 91% 5-yr, 86% 7-yr, 78%  3-yr, 89% 5-yr, 82% 7-yr, 74%  <i>P</i> = .29	7 (3.5)  11 (5.5)  <i>P</i> = .32	17 (8.5)  18 (9)  <i>P</i> = .83
Hoskin <sup>12</sup> 1997-2005*	EBRT-HDB EBRT	109 111 Low: 9; intermediate: 91; high: 116	68.9 (47-79)	30	bDFS: 5.1 yr (95% CI, 4.6 to 5.5) bDFS: 4.3 yr (95% CI, 3.8 to 4.8) <i>P</i> = .04	7-yr, 81% 7-yr, 88% <i>P</i> = .2	NR	NR
Sathya <sup>13</sup> 1992-1997	EBRT-B EBRT	51 53 Intermediate: 42; high: 62	65 (49-74) 66 (57-74)	98.4	BCF: 71% BCF: 39% HR, 0.42; 95% CI, 0.23 to 0.75; <i>P</i> = .0024	NR	NR	NR

Abbreviations: B, brachytherapy; BCF, biochemical failure; bDFS, biochemical disease-free survival; DE-EBRT, dose-escalated external beam radiotherapy; EBRT, external beam radiotherapy; EBRT-B, external beam radiotherapy plus brachytherapy; HDB, high-dose brachytherapy; HR, hazard ratio; LDR-B, low-dose rate brachytherapy; MFSR, metastasis-free survival rate; NR, not reported; OS, overall survival; PCSM, prostate cancer-specific mortality; PFS, progression-free survival; PSA, prostate-specific antigen; RCT, randomized controlled trial; RTOG, Radiation Therapy Oncology Group.

\*Definitions of biochemical disease-free survival: Morris et al<sup>5,6</sup>: Phoenix nadir + 2 ng/mL; Hoskin et al<sup>12</sup>: ASTRO, defined as three consecutive PSA increases after a nadir with the date of failure as the point halfway between the nadir date and the first increase or any increase great enough to provoke initiation of therapy; Sathya et al<sup>13</sup>: ASTRO as above.

†Comprising clinic visits every 6 months until 5 years (yearly thereafter) for prospective collection of patient- and physician-reported adverse effects, complications, and quality of life; PSA and testosterone levels measured every 6 months to assess predefined primary end point of PFS standard nadir + 2 ng/mL (Phoenix) threshold.

was progression-free survival (PFS; American Society for Radiation Oncology nadir + 2 biochemical failure, clinical failure, or death from any cause). After 6.7 years of median follow-up, the independent Data Monitoring Committee recommended releasing the data after the fifth interim analysis. There was no difference in 5-year PFS (85% *v* 86%; HR, 1.02; fertility *P* < .001). There were no differences in acute grade 3 or higher toxicity (8% in each arm) but worse grade 3 or higher late toxicity in the brachytherapy boost arm (12% *v* 7% overall; 7% *v* 3% for GU; 3% *v* 2% for GI; no *P* values provided).

The fifth trial, a phase II trial reported by Morton et al<sup>14</sup> in 2016, randomly assigned 170 patients with low- and intermediate-risk prostate cancer to two HDR monotherapy regimens (ie, no EBRT was used). Patients received 27 Gy, two fractions over 1 week or 19 Gy in a single fraction. Eligible patients also had a prostate volume < 60 mL, International Prostate Symptom Score ≤ 18, no previous prostate surgery, and no use of ADT. The primary outcome was grade 2 or higher toxicity. After a median follow-up of 20 months, the only significant difference in acute toxicity detected between the treatment arms was for fatigue in favor of the single fraction (16% *v* 32%; *P* = .029). There were no differences in acute grade 2 or higher GU toxicity, acute grade 2 or higher GI toxicity, or quality of life (measured by Expanded Prostate Index Composite every 6 months). For late toxicity, a difference was detected between treatment arms in favor of the single fraction for

grade 2 erectile dysfunction (12% *v* 29%; *P* = .025). No differences in late GI toxicity were reported. bDFS was not reported.

There may be higher late GU toxicities associated with LDR-B compared with HDR-B. In the ASCENDE-RT<sup>5</sup> study, there were 20% grade 3 to 4 GU toxicities, half of which were due to urinary strictures requiring dilatation (S. Tyldesley, personal communication, November 2015). In the Hoskin et al study, 6% of patients in the HDR boost arm had urethral stricture at 5 years post-treatment.<sup>17</sup> In a widely used dose fractionation scheme internationally (HDR-B 15 Gy in one fraction followed by EBRT 37.5 Gy, 15 fractions), there was 0.8% grade 3 to 4 GU toxicity (0% strictures).<sup>19</sup> The differences in toxicity between these brachytherapy procedures may be due to relative dose sparing of the membranous urethra, which is associated with lower stricture rates. However, because cross-trial comparisons should only be used for hypothesis generation, we will have to await the results of randomized data. The Canadian Cancer Trials Group launched a national phase III LDR versus HDR monotherapy RCT in 2016 ([clinicaltrials.gov](https://clinicaltrials.gov) NCT pending).

#### UPDATED RECOMMENDATIONS

Please refer to the Bottom Line Box for the updated recommendations and the accompanying Qualifying Statements.



Table 2. Adverse Effects

RCT	Treatment (dose)	No. of Patients	Genitourinary Toxicity		GI Toxicity	
			Grade 3	Grade 4	Grade 3	Grade 4
Prestidge <sup>15</sup>	LDR-B	292	3%		3%	
RTOG 0232	EBRT	287	7%		2%	
2003-2012 (abstract)			<i>P</i> = NR		<i>P</i> = NR	
Morris <sup>5</sup>	LDR-B	198	19%	1%	9%	1%
ACENDE-RT	DE-EBRT	200	5%	1%	4%	0
2002-2011 (abstract)			<i>P</i> < .001	<i>P</i> = .547	<i>P</i> = .12	<i>P</i> = NR
			5-year cumulative incidence (worst grade recorded)	5-year cumulative incidence (worst grade recorded)	5-year cumulative incidence (worst grade recorded)	5-year cumulative incidence (worst grade recorded)
Hoskin <sup>12</sup>	EBRT-HDB	109	31		7	
1997-2005	EBRT	111	30		6	
			<i>P</i> = .5		<i>P</i> = .8	
Sathya <sup>13</sup>	EBRT-B	51	13.7%		3.9%	
1992-1997	EBRT	53	3.8%		1.9%	
			<i>P</i> = .09		<i>P</i> = .61	
			> 18 months, any grade 3 or 4		> 18 months, any grade 3 or 4	

NOTE: Adverse effects scales used: Morris et al<sup>5</sup>; Late Effects Normal Tissue Task Force–Subjective, Objective, Management, Analytic; Hoskin et al<sup>12</sup>; RTOG and Common Toxicity Criteria Version 3.0; Sathya et al<sup>13</sup>; National Cancer Institute of Canada Clinical Trials Group Expanded Common Toxicity Criteria. Abbreviations: DE-EBRT, dose-escalated external beam radiotherapy; EBRT-B, external beam radiotherapy plus brachytherapy; HDB, high-dose brachytherapy; LDR-B, low-dose rate brachytherapy; NR, not reported; RCT, randomized controlled trial; RTOG, Radiation Therapy Oncology Group.

## COST CONSIDERATIONS

ASCO recognizes that there is often a wide array of choices for treating many cancer types, with often a wide disparity in cost to patients and payers (despite much difference in effectiveness or toxicity).<sup>20</sup> Halpern et al<sup>21</sup> reported that of the radiation modalities used in the treatment of prostate cancer, from the Medicare payer perspective, LDR brachytherapy is the cheapest (compared with SABR, EBRT, or protons). Helou et al<sup>22</sup> showed that in the Canadian health care context, SABR had the higher quality-adjusted life-years and was more cost effective compared with LDR (and both were better than EBRT). Further work is needed to articulate cost, cost-effectiveness, and cost-utility differences between the various prostate cancer treatment approaches.

## LIMITATIONS OF THE RESEARCH

There are four<sup>5,12,13,15</sup> small- to medium-sized RCTs addressing the question of brachytherapy boost. The largest and most contemporaneously relevant (because the control arm used an external beam dose of 78 Gy in 39 fractions) trial (ASCENDE-RT, Morris

et al<sup>5,6</sup>) has published the survival outcomes;<sup>6</sup> however, the toxicity data are only available in abstract form. When the toxicity data are published, these guidelines recommendations will have to be revised if the toxicities are significantly higher than was presented to date.

There are also insufficient data for comment on a meaningful difference in overall survival, because all trials were powered for PFS only. The guideline panel will re-evaluate the recommendations as new data emerge, especially from the ASCENDE-RT and Radiation Therapy Oncology Group 0232 trials.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at [jco.org](http://jco.org).

## AUTHOR CONTRIBUTIONS

**Manuscript writing:** All authors

**Final approval of manuscript:** All authors

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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

## Brachytherapy for Patients With Prostate Cancer: American Society of Clinical Oncology/Cancer Care Ontario Joint Guideline Update

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### Appendix

**Table A1.** Update Panel Membership

Member	Affiliation
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Abbreviations: ASCO, American Society of Clinical Oncology; CCO, Cancer Care Ontario; PGIN, Practice Guideline Implementation Network.

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