Evidence-Based Series 3-10 Version 2

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Low-Dose Rate Brachytherapy for Patients with Low- or Intermediate-Risk Prostate Cancer

G. Rodrigues, X. Yao, A. Loblaw, M. Brundage, J. Chin, and the Genitourinary Cancer Disease Site Group

Report Date: October 31, 2012

An assessment conducted in November 2015 deferred the review of Evidence-based Series (EBS) 3-10 Version 2. This means that the document remains current until it is assessed again next year. The PEBC has a formal and standardize process to ensure the currency of each document (PEBC Assessment & Review Protocol).

This Evidence-Based Series (EBS), which is available on the CCO Website, consists of the following three sections:

- **Section 1:** Guideline Recommendations
- **Section 2:** Evidentiary Base
- **Section 3:** Development Methods, Recommendations Development and External Review Process

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Evidence-Based Series 3-10 Version 2: Section 1

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Low-Dose Rate Brachytherapy for Patients with Low- or Intermediate-Risk Prostate Cancer: Guideline Recommendations

G. Rodrigues, X. Yao, A. Loblaw, M. Brundage, J. Chin, and the Genitourinary Cancer Disease Site Group

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TARGET POPULATION
Patients with newly diagnosed low- or intermediate-risk prostate cancer (low-risk patients are defined as having a prostate-specific antigen [PSA] < 10 ng/ml, clinical stage T1c-T2a, and Gleason score < 7; intermediate-risk patients are defined as having a PSA ≥10 ng/ml but < 20 ng/ml or a clinical stage T2b-T2c or a Gleason score = 7) who require or choose active treatment and are not considering or are not suitable for active surveillance.

QUESTIONS
1. What is the efficacy of low-dose rate brachytherapy (LDR-BT) alone for clinical outcomes (i.e., biochemical relapse-free survival [bRFS], overall survival [OS] or overall mortality [OM], prostate cancer-specific mortality [PCSM], negative biopsy rate, salvage treatment rate, toxicity, or patient-reported outcomes including quality of life [QOL]) compared with external beam radiation therapy (EBRT) alone, or radical prostatectomy (RP) alone?
2. What is the efficacy of LDR-BT combined with EBRT for clinical outcomes compared with LDR-BT alone, EBRT alone, or RP alone?
3. Among three isotopes used for LDR-BT (Iodine-125 [I-125], Palladium-103 [Pd-103], and Cesium-131 [Cs-131]), which isotope maximizes clinical outcomes?

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

INTRODUCTION
In 2001, the Genitourinary Disease Site Group (DSG) and the PEBC in Ontario, Canada, developed a guideline on LDR-BT in patients with early-stage low-grade prostate cancer (EBS 3-10 The Use of Brachytherapy in T1 or T2 Prostate Cancer) (1). Since the main evidence in the 2001 guideline was from single-arm studies and stronger levels of evidence such as comparative studies or randomized controlled trials (RCTs) have become available during the last decade, an updated guideline has been deemed necessary. To date, the following three
isotopes are available for LDR-BT in patients with prostate cancer: I-125, Pd-103, and Cs-131, each having a different half-life time: 59.4 days, 17.0 days, and 9.7 days, respectively (2). It is unclear which isotope maximizes clinical outcomes when used in patients with newly diagnosed low- or intermediate-risk prostate cancer. This current updated guideline focuses on the above three research questions regarding LDR-BT alone, LDR-BT with EBRT, and selection of an isotope. As noted in the questions, the target patients for this guideline are those who require or choose active treatment and not those who are considering and are suitable for active surveillance. A separate guideline (EBS 17-9 Active Surveillance for the Management of Localized Low-Risk Prostate Cancer) is being developed by the PEBC and will be available on the CCO web site in 2013.

RECOMMENDATIONS AND KEY EVIDENCE

The Genitourinary DSG and the PEBC offer the following recommendations based on the current evidence assessed in conjunction with this systematic review:

- For patients with newly diagnosed low-risk or intermediate-risk prostate cancer who require or choose active treatment, LDR-BT alone is a treatment option as an alternative to EBRT alone or RP alone.
- I-125 and Pd-103 are each reasonable isotope options in patients with prostate cancer.
- No recommendation can be made for or against using Cs-131 or the combination of EBRT and LDR-BT in the target patient population.
- Patients should be encouraged to participate in clinical trials to test novel or targeted approaches to this disease.

Qualifying Statement

- The following LDR-BT doses were suggested from the included studies when LDR-BT was used alone: 140-160 Gray for I-125 or 108-125 Gray for Pd-103.
- LDR-BT monotherapy may not be appropriate for all patients with intermediate-risk disease. Patients with multiple risk factors (PSA > 10 ng/ml, Gleason score 7, Gleason primary pattern 4, T2c disease, and high positive core positivity) may be more appropriately treated with other modalities (or combinations of modalities). The exact definition for high-intermediate disease has not yet appeared in the literature or been agreed upon by other consensus approaches.
- Patient preference should be considered in treatment selection due to the different approaches involved with these three treatments (LDR-BT, EBRT, and RP) and their different acute and long-term impacts on patients.
- The 2012 National Comprehensive Cancer Network (NCCN) guideline (3) and the 2012 American Brachytherapy Society consensus guideline (4) may provide clinicians with broader information about LDR-BT implementation in clinical practice beyond the scope of this guideline, including patient selection for LDR-BT (absolute or relative contraindications) and details of the intraoperative procedure.

Key Evidence

- There were 10 systematic reviews (5-14) and 55 study articles (15-69) included in this guideline; 36 articles summarized in Section 2. Tables 2 to 4 were the primary evidence base on which the recommendations were made. Among them, six articles reported on three RCTs, 14 on prospective studies, and 16 on retrospective studies. The quality of evidence from the included studies was considered to be low to moderate.
- For bRFS at ≥ 5 years:
  - LDR-BT compared with EBRT: Three retrospective studies with 1529 patients showed there were no significant differences between the two groups (20,25,60). One of these
retrospective studies reported \( p > 0.25 \) in low-risk patients (25); another one reported the bRFS rate as 90% for LDR-BT and 86% for EBRT (\( p = 0.969 \)) in intermediate-risk patients (60); the third one reported a hazard ratio (HR) of 1.04 (95% confidence interval [CI], 0.56 to 1.94; \( p = 0.900 \)) in mixed low- or intermediate-risk patients and \( \leq 20\% \) of high-risk patients (20).

- LDR-BT compared with RP: One RCT with 200 low-risk patients (LDR-BT = 92\% versus [vs.] RP = 91\%) (31) and one retrospective study with 927 low-risk patients (risk ratio [RR], 1.1; CI, 0.3 to 3.6) (25) showed no statistical difference between the two groups. Two retrospective studies showed that LDR-BT led to a higher bRFS rate than did RP in 437 intermediate-risk patients (90\% vs. 60%-80\%) (60) and in 674 mixed low-, intermediate- and \( \leq 20\% \) of high-risk patients (HR, 0.44; CI, 0.25 to 0.77) (20), respectively.

- LDR-BT, I-125 compared with Pd-103: One RCT with 263 low-risk patients showed no significant differences between the two groups (bRFS 96.8\% vs. 99.2\%, \( p = 0.149 \)) (41).

- For PCSM/OM at \( \geq 10 \) years:
  - LDR-BT compared with RP: One retrospective study with 41,395 mixed low-risk and intermediate-risk patients reported no statistical difference between the two groups for PCSM or OM, regardless of age. For men < 60 years old, PCSM was 0.5\% vs. 1.3\% (\( p = 0.380 \)) and OM was 7.9\% vs. 7.8\% (\( p = 0.908 \)), respectively; for men \( \geq 60 \) years old, PCSM was 5.3\% vs. 3.8\% (\( p = 0.595 \)) and OM was 37.1\% vs. 27.4\% (\( p = 0.625 \)), respectively (59).

- For toxicity:
  - LDR-BT compared with EBRT: One retrospective study with 729 low-risk patients reported that LDR-BT may lead to more late grade 2 genitourinary and gastrointestinal toxicities but less impotence than does EBRT and that there may be no difference for the late grade 3 genitourinary and gastrointestinal toxicities between the two groups (68). Another retrospective study reported that LDR-BT may lead to less second primary cancers at 2.8 to 5.3 years than might EBRT in 58,623 mixed low- or intermediate-risk patients and \( \leq 20\% \) of high-risk patients (15).

- For patient-reported outcomes:
  - LDR-BT compared with EBRT: Two prospective studies showed no difference between the two groups for urinary domains, but LDR-BT led to less sexual and rectal problems than did EBRT (low- and intermediate-risk patients were both included) (27,45).
  - LDR-BT compared with RP: Three prospective studies showed that urinary incontinence and sexual potency favored LDR-BT, while urinary irritation favored RP; for bowel patient-reported outcomes, one study favored RP but two other studies found no difference (low- and intermediate-risk patients together) (21,32,45). In an RCT in low-risk patients, results were consistent with the above observational studies at one year, but these differences for patient-reported outcomes were not sustained at five years (31).
  - For LDR-BT, I-125 compared with Pd-103: One RCT reported that Pd-103 resulted in worse overall QOL than did I-125 at one month, and I-125 resulted in worse overall QOL than did Pd-103 at six months, but there was no difference between the two groups at one and two years (33).

**Justification for Recommendation**

Many studies included in this guideline are retrospective studies. Retrospective studies may have more biases than prospective studies and RCTs and may overestimate the effects of the treatments. For this reason, a high criterion for sample size in retrospective studies of greater than or equal to 500 subjects was used. Although the quality of evidence from...
included studies is low to moderate in this guideline, the evidence across the eligible studies consistently supports the conclusion that there is no difference in efficacy between LDR-BT and EBRT, or between LDR-BT and RP in patients with favourable risk prostate cancer (predominately low-, or intermediate-risk patients, but studies were allowed to include ≤ 20% of high-risk patients with prostate cancer). From clinical experience, LDR-BT does have advantages over EBRT and RP for convenience and recovery: only one outpatient treatment visit is required for LDR-BT compared to 35 to 44 treatment visits for EBRT; recovery is significantly shorter for LDR-BT (generally within a few days) than for RP (one to four weeks depending on the procedures).

When considering toxicity and patient-reported outcomes, including QOL, the evidence consistently supports the conclusion that LDR-BT does not cause more toxicity than does EBRT or RP, and LDR-BT may lead to less second primary cancers at 2.8 to 5.3 years than may EBRT. During the six months to three years after treatment, the data suggests that LDR-BT is associated with less urinary incontinence and sexual impotency when compared with RP, and RP leads to less urinary irritation and less rectal morbidity than does LDR-BT. However, these differences may diminish over time. When LDR-BT was compared with EBRT, it seems that LDR-BT results in less sexual impotency and rectal morbidity in the three years after treatment. Patient preference should be considered in the treatment selection due to the different approaches involved with these three treatments (LDR-BT, EBRT, and RP) and their different acute and long-term impacts on patients.

Hence, after balancing treatment benefit and harm, for patients with newly diagnosed low-risk prostate cancer, LDR-BT should continue to be a treatment option in Ontario (the alternatives being EBRT or RP alone) as there is insufficient evidence to support one of the three treatment options being more effective than the others, and all have comparable effects on patient-reported outcomes (albeit in different domains). For patients with newly diagnosed intermediate-risk prostate cancer, and since EBRT and RP are already treatment options in Ontario, LDR-BT should become a treatment option as well, based on the above evidence.

One RCT showed that I-125 and Pd-103 were not different for bRFS at six years and for QOL at two years in patients with low-risk prostate cancer. Thus, I-125 and Pd-103 are each reasonable isotope options for patients with prostate cancer.

It should be noted that high-dose rate brachytherapy is another promising technique for patients with prostate cancer (70), but its study is beyond the scope of this guideline. Costing outcomes were also outside the scope of this work.

FUTURE RESEARCH
A search of the National Cancer Institute (NCI) clinical trials database (http://www.cancer.gov/clinicaltrials) on March 20, 2012 and the Radiation Therapy Oncology Group web site (http://www.rtog.org/ClinicalTrials) on September 12, 2012 for ongoing trials resulted in six ongoing RCTs that met the selection criteria for this guideline. Two of the RCTs are already included in this guideline (41,63), but the results of preplanned full sample size analyses have not been published. The third ongoing trial compares LDR-BT plus 20 Gy EBRT with LDR-BT alone in patients with intermediate-risk prostate cancer. The fourth trial investigates the effect of LDR-BT versus RP in patients with low- or intermediate-prostate cancer. The fifth trial tests neo-adjuvant hormonal therapy (neo-HT) plus concurrent and adjuvant androgen suppression (adj-HT) plus elective pelvic nodal irradiation (EPNI) plus high dose conformal EBRT, against neo-HT plus adj-HT plus EPNI plus I-125 in patients with intermediate- or high-risk prostate cancer. The sixth one will determine whether the combined EBRT and LDR-BT will result in better freedom from progression for five years compared to LDR-BT alone in selected patients with intermediate-risk prostate cancer. This
The guideline has highlighted the fact that many important questions remain potential subjects of further investigation, including the effect of Cs-131 and the effect of the combination of EBRT and LDR-BT on the target patient population. Well-designed and good-quality RCTs and prospective comparative studies are required to answer these research questions in patients with low- or intermediate-risk prostate cancer.

**RELATED GUIDELINES**

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REFERENCES


Low-Dose Rate Brachytherapy for Patients with Low- or Intermediate-Risk Prostate Cancer: Evidentiary Base

G. Rodrigues, X. Yao, A. Loblaw, M. Brundage, J. Chin, and the Genitourinary Cancer Disease Site Group

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QUESTIONS

1. In patients with newly diagnosed low- or intermediate-risk prostate cancer, what is the efficacy of low-dose rate brachytherapy (LDR-BT) alone for clinical outcomes (i.e., biochemical relapse-free survival [bRFS], overall survival [OS] or overall mortality [OM], prostate cancer-specific mortality [PCSM], negative biopsy rate, salvage treatment rate, toxicity, or patient-reported outcomes including quality of life [QOL]) compared with external beam radiation therapy (EBRT) alone, or radical prostatectomy (RP) alone?

2. In patients with newly diagnosed low- or intermediate-risk prostate cancer, what is the efficacy of LDR-BT combined with EBRT for clinical outcomes compared with LDR-BT alone, EBRT alone, or RP alone?

3. Among three isotopes used for LDR-BT (Iodine-125 [I-125], Palladium-103 [Pd-103], and Cesium-131 [Cs-131]), which isotope maximizes clinical outcomes when used in patients with newly diagnosed low- or intermediate-risk prostate cancer?

INTRODUCTION

In Canada in 2012, there will be an expected 26,500 new prostate cancer cases, with the highest estimated cancer incidence rate being 121 per 100,000, and 4000 deaths related to prostate cancer, with the third highest incidence for estimated deaths and age-standardized mortality being 21 per 100,000 in male cancer patients (1). In 2021, yearly prostate cancer cases will likely increase by about 40% to approximately 35,000 due to the aging of the Canadian population (2).

The Genitourinary Radiation Oncologists of Canada (3) and the National Comprehensive Cancer Network (NCCN) (4) clinical practice guidelines provide the following definitions of risk for patients with prostate cancer:

- Low-risk patients have a prostate-specific antigen (PSA) < 10 ng/ml and clinical stage T1c-T2a and Gleason score < 7.
- Intermediate-risk patients have a PSA ≥ 10 ng/ml but < 20 ng/ml or clinical stage T2b-T2c or Gleason score = 7.
- High-risk patients are defined as having PSA ≥ 20 ng/ml or clinical stage > T2c or Gleason score > 7.
Common active treatment options for low- or intermediate-risk patients with prostate cancer include RP, EBRT, brachytherapy, androgen deprivation therapy, or some combination of these options (4).

In theory, LDR-BT emits short-range radiation directly into the prostate tumour, which should confine radiation doses to the target tissue and consequently protect the surrounding normal tissue, when compared with EBRT (5). In 2001 in Canada, the PEBC, Cancer Care Ontario, through its Genitourinary Cancer Disease Site Group (DSG) developed a guideline on LDR-BT in patients with early-stage low-grade prostate cancer (Evidence-Based Series [EBS] 3-10 The Use of Brachytherapy in T1 or T2 Prostate Cancer) (6). Because the main evidence in this guideline was from single-arm studies and because stronger levels of evidence such as comparative studies or RCTs have become available during the last decade, an updated guideline was necessary. To date, the following three isotopes are available for LDR-BT in patients with prostate cancer: I-125, Pd-103, and Cs-131, each having a different half-life time: 59.4 days, 17.0 days, and 9.7 days, respectively (7). It is unclear which isotope maximizes clinical outcomes when used in patients with newly diagnosed low- or intermediate-risk prostate cancer. This current updated guideline focuses on the above three research questions regarding LDR-BT alone, LDR-BT with EBRT, and selection of an isotope.

For this guideline those individuals who require or choose active treatment are the target population and not those who are considering and are suitable for active surveillance. The PEBC is developing a separate guideline (EBS 17-9 Active Surveillance for the Management of Localized Low-Risk Prostate Cancer), which will be available on the CCO web site in 2013, because the topic of active surveillance warrants a thorough and separate guideline development process.

METHODS

The EBS guideline developed by the PEBC uses the methods of the Practice Guidelines Development Cycle (8). For this project, the core methodology used to develop the evidentiary base was the systematic review. Evidence was selected and reviewed by the Working Group, which included four Genitourinary DSG members (GR, AL, MB, and JC) and one methodologist from the PEBC (XY) (Appendix 1). All data were audited by a second, independent auditor. Evidence from the available medical literature forms the basis for the recommendations developed by the Genitourinary Cancer DSG (including a patient representative; Appendix 1), which are published in Section 1 of this document. The systematic review and companion recommendations are intended to promote evidence-based practice in Ontario, Canada. The PEBC is supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

Literature Search Strategy

To update the 2001 systematic review and find more recent eligible full text reports, a literature search was performed through the Ovid search engine from January 1, 1996 to October 27, 2011 using MEDLINE and EMBASE. The search strategies are fully reported in Appendices 2 and 3. The following resources were checked for existing systematic reviews and systematic reviews that form a part of practice guidelines: the Cochrane Library (to Issue 10, 2011); National Guideline Clearinghouse, National Health and Medical Research Council (Australia), New Zealand Guidelines Group, American Society of Clinical Oncology (ASCO), National Comprehensive Cancer Network, National Institute for Health and Clinical Excellence, Scottish Intercollegiate Guidelines Network, American Society for Radiation Oncology (ASTRO), European Society of Radiotherapy & Oncology (ESTRO), American Urological Association (AUA), European Association of Urology (EAU), American Brachytherapy...
Society (ABS) (to October 21, 2011); and the Standards and Guidelines Evidence Inventory of Cancer Guidelines (9), which included over 1,100 English-language cancer control guidelines and standards released from 2003 through June 2010 when it was accessed on October 26, 2011. The included studies in the 2001 guideline were checked, and only those that met the current study selection criteria were eligible for inclusion in this review.

The ASCO, ASTRO, ESTRO, AUA, EUA, ABS, and Canadian Association of Radiation Oncology (CARO) Annual Meeting Abstracts from 2009 to October 2011 were checked for eligible abstracts.

Study Selection Criteria

Inclusion Criteria

Articles or abstracts were eligible for inclusion in this systematic review if they met all the following preplanned criteria:

1. Full text reports were published in the period from January 1, 1996, to October 27, 2011 or abstracts were published from January 1, 2009, to October 31, 2011.
2. Full text reports were systematic reviews (defined as describing search databases, time period, search terms, and study selection criteria), clinical practice guidelines based on a systematic review, RCTs, prospective comparative studies with analyzed sample size more than or equal to 30 for any intervention groups, or retrospective comparative studies with sample size more than or equal to 500 at the baseline for patients with newly diagnosed low-risk and/or intermediate-risk prostate cancer; or published abstracts were RCTs.
3. Studies compared LDR-BT with EBRT alone or RP alone, LDR-BT plus EBRT with LDR-BT alone or EBRT alone or RP alone, different doses of LDR-BT alone or LDR-BT plus EBRT; or any two of the three isotopes (I-125, Pd-103, and Cs-131).
4. Studies reported on at least one of the following clinical outcomes: OS/OM, bRFS, negative biopsy rate, salvage treatment rate, toxicity, and/or patient-reported outcomes.

Exclusion Criteria

Articles or abstracts were excluded if they met any of the following preplanned criteria:

1. Full text reports or abstracts were published in a language other than English.
2. They were published in the form of letters, editorials or commentaries.
3. Studies reported the outcomes on mixed > 20% high-risk patients in one intervention group and did not report the comparison among other groups that had ≤ 20% high-risk patients or did not have the subgroup analyses for either low-risk or intermediate-risk patients separately.
4. Different treatment options were delivered on different patient populations within one study (for example, patients with PSA < 10 ng/ml receiving LDR-BT and patients with PSA ≥ 10 ng/ml receiving EBRT).

Synthesizing the Evidence

If possible, a meta-analysis of each clinical outcome would be considered and conducted. Any data for which denominators were less than 30 should be considered carefully because they usually have a large 95% confidence interval (CI) and are unlikely to be statistically significant. Thus, data from subgroups with less than 30 patients were not extracted.
RESULTS

Literature Search Results

No clinical practice guidelines based on a systematic review were found that focused on all three research questions. If the guidelines, which were published from 2005 to October 2011, had content related to at least one of the above three research questions, their included studies were cross-referenced to our literature search.

Of 5,444 citations identified from the MEDLINE and EMBASE searches (Figure 1), 5,129 articles were excluded after reviewing the titles and abstracts, and 252 were disqualified after reviewing the full texts. No additional eligible studies were found after checking existing guidelines. The reference lists of the included articles were hand-searched, and two further eligible papers were found. A check of abstracts from the ASCO, ASTRO, ESTRO, AUA, EUA, ABS, and CARO annual meeting abstracts yielded no abstracts that met the study selection criteria. Ultimately, a total of 10 systematic reviews (10-19) and 55 full text articles (20-74) were included in this systematic review. None of the systematic reviews covered the research questions in a manner that allowed for that review to be used instead of a comprehensive review conducted by the PEBC. In addition, a check of the included studies in the 10 systematic reviews revealed that all of them either replicated some of the 55 eligible articles or did not meet the study selection criteria. Therefore, these reviews provide no unique evidence to aid in the development of recommendations and are not discussed further.

Seven studies that either provided the raw data for each intervention group without statistical comparison or the comparison within but not between groups are not summarized in the tables and text (23,49,54,58,61,63,74) as these data are not useful for developing recommendations with respect to the guideline questions. There are another seven papers that included patients who either received LDR-BT or LDR-BT plus EBRT in one intervention group to compare with EBRT alone or RP alone (27,39,47,52,53,59,70); the efficacy of LDR-BT alone cannot be distinguished from that of LDR-BT plus EBRT, therefore, those study outcomes are not summarized.

Several identified articles that are multiple reports from the same source study population warrant further comment. The 2005 Sharkey et al study (56) included 1,707 patients, of whom 1305 overlapped with those in the 2002 Sharkey et al study (55). However, some patients in the 2005 study received LDR-BT plus EBRT and were analysed together with the patients who received LDR-BT alone. The 2007 Merrick et al trial (46) updated the 2003 Wallner et al trial (69), the 2005 Herstein et al trial (38) updated the 2000 and 2002 Wallner et al trials (66,67), and the 2009 Lev et al study (43) updated the 2006 Eller et al study (31). As a result, the 2000, 2002, and 2003 Wallner et al trials, the 2005 Sharkey et al study, and the 2006 Eller et al study were not included in the tables and text.

The 2003 Ghaly et al trial (35), 2004 Sherertz et al trial (57), and Wallner 2005 et al trial (68) included a subset of patients from an RCT, but, because they reported different data and outcomes, these articles are summarized in the tables and text.

Thus data were ultimately abstracted and summarized from 36 articles in this systematic review (20-22,24-26,28-30,32-38,40-46,48,50,51,55,57,60,62,64,65,68,71-73). Nine studies did not make clear the proportion of high-risk patients in any treatment group (21,32,42,47,50,54,59,61,70), and the data from these studies were summarized at the end of each table but were not interpreted in the text.
Figure 1. Flow of studies considered for this systematic review.

Study Design and Quality

Among these 36 articles, six reported different outcomes for three RCTs. One RCT (Dr. Merrick, principal investigator [PI]) investigated different doses of EBRT plus different doses of Pd-103 in patients with intermediate-risk prostate cancer (57,68). Another RCT (Dr. Wallner, PI) compared I-125 with Pd-103 in patients with low-risk prostate cancer (38,46). One paper (35) reported additional patient-reported outcomes for the above two RCTs. The third RCT was reported by Giberti et al (36). The risks of bias for RCTs were assessed by the modified Cochrane Collaboration’s tool (75) in Table 1.

All three RCTs had limitations in study design or execution. The Merrick et al and Wallner et al RCTs were planned to recruit 600 patients, and a minimum of 172 subjects per treatment arm was required to achieve a study power of 80% at an alpha of 0.05 for survival outcome. There was no preplanned interim analysis. However, the five papers in Table 1 only reported the selected outcomes from a section of the patients and only the 2005 Herstein et
al article reached the minimal patient requirement (38). The randomization method and allocation concealment were clearly reported, but the patients and clinicians were unblinded in both RCTs.

The 2009 Giberti et al RCT demonstrated good quality on the randomization method and allocation concealment (36). Although the patients and clinicians were unblinded, outcome assessors were blinded to patient treatment. The follow-up rate was 87% in over five years. However, there was no expected effect, power, or planned sample size calculated; no intention-to-treat analysis; and no information about funding resources. Overall, the quality of evidence from all these RCTs was poor to moderate.

Fourteen articles were prospective studies, and 16 were retrospective studies. They were assessed for study quality according to the modified Newcastle-Ottawa Scale (76), which has been used in the non-randomized studies (NRS) method workshops of the Cochrane Collaboration to illustrate issues in data extraction from primary NRS (75). The baseline patient characteristics or the proportion of different risk patients among the treatment groups were significantly different in 21 studies (20,21,25,26,28,29,32,37,42-45,48,50,51,60,62,65,71-73). There was no statistical comparison for patient characteristics at the baseline among intervention groups in six studies (22,33,34,41,55,64). The baseline characteristics were not significantly different among the intervention groups in the 1998 D’Amico et al study (30), but patient age data were not provided and compared. In the 2004 Borchers et al and the 2008 Kirschner-Hermanns et al studies (24,40), the patient baseline characteristics were not significantly different among the treatment groups, except that patient age was different among the groups in each study. Only the Kirschner-Hermann et al study reported a blinded assessment of outcomes (40). Although the follow-up rates in most studies were over 80%, only 10 studies had at least one group with more than or equal to five years for the median or mean follow-up time (20-22,25,28,42,62,65,71,73). Overall, the quality of evidence from the non-RCTs was poor to moderate.

Outcomes

Meta-analyses of the trial results were not feasible because patient characteristics, interventions, intervention doses, PSA failure definitions, toxicity assessment criteria, and QOL assessment tools among the included studies are so different.

Since “benign PSA bounce” (using the Phoenix PSA definition of failure, patients who met the criteria for biochemical relapse but who had a subsequent decrease in PSA level without intervention to a new nadir of ≤ 0.5 ng/ml), can happen within five years after LDR-BT or EBRT (77,78), the data of bRFS rates at less than five years are not analyzed in this text.

The relative 10-year and 15-year survivals are 98% and 91%, respectively, for all prostate cancer patients with any treatment (79). It would be hard to identify the difference between treatments if the reported time for the OS or PCSM was less than 10 years. Therefore, the data of OS or PCSM at < 10 years are not interpreted in the text.

Among the eligible papers, when LDR-BT was used alone, the dose was 140-160 Gray (Gy) for I-125 and 108-125 Gy for Pd-103; when LDR-BT was combined with EBRT, the dose was 41.4-45 Gy EBRT followed by 100-120 Gy I-125, or 20-50.4 EBRT followed by 90-115 Gy Pd-103.
Table 1. Assessment of study quality for RCT by modified Cochrane Collaboration Tool.\(^a\)

<table>
<thead>
<tr>
<th>Study</th>
<th>Randomization method</th>
<th>Allocation concealment</th>
<th>Blinding (participants, personnel, outcome assessment)</th>
<th>Follow-up time (range)</th>
<th>Follow-up rate</th>
<th>Expected Effect, Power, and Planned Sample Size</th>
<th>Intention-to-treat analysis</th>
<th>Selective reporting</th>
<th>Funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ghaly 2003(^b) (35)</td>
<td>Yes</td>
<td>Yes</td>
<td>Patients and clinicians were unblinded.</td>
<td>12 mo</td>
<td>NA</td>
<td>A minimum of 344 subjects were required to achieve a power of 80% at an alpha of 0.05 for a 15% difference in time-to-event survival assuming proportional hazards.)</td>
<td>No</td>
<td>Yes</td>
<td>Data management funding provided in part by Johnson &amp; Johnson and Theragenics Corporation</td>
</tr>
<tr>
<td>Sherertz 2004 (57)</td>
<td></td>
<td></td>
<td>At least 24 mo</td>
<td>100%</td>
<td></td>
<td></td>
<td>Unclear</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Wallner 2005 (68)</td>
<td></td>
<td></td>
<td>Median 2.9 y</td>
<td>96%</td>
<td></td>
<td></td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Ghaly 2003(^b) (35)</td>
<td>Yes</td>
<td>Yes</td>
<td>Patients and clinicians were unblinded.</td>
<td>12 mo</td>
<td>NA</td>
<td>Similar to the above RCT, a minimum of 344 subjects were required.</td>
<td>No</td>
<td>Yes</td>
<td>Data management funding provided by Johnson &amp; Johnson</td>
</tr>
<tr>
<td>Herstein 2005 (38)</td>
<td></td>
<td></td>
<td>At least 24 mo</td>
<td>94%</td>
<td></td>
<td></td>
<td>No</td>
<td>No(^c)</td>
<td></td>
</tr>
<tr>
<td>Merrick 2007 (46)</td>
<td></td>
<td></td>
<td>Median 53 mo</td>
<td>NA</td>
<td></td>
<td></td>
<td>Unclear</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Giberti 2009 (36)</td>
<td>Yes</td>
<td>Yes</td>
<td>Patients and doctors were unblinded; Outcome assessors were blinded to patient treatment.</td>
<td>Mean: 68 (60-102) mo</td>
<td>87%</td>
<td>Not stated</td>
<td>No</td>
<td>Yes</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: RCT = randomized controlled trial, Int = intermediate, mo = months, y = year, NA = not available.

\(^a\) Yes = high quality; No = low quality.

\(^b\) Patients seen between January 2000 and January 2001 in the two RCTs were chosen for this study; Both RCTs started in 1999.

\(^c\) Modified Radiation Therapy Oncology Group criteria were used to measure rectal morbidity and urinary incontinence, but the results were not reported because the investigators thought they were unsuitable for publication due to a high degree of variability in patients' degree of incontinence on the aggressive use of alpha-blockers.
Table 2. Clinical outcomes.

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment (dose)</th>
<th>Risk patients b</th>
<th>Median age</th>
<th>Median F-up time; F-up rate</th>
<th>bRFS rate</th>
<th>PCSM/OM/OS rate</th>
<th>CRFSR/DMFSR/TIST/LDR/DCR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RCT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Wallner 2005\textsuperscript{a} (68)</td>
<td>EBRT (44 Gy) + LDR-BT (90 Gy Pd-103) vs. EBRT (20 Gy) + LDR-BT 115 Gy Pd-103</td>
<td>Int + (\leq 20%) high: 80 vs. 85</td>
<td>67 vs. 67 y</td>
<td>2.9 y; 96%</td>
<td>At 3 y': 88% vs. 83%, NS</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Merrick 2007\textsuperscript{a} (46)</td>
<td>I-125 (144 Gy) vs. Pd-103 (125 Gy)</td>
<td>Low: 127 vs. 136</td>
<td>65 vs. 66 y</td>
<td>4.2 y; NA</td>
<td>At 6 y': 96.8% vs. 99.2%, NS</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Giberti 2009\textsuperscript{a} (36)</td>
<td>LDR-BT (&gt;140 Gy I-125) vs. RP+nerve-sparing</td>
<td>Low: 100 vs. 100</td>
<td>Mean: 66 vs. 65 y</td>
<td>Mean: 68 mo; 87%</td>
<td>At 5 y: LDR-BT\textsuperscript{a}=92% vs. RP\textsuperscript{a}=91%, NS</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Non-RCT: 1. Comparisons with LDR-BT: LDR-BT vs. EBRT; LDR-BT vs. RP</strong> (grey shaded rows - studies adjusted for baseline characteristics)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D'Amico 1998\textsuperscript{a}, Retro (30)</td>
<td>LDR-BT (115 Gy Pd-103) vs. EBRT (66-70 Gy) vs. RP</td>
<td>Low: 32 vs. 225 vs. 402</td>
<td>NA</td>
<td>41 vs. 38 vs. 38 mo; 100%</td>
<td>At 5 y: LDR-BT vs. EBRT, p=0.25; LDR-BT vs. RP, p=0.25</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>   </td>
<td>LDR-BT (115 Gy Pd-103) + neo-HT vs. EBRT (66-70 Gy)</td>
<td>Int\textsuperscript{a}: 38 vs. 232</td>
<td>NA</td>
<td>41 vs. 38 mo; 100%</td>
<td>At 5 y: LDR-BT + neo-HT vs. EBRT, p=0.25</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>   </td>
<td>LDR-BT (115 Gy Pd-103) + neo-HT vs. RP</td>
<td>Low: 38 vs. 402</td>
<td>NA</td>
<td>41 vs. 38 mo; 100%</td>
<td>At 1 y: LDR-BT + neo-HT vs. RP, p&lt;0.001</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>D'Amico 2003\textsuperscript{a}, Retro (29)</td>
<td>LDR-BT vs. RP</td>
<td>Low + Int: 227 vs. 406</td>
<td>62 vs. 60 y</td>
<td>4.0 vs. 4.2 y; 82%</td>
<td>At 5 y: LDR-BT\textsuperscript{a}=95% vs. RP\textsuperscript{a}=93%, NS</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Borchers 2004\textsuperscript{a}, Pros (24)</td>
<td>LDR-BT vs. RP + RP+nerve-sparing</td>
<td>Low: 52 vs. 42 vs. 38</td>
<td>Mean: 67 vs. 65 vs. 59 y</td>
<td>Mean: 27 mo; 79%</td>
<td>At 27 mo: LDR-BT\textsuperscript{a} = 85% (CI 74-95%) vs. RP\textsuperscript{a} and RP+nerve-sparing = 96% (CI 91-100%), p=0.04\textsuperscript{b}</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Kupelian 2004\textsuperscript{a}, Retro (42)</td>
<td>LDR-BT (144 Gy I-125 or 136 Gy Pd-103, 24% of pts with neo-HT) vs. EBRT (63-70 Gy, 5% with neo-HT) vs. EBRT (72-83 Gy, 39% with neo-HT)</td>
<td>Low (only low-risk patients met the selection criteria; no sample size reported)</td>
<td>Mean: 70 vs. 70 vs. 68 vs. 69 vs. 63 y</td>
<td>56 mo; NA</td>
<td>At 7 y: LDR-BT\textsuperscript{a} + EBRT\textsuperscript{a} (&lt;72 Gy) vs. EBRT (&lt;72 Gy) vs. EBRT+ LDR-BT vs. RP\textsuperscript{a}, p&lt;0.001; LDR-BT vs. EBRT (≥72 Gy) vs. EBRT+ LDR-BT vs. NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Study</td>
<td>Treatment (dose)</td>
<td>Risk patients</td>
<td>Median age</td>
<td>Median F-up time; F-up rate</td>
<td>bRFS rate</td>
<td>PCSM/OM/OS rate</td>
<td>CRFSR/DMFSR/TIST/LDR/DCR</td>
</tr>
<tr>
<td>-------</td>
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</tr>
<tr>
<td>Tward 2006&lt;sup&gt;1,9&lt;/sup&gt;, Retro (64)</td>
<td>LDR-BT vs. RP</td>
<td>Low + Int&lt;sup&gt;4&lt;/sup&gt;: 6637 vs. 34,758</td>
<td>For men &lt;60 y: 56 vs. 55 y, For men ≥60 y: 69 vs. 66 y</td>
<td>46 mo; NA</td>
<td>NA</td>
<td>At 10 y, For men &lt;60 y: LDR-BT=0.5% vs. RP=1.3%, NS for PCSM; LDR-BT=7.9% vs. RP=7.8%, NS for OM. For men ≥60 y: LDR-BT=5.3% vs. RP=3.8%, NS for PCSM; LDR-BT=37.1% vs. RP=27.4%, NS for OM.</td>
<td>NA</td>
</tr>
<tr>
<td>Burdick 2009&lt;sup&gt;1,9&lt;/sup&gt;, Retro (25)</td>
<td>LDR-BT (144 Gy for I-125) vs. EBRT (minimum of 70 Gy) vs. RP (with neo-HT)</td>
<td>Low + Int&lt;sup&gt;4&lt;/sup&gt;: 127 vs. 268 vs. 310</td>
<td>66 y</td>
<td>54 mo; NA</td>
<td>At 5 y: LDR-BT&lt;sup&gt;4&lt;/sup&gt; vs. EBRT&lt;sup&gt;4&lt;/sup&gt;, HR=1.04 (CI 0.56-1.94), NS; LDR-BT vs. RP&lt;sup&gt;5&lt;/sup&gt;, HR=0.44 (CI 0.25-0.77), p=0.004&lt;sup&gt;4&lt;/sup&gt;</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Klein 2009&lt;sup&gt;1,9&lt;/sup&gt;, Retro (41)</td>
<td>LDR-BT (144 Gy I-125) vs. EBRT (median 81 Gy) vs. RP</td>
<td>Int&lt;sup&gt;4&lt;/sup&gt;: 204 vs. 321 vs. 336</td>
<td>NA</td>
<td>39 vs. 58 vs. 59 mo; 100%</td>
<td>At 8 y: LDR-BT&lt;sup&gt;4&lt;/sup&gt; vs. 3D-CRT&lt;sup&gt;4&lt;/sup&gt;, HR=0.79 (CI 0.55-1.15), NS; LDR-BT vs. LDR-CRT&lt;sup&gt;5&lt;/sup&gt;, HR=0.44 (CI 0.25-0.77), p=0.004&lt;sup&gt;4&lt;/sup&gt;</td>
<td>OS at 8 y: LDR-BT=94% vs. 3D-CRT/IMRT=82% vs. RT=63%, p=0.052</td>
<td>CRFSR at 8 y: LDR-BT=81% vs. 3D-CRT/IMRT&lt;sup&gt;5&lt;/sup&gt; vs. RT=98%, p=0.019</td>
</tr>
<tr>
<td>Vassil 2010&lt;sup&gt;1,9&lt;/sup&gt;, Retro (65)</td>
<td>LDR-BT (144 Gy I-125, 31% with neo-HT) vs. EBRT (70-80 Gy, 53% with neo-HT) vs. LRP (8% with neo-HT) vs. RRP (9% with neo-HT)</td>
<td>Int: 256 vs. 305 vs. 64 vs. 354</td>
<td>69 vs. 68 vs. 63 vs. 62 y</td>
<td>65 mo; NA</td>
<td>At 5 y: LDR-BT=90% vs. EBRT=86%, p=0.969; LDR-BT&lt;sup&gt;5&lt;/sup&gt; vs. LRP&lt;sup&gt;5&lt;/sup&gt;=60%, p=0.001&lt;sup&gt;4&lt;/sup&gt;; LDR-BT&lt;sup&gt;4&lt;/sup&gt;=90% vs. LDR-CRT&lt;sup&gt;4&lt;/sup&gt;=80%, p=0.003&lt;sup&gt;4&lt;/sup&gt;</td>
<td>NA</td>
<td>TIST: LDR-BT=47 mo vs. 3D-CRT/IMRT=48 mo, NS; LDR-BT=47 mo vs. RRP&lt;sup&gt;1&lt;/sup&gt;=21 mo, p=0.001&lt;sup&gt;4&lt;/sup&gt;; LDR-BT vs. RRP=26 mo, p=0.001&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>Arvold 2011&lt;sup&gt;1,9&lt;/sup&gt;, Pros (21)</td>
<td>LDR-BT (144 Gy for I-125, 108 Gy for Pd-103, or Cs-131)&lt;sup&gt;1&lt;/sup&gt; vs. RP (some pts receiving adjuvant 66 Gy EBRT and/or HT)</td>
<td>Low: 3,851 vs. 1,909</td>
<td>69 vs. 61 y</td>
<td>3.6 vs. 6.1 y; NA</td>
<td>PCSM at 4.2 y: LDR-BT vs. RP, HR=1.62 (0.59-4.45), p=0.35</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Zelefsky 2011&lt;sup&gt;1,9&lt;/sup&gt;, Retro (73)</td>
<td>LDR-BT (144 Gy I-125, 31% with neo-HT) vs. EBRT (81 Gy, 32% with neo-HT)</td>
<td>Low: 448 vs. 281</td>
<td>62% of pts ≥65 y</td>
<td>77 mo; NA</td>
<td>At 7 y: LDR-BT&lt;sup&gt;1&lt;/sup&gt;=95% vs. EBRT=89%, p=0.004&lt;sup&gt;4&lt;/sup&gt;; in pts without neo-HT, p=0.001&lt;sup&gt;4&lt;/sup&gt;</td>
<td>DMFSR at 7 y: LDR-BT=100% vs. EBRT=99.2%, NR for p-value</td>
<td>NA</td>
</tr>
</tbody>
</table>
**Unclear proportion of high-risk patients in any treatment group (grey shaded rows - studies adjusted for baseline characteristics)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment (dose)</th>
<th>Risk patientsa</th>
<th>Median age</th>
<th>Median F-up time; F-up rate</th>
<th>bRFS rate</th>
<th>PCSM/OM/OS rate</th>
<th>CRFSR/DMFSR/TIST/LDR/DCR/</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sharkey 2002*, Retro (55)</td>
<td>LDR-BT (Pd-103; about 50% with HT before and after BT) vs. RP</td>
<td>Low + Int + maybe &gt;20% high: 869 vs. 208</td>
<td>Mean age: 72 y vs. 64 y</td>
<td>3 y; 83%</td>
<td>At 7 y: LDR-BT=76% vs. RP=74%, NS</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Wong 2009a,b, Retro (71)</td>
<td>LDR-BT (144 Gy l-125 or 120 Gy Pd-103, 32% with neo-HT) vs. 3D-CRT (66-71 Gy, 17% with neo-HT) vs. IMRT (75.6-77.4 Gy, 36% with neo-HT) vs. 3D-CRT+BT (45 Gy 3D-CRT + 110 Gy I-125 or 90 Gy Pd-103, 27% with neo-HT)</td>
<td>Low + Int + maybe &gt;20% high: 225 vs. 270 vs. 314 vs. 44</td>
<td>NA</td>
<td>49 y vs. 62 y vs. 56 y vs. 63 mo; 100%</td>
<td>At 5 y: LDR-BT=94% vs. 3D-CRT=74% or IMRT=87% vs. 3D-CRT+ LDR-BT=94%, p=0.001 in favour of LDR-BT, IMRT, and 3D-CRT+ LDR-BT</td>
<td>NA for comparison</td>
<td>1). LCR at 5 y: LDR-BT=100% vs. 3D-CRT=93% vs. IMRT=99% vs. 3D-CRT+ LDR-BT =100%, NS 2). DCR at 5 y: LDR-BT=99% vs. 3D-CRT=96% vs. IMRT=97% vs. 3D-CRT+ LDR-BT =97%, NS</td>
</tr>
</tbody>
</table>

**Non-RCT: 2. Comparisons with EBRT + LDR-BT: EBRT + LDR-BT vs. BT; EBRT + LDR-BT vs. EBRT; EBRT + LDR-BT vs. RP (grey shaded rows - studies adjusted for baseline characteristics)**

| Stock 2009*, Retro (62) | LDR-BT (120 Gy l-125 or 100 Gy Pd-103) + EBRT (median 45 Gy, 89% with neo-HT and adjuvant HT) vs. LDR-BT (160 Gy I-125 or 124 Gy Pd-103, 41% with neo-HT) | Low + Int + maybe>20% high: 224 vs. 518 | NA | 6.9 y; 100% | bRFS’ at 10 y: LDR-BT+EBRT = 100% vs. LDR-BT+EBRT+HT = 99% vs. LDR-BT = 95% vs. LDR-BT+neo-HT = 99%, p=0.5 | bRFS’ at 10 y: LDR-BT+EBRT = 100% vs. LDR-BT+EBRT+HT = 98% vs. BT= 93% vs. LDR-BT+neo-HT = 97%, p=0.7 | NA for comparison | NA for comparison |

Abbreviations: F-up = follow-up, bRFS = biochemical relapse-free survival, PCSM = prostate cancer-specific mortality, OM = overall mortality, OS = overall survival, CRFSR = clinical recurrence-free survival rate, DMFSR = distant metastasis-free survival rate, TIST = time to initiation of salvage therapy, LCR = local control rate, DCR = distant control rate, RCT = randomized controlled trial, EBRT = external beam radiation therapy, Gy = gray, LDR-BT = low-dose rate brachytherapy, Pt-103 = palladium-103, I-125 = iodine-125, vs. = versus, Int = intermediate, y = year, NS = not statistically significant, NA = not available, p = p-value, RP = radical prostatectomy, mo = month, Retro =retrospective, Pros = prospective, neo HT = neo-adjuvant hormonal therapy, pts = patients, 3-D-CRT = 3-D conformed radiation therapy, IMRT = intensity-modulated radiotherapy, HR = hazard ratio, CI = 95% confidence interval, LRP = laparoscopic RP, RRP = retropubic RP, Cs-131 = cesium-131.

a Low-risk patients were defined as having PSA < 10 ng/ml and clinical stage T1c to T2a and Gleason score < 7, intermediate-risk patients were defined as having PSA <20 ng/ml or clinical stage T2b-T2c or Gleason score = 7 and are not otherwise low-risk patients, high-risk patients were defined as having PSA ≥ 20 ng/ml or clinical stage >T2c or Gleason score > 7 in tumor.

b The baseline clinical characteristics were not statistically different among the intervention groups.

c The biochemical failure was defined as a PSA > 0.5 ng/ml after nadir.
The biochemical failure was followed the Radiation Therapy Oncology Group (RTOG) of the American Society of Therapeutic Radiation and Oncology (ASTRO) Phoenix consensus that PSA should be higher than nadir plus 2 ng/ml.

The definition of failed PSA was followed ASTRO 1996 consensus statement that patients had three consecutive rising PSA values each obtained at least three months apart.

Intermediate-risk patients were defined as having PSA < 20 ng/ml or ≥10 ng/ml, clinical stage T2b, or Gleason score = 7; high-risk patients were defined as having PSA ≥ 20 ng/ml or clinical stage ≥ T2c or Gleason score > 7 in tumour.

Significance favored ERBT.

The original author stated that the study was not adequately powered to detect this difference.

The baseline clinical characteristics were significantly different among the intervention groups.

In the RP group, a PSA level > 0.2 ng/ml was considered a failure.

For the RP or PR+nerve-sparing group, a PSA level > 0.1 ng/ml was considered a failure.

Significance favored RP.

The baseline characteristics were not significantly different among the intervention groups except patients in RP group with nerve-sparing procedure were younger.

There was no statistical comparison for patient characteristics at the baseline between intervention groups.

Multivariate analysis was used to adjust baseline confounders.

Patients with grade I had Gleason scores 2-4 and patients with grade II had Gleason scores 5-7 and patients with grade III had Gleason scores 8-10 before January 1st, 2003, but after 2003, patients with Gleason score 7 moved to grade III.

In the RP group, a PSA level > 0.3 ng/ml was considered a failure.

Significance favored LDR-BT.

In the RP group, a PSA level ≥0.4 ng/ml was considered a failure.

The doses of BT were extracted from the reference 12 in the original study.

In the LDR-BT group, a PSA level > 1.5 ng/ml and a positive biopsy, or a PSA level > 1.5 ng/ml and it was higher than the previous one was considered a failure.
Biochemical Relapse-free Survival

For the non-RCTs in which the baseline patient characteristics were significantly different between treatment groups and the confounders were not controlled for when the outcomes were reported, it is unknown whether the bRFS rate results between the two groups were due to the treatment effects or influenced by the different patient and tumour characteristics. The studies that clarified that there was no significant difference in the baseline patient characteristics among treatment groups and that used multivariate analysis to adjust for confounding factors when reporting the outcomes of bRFS, survival, negative biopsy rate, or salvage treatment rate are highlighted in grey shading in Table 2.

Three RCTs and 11 non-RCTs reported bRFS rates, and five of 11 non-RCTs were marked in grey shading in Table 2. Four definitions for PSA failure were used in LDR-BT, EBRT, or LDR-BT plus EBRT groups; and six definitions were used in RP groups in different studies (see the definitions in the footnotes under Table 2). The key evidence from the RCTs and studies highlighted in grey shading is further summarized in the Summary bRFS Table below.

Summary bRFS Table. Key evidence from Table 2 for bRFS outcome.

<table>
<thead>
<tr>
<th>Patient risk</th>
<th>Treatment</th>
<th>bRFS at ≥ 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>LDR-BT vs. EBRT</td>
<td>NS: p&gt;0.25 (30)</td>
</tr>
<tr>
<td></td>
<td>LDR-BT vs. RP</td>
<td>NS: LDR-BT=92% vs. RP=91% (36); NS: RR = 1.1 (95% CI, 0.3-3.6), p=0.91 (30)</td>
</tr>
<tr>
<td></td>
<td>L-125 vs. Pd-103</td>
<td>NS: L-125=96.8% vs. Pd-103=99.2%, p=0.149 (46)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>LDR-BT vs. EBRT</td>
<td>NS: LDR-BT=90% vs. EBRT=86%, p=0.969 (65)</td>
</tr>
<tr>
<td></td>
<td>LDR-BT vs. RP</td>
<td>Favour ed LDR-BT, LDR-BT=90% vs. RP=60-80%, p&lt;0.05 (65)</td>
</tr>
<tr>
<td>Low + intermediate + ≤20% high</td>
<td>LDR-BT vs. EBRT</td>
<td>NS: HR = 1.04 (CI 0.56-1.94), p=0.900 (25)</td>
</tr>
<tr>
<td></td>
<td>LDR-BT vs. RP</td>
<td>Favour ed LDR-BT: HR=0.44 (CI 0.25-0.77), p=0.004 (25)</td>
</tr>
</tbody>
</table>

Abbreviation: bRFS = biochemical relapse-free survival, LDR-BT = low-dose rate brachytherapy, EBRT = external beam radiation therapy, NS= not significant difference, p = p-value, RP = radical prostatectomy, RR = risk ratio, CI = confidence interval, HR = hazard ratio.

Survival, Negative Biopsy Rate, and Salvage Treatment Rate

Table 2 also summarizes the outcomes of OS, OM, PCSM, clinical recurrence-free survival rate, distant metastasis-free survival rate, local control rate, distant control rates, and time to initiation of salvage therapy rate. No study reported on the negative biopsy rate.

One retrospective study with 41,395 mixed low-risk and intermediate-risk patients reported that there was no statistical difference for PCSM or OM, regardless of age. For men < 60 years old, PCSM was 0.5% versus 1.3% (p = 0.380) and OM was 7.9% versus 7.8% (p = 0.908), respectively; for men ≥ 60 years old, PCSM was 5.3% versus 3.8% (p = 0.595) and OM was 37.1% versus 27.4% (p = 0.625), respectively (64).

There was no study that compared EBRT plus LDR-BT with LDR-BT, EBRT, or RP for treatment benefit outcomes in patients with newly diagnosed low- or intermediate-prostate cancer, or ≤ 20% of high-risk prostate cancer. Additionally, there was no study that investigated the efficacy of Cs-131 in the target patients.

Toxicity

Four non-RCTs that reported ≥ grade 2 toxicity are summarized in Table 3. One study used the National Cancer Institute (NCI) common toxicity criteria for toxicity grading (73), two used the modified Radiation Therapy Oncology Group scale (34,71), and a fourth study reported second primary cancers only after treatment (20).

One retrospective study with 729 low-risk patients reported that LDR-BT might lead to more late grade 2 genitourinary and gastrointestinal toxicities but less sexual problems than might EBRT and that there may be no difference in the late grade 3 genitourinary and...
gastrointestinal toxicities between the two treatment groups (73). Another retrospective study, with 58,623 mixed low- or intermediate-risk patients and ≤ 20% of high-risk patients, reported that LDR-BT may lead to less second primary cancers at 2.8-5.3 years than might EBRT (20). The third retrospective study found no difference on grades 2-3 gastrointestinal toxicity between EBRT plus LDR-BT and LDR-BT in 825 mixed low- or intermediate-risk patients and ≤20% of high-risk patients (34).

**Patient Reported Outcomes Including Quality of Life**

Three RCTs (35,36,38,57) and 16 non-RCTs (22,24,26,28,32,33,37,40,43-45,48,50,51,60,72) provided data on patient-reported outcomes by using 20 different instruments. Table 4 summarizes the RCTs and the non-RCTs that reported no statistically significant differences at baseline for QOL among intervention groups, compared the changes of QOL from the baseline to the end of the study among treatment groups, or adjusted the baseline imbalances when reporting QOL outcomes.

When LDR-BT was compared with EBRT, two prospective studies with 792 patients showed no difference between the two groups for urinary domains, but LDR-BT led to less sexual and rectal problems than did EBRT in patients with mixed low-, intermediate-, and mixed ≤ 20% of high-risk patients (32,50).

When LDR-BT was compared with RP, three prospective studies with 913 patients in mixed low-, intermediate-, and ≤ 20% of high-risk showed that urinary incontinence and sexual potency favoured LDR-BT, while other urinary problems favoured RP; for bowel QOL, one study favoured RP, but the two other studies found no difference (26,37,50). In an RCT with 200 low-risk patients, results were consistent with the above observational studies at one year, but these differences in QOL were not sustained at five years (36).

When I-125 was compared with Pd-103, one RCT with 314 low-risk patients reported that Pd-103 resulted in worse overall QOL than did I-125 at one month, and I-125 resulted in worse overall QOL than did Pd-103 at six months, but there was no difference between the two groups at one and two years (38).

**ONGOING TRIALS**

The NCI clinical trials database (http://www.cancer.gov/clinicaltrials) was searched on March 20, 2012 and the Radiation Therapy Oncology Group web site (http://www.rtog.org/ClinicalTrials) were searched on September 12, 2012 for potential trials meeting the selection criteria for this systematic review. There are six eligible ongoing RCTs that would be eligible for inclusion in this systematic review (Appendix 4). The first two RCTs in Appendix 4 are the same RCTs as the Merrick et al and Wallner et al RCTs that were included in this review (46,68). The third ongoing trial compares LDR-BT plus 20 Gy EBRT with LDR-BT alone in patients with intermediate-risk prostate cancer. The fourth trial investigates the effect of LDR-BT against RP in patients with low- or intermediate-risk prostate cancer. The fifth trial tests neo-adjuvant plus concurrent and adjuvant androgen suppression (neo-HT plus adj-HT) plus elective pelvic nodal irradiation (EPNI) plus high dose conformal EBRT, against neo-HT plus adj-HT plus EPNI plus I-125 in patients with intermediate- or high-risk prostate cancer.

The sixth one will determine whether the combined EBRT and LDR-BT will result in better freedom from progression for five years compared to LDR-RT alone in selected patients with intermediate-risk prostate cancer.
Table 3. More than or equal to grade 2 toxicity.

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment (dose)</th>
<th>Risk (n) patients</th>
<th>Median age</th>
<th>Median F-up time; F-up rate</th>
<th>Second primary cancer</th>
<th>GU toxicity</th>
<th>Impotence</th>
<th>Gl toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdel-Wahab 20082, Retro (20)</td>
<td>LDR-BT vs. EBRT</td>
<td>Low + Int + ≤20%</td>
<td>67 y</td>
<td>2.8-3.3 vs. 4.2-5.3 y; NR</td>
<td>All-risk: 4.7% vs. 10.3%, p=0.001&lt;sup&gt;d&lt;/sup&gt;</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Zelefsky 20113, Retro (73)</td>
<td>LDR-BT (144 Gy I-125, 31% of pts with neo-HT) vs. EBRT (81 Gy, 32% with neo-HT)</td>
<td>Low: 448 vs. 281</td>
<td>62% of pts ≥65 y</td>
<td>77 mo, NA</td>
<td>Late grade 2: 15.6% vs. 4.3%, p&lt;0.001&lt;sup&gt;f&lt;/sup&gt;; late grade 3: 2.2% vs. 1.4%, NS</td>
<td>35% vs. 44%&lt;sup&gt;d&lt;/sup&gt;, p=0.04&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Late grade 2: 5.1% vs. 1.4%, p=0.018&lt;sup&gt;d&lt;/sup&gt;; late grade 3: 1.1% vs. 0.0%, NS</td>
<td></td>
</tr>
<tr>
<td>Gelblum 20004, Retro (34)</td>
<td>EBRT (41.4-45 Gy) + LDR-BT (100 Gy I-125 or 90 Gy Pd-103) vs. LDR-BT (144 Gy I-125 or 120 Gy Pd-103)</td>
<td>Low + Int + ≤20% high: 140 vs. 685</td>
<td>67 y</td>
<td>48 mo; 100%</td>
<td>NA</td>
<td>NA</td>
<td>Grade 2: 7.1% vs. 6.5%, NS; grade 3: 0.7% vs. 0.4%, NS</td>
<td></td>
</tr>
</tbody>
</table>

Unclear proportion of high-risk patients in any treatment group

| Wong 20095, Retro (71)         | LDR-BT (144 Gy I-125 or 120 Gy Pd-103, 32% with neo-HT) vs. 3D-CRT (66-71 Gy, 17% with neo-HT) vs. IMRT (76.5-77.4 Gy, 36% with neo-HT) vs. 3D-CRT + LDR-BT (45 Gy 3D-CRT + 110 Gy I-125 or 90 Gy Pd-103, 27% with neo-HT) | Low + Int + maybe ≤20% high: | NA | 49 vs. 62 vs. 56 vs. 63 mo; 100% | NA | 1). Acute grade 2: LDR-BT=68% vs. 3D-CRT=39% vs. IMRT=49% vs. 3D-EBRT+LDR-BT=73% and grade 3: 6% vs. 1% vs. 3% vs. 2%, p<0.001<sup>g</sup>; 2) Late grade 2: 45% vs. 16% vs. 27% vs. 52% and grade 3: 18% vs. 5% vs. 5% vs. 18%, p<0.001<sup>g</sup> | NA | 1). Acute grade 2: LDR-BT<sup>e</sup> vs. 3D-CRT<sup>e</sup>; IMRT<sup>e</sup> vs. 3D-CRT<sup>e</sup>; LDR-BT<sup>e</sup>; grade 3: 0% vs. 2%, p<0.001<sup>e</sup> 2). Late grade 2: 12% vs. 15% vs. 14% vs. 23% and grade 3: 1% vs. 2% vs. 1% vs. 5%, p<0.001<sup>e</sup> |

Abbreviations: n = sample size, F-up = follow-up, GU = genitourinary, GI = gastrointestinal, RCT = randomized controlled trial, Retro = retrospective, LDR-BT = low-dose rate brachytherapy, EBRT = external beam radiation therapy, Int = intermediate, vs. = versus, y = years, NR = not reported, p = p-value, NA = not available, Gy = gray, I-125 = iodine-125, pts = patients, neo-HT = neo-adjuvant hormonal therapy, IMRT = intensity-modulated radiotherapy, 3D-CRT = 3-D conformal radiation therapy, mo = month, NS = no significant difference, Pd-103 = palladium-103.

<sup>a</sup> Low-risk patients were defined as having prostate-specific antigen (PSA) < 10 ng/ml and clinical stage T1c to T2a and Gleason score < 7, intermediate-risk patients were defined as having PSA < 20 ng/ml or clinical stage T2b to T2c or Gleason score = 7 and are not otherwise low-risk patients, high-risk patients were defined as having PSA ≥ 20 ng/ml or clinical stage > T2c or Gleason score > 7 in tumor.

<sup>b</sup> Patients with grade I had Gleason scores 2-4 and patients with grade II had Gleason scores 5-7 and patients with grade III had Gleason scores 8-10 before January 1st, 2003, but after 2003, patients with Gleason score 7 moved to grade III.

<sup>c</sup> There was no statistical comparison for patient characteristics at the baseline between intervention groups. However, the EBRT group had more patients ≥ 65 years old (82% vs. 63%) and more high-risk patients (19.6% vs. 5.4%) than those in the LDR-BT group.

<sup>d</sup> Significance favored LDR-BT.

<sup>e</sup> Toxicity was measured by National Cancer Institute Common Toxicity Criteria for Adverse Events, version 3.0 toxicity scale.

<sup>f</sup> The baseline clinical characteristics were significantly different among the intervention groups.

<sup>g</sup> Significance favored 3D-CRT or IMRT.

<sup>h</sup> There was no statistical comparison for patient characteristics at the baseline between intervention groups. However, the lowest proportion of high-risk patients in the LDR-BT group.

<sup>i</sup> Toxicity was measured by a modified Radiation Therapy Oncology Group scale.

<sup>j</sup> There was no statistical comparison for patient characteristics at the baseline between intervention groups.
Table 4. Key evidence for patient reported outcomes.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PRO/QOL</th>
<th>Favouring LDR-BT</th>
<th>No Significant Difference</th>
<th>Favouring Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low-risk, Intermediate-risk, or &lt;20% high-risk patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDR-BT vs. EBRT</td>
<td>Urinary incontinence</td>
<td>• NS at 2-3 y (32,50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Urinary irritation</td>
<td>• NS at 2-3 y (32,50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sexual function</td>
<td>• Favoured LDR-BT at 2-3 y (32,50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rectal morbidity</td>
<td>• Favoured LDR-BT at 2-3 y (32,50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Overall QOL</td>
<td>• NS at 3 y (50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDR-BT vs. RP</td>
<td>Urinary incontinence</td>
<td>• NS at 12 mo and 5 y (36)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Urinary irritation</td>
<td>• NS at 5 y (36)</td>
<td>• Favoured RP at 6 and 12 mo (36)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sexual function</td>
<td>• Favoured LDR-BT at 6 and 12 mo (36)</td>
<td>• Favoured RP at 2-3 y (26,32,37,50)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rectal morbidity</td>
<td>• NS at 12 mo and 5 y (36)</td>
<td>• NS at 2-3 y (32,37,50)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Overall QOL</td>
<td>• NS, both LDR-BT and RP decreased by 1 y; returned to baseline level at 5 y (36)</td>
<td>• NS at 12 mo (24)</td>
<td>• Favoured RP at 2 y (26)</td>
</tr>
<tr>
<td>EBRT + LDR-BT vs. LDR-BT</td>
<td>Urinary function and bother</td>
<td>• Favoured LDR-BT at 21 mo (72)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sexual function and bother</td>
<td>• NS at 21 mo (72)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rectal function and bother</td>
<td>• NS at 21-24 mo (57,72)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Overall QOL</td>
<td>• NS at 21 mo (72)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I-125 vs. Pd-103</td>
<td>AUA score</td>
<td>• NS at 12 and 24 mo (38)</td>
<td>• Favoured Pd-103 at 6 mo (38)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rectal morbidity</td>
<td>• NS at 12 and 24 mo (38)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Low-risk + Intermediate-risk + unclear proportion of high-risk patients in in any treatment group</strong></td>
<td></td>
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<tr>
<td>LDR-BT vs. EBRT</td>
<td>Urinary function, bother, and incontinence:</td>
<td>• NS at 3.5-4.7 y (33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Urinary irritation</td>
<td>• Favoured EBRT at 3.5-4.7 y (33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sexual function and bother</td>
<td>• NS at 3.5-4.7 y (33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bowel function</td>
<td>• Favoured LDR-BT at 3.5-4.7 y (33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bowel bother:</td>
<td>• NS at 3.5-4.7 y (33)</td>
<td></td>
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</table>
### Treatment\(^a\) vs. PRO/QOL\(^b\) vs. Favouring LDR-BT vs. No Significant Difference vs. Favouring Comparator

<table>
<thead>
<tr>
<th>Treatment(^a)</th>
<th>PRO/QOL(^b)</th>
<th>Favouring LDR-BT</th>
<th>No Significant Difference</th>
<th>Favouring Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDR-BT vs. RP</td>
<td>Urinary function:</td>
<td>• Favoured LDR-BT at 1 y (48)</td>
<td>• NS at 1 y (48)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Urinary bother</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sex function</td>
<td>• Favoured LDR-BT at 1 y (48)</td>
<td>• NS at 1 y (48)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rectal problems</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Overall QOL</td>
<td></td>
<td>• NS at 1 y (48)</td>
<td></td>
</tr>
<tr>
<td>LDR-BT vs. EBRT vs. EBRT + LDR-BT</td>
<td>Sexual function and bother</td>
<td>• NS at 4 y (60)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDR-BT vs. 3D-CRT vs. IMRT vs. 3D-CRT + LDR-BT</td>
<td>Urinary function and urinary symptoms</td>
<td>• Favoured EBRT at median 16 mo (51)</td>
<td>• NS at median 16 mo (51)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sexual potency</td>
<td>• NS at median 16 mo (51)</td>
<td>• NS at median 16 mo (51)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rectal morbidity</td>
<td>• NS at median 16 mo (51)</td>
<td>• NS at median 16 mo (51)</td>
<td></td>
</tr>
<tr>
<td>EBRT vs. LDR-BT vs. RP</td>
<td>Urinary symptoms</td>
<td>• Favoured RP at 1 y (43)</td>
<td>• Favoured RP at 1 y (43)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sexual function</td>
<td>• NS at 1 y (43)</td>
<td>• Favoured RP at 1 y (43)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rectal morbidity</td>
<td>• NS at 1 y (43)</td>
<td>• Favoured RP at 1 y (43)</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** QOL = quality of life, LDR-BT = low-dose rate brachytherapy, vs. = versus, RP = radical prostatectomy, mo = months, y = years, I-125 = iodine-125, Pd-103 = palladium-103, AUA = the American Urological Association Symptom Index, NS = not statistically significant, Int = intermediate, EBRT = external beam radiation therapy, 3D-CRT = 3-D conformed radiation therapy, IMRT = intensity-modulated radiotherapy.

\(^a\) Some patients may have neo-adjuvant hormonal therapy in any treatment group.

\(^b\) Only RCTs and the following studies are shown in the table: patient QOL among intervention groups was not statistically different at the baseline, or the QOL changes from the baseline and the end of the study were compared, or studies adjusted the potential confounding factors.
DISCUSSION

Generally, high-quality RCTs provide the highest level of evidence to answer interventional research questions. Although observational studies often reach misleading conclusions because of their inability to control for confounding factors and the corresponding bias in the study results, such studies may be adequate to determine the toxicities of treatments (80). When RCTs are not high in quality, well-designed prospective comparative studies may provide supplemental evidence that can address the research questions. It should be noted that an American College of Surgeons Oncology Group phase III trial (SPIRIT) comparing RP and LDR-BT for patients with low-risk prostate cancer opened in 2002 but was closed in 2004 due to poor accrual (28). There are a lot of challenges to conducting an RCT in prostate cancer patients, including strong patient treatment preferences and concerns about receiving non-standard of care approaches (81). Therefore, comparative observational studies are also included in this systematic review if they meet the study selection criteria.

In this systematic review, even though 10 systematic reviews and 55 articles met the study selection criteria, there is no strong evidence to answer all three research questions fully. First, all the evidence has substantial potential for bias and considerable uncertainty associated with it (see the details in the Study Design and Quality section). Second, the 14 studies reporting bRFS used four different definitions for PSA failure in LDR-BT, EBRT, or LDR-BT plus EBRT groups; and six definitions in the RP group. That makes it hard to interpret and compare the data among the included studies. For LDR-BT, most publications before 2006 used the 1996 ASTRO definition (three consecutive rising PSA values each obtained at least three months apart) (82); after 2006, most publications followed the 2006 ASTRO definition (PSA should be higher than nadir plus 2 ng/ml) because of “benign PSA bounces” (83). For RP, the most common definition for PSA failure was a PSA value ≥ 0.2 ng/ml, > 0.3 ng/ml, or > 0.4 ng/ml. When LDR-BT was compared with RP, using the ASTRO 2006 definition for PSA failure creates a bias favouring LDR-BT, but adequate follow-up will reduce this bias (83), which is why only the outcome of bRFS at five years or more was analyzed and interpreted in this guideline. Third, about one half the included studies used neo-HT for some patients in one or all treatment groups typically intended to reduce the prostate size before treatment. Again, without the protection of randomization, it is unclear whether neo-HT impacted the treatment outcomes. Additionally, the role of neo-HT in prostate cancer treatment is beyond the scope of this systematic review. Fourth, before 2000, most publications on EBRT alone used a dose of 63 to 70 Gray; after 2000, most used a dose of 70 to 81 Gray. What the appropriate dose is for EBRT alone is beyond the scope of this guideline; however, the low-dose EBRT before 2000 may underestimate the effect of EBRT. Since most publications before 2001 used the 1996 ASTRO definition for PSA failure for LDR-BT, which would underestimate the effect of LDR-BT compared with that of RP or EBRT, that might balance the underestimation of low-dose EBRT as in the 1998 D’Amico et al study (30).

Although the quality of evidence from included studies was low to moderate in nature within this guideline, the evidence across the eligible studies consistently supports the conclusion that there is no difference in treatment efficacy between LDR-BT, EBRT, and RP in patients with low-, or intermediate-risk prostate cancer. When considering the toxicity and patient reported outcomes after these treatments, the consistent evidence supports the conclusion that LDR-BT does not cause more toxicity than EBRT or RP in the target population and suggests LDR-BT may lead to less second primary cancers at 2.8 to 5.3 years than would EBRT. When LDR-BT was compared with RP, LDR-BT seemed to have less urinary incontinence and sexual impotency and RP less urinary irritation and less rectal morbidity during the six to 12 months or even during the three years after treatment; however, these differences may diminish over time. When LDR-BT was compared with EBRT, it seems that LDR-BT has less sexual impotency and rectal morbidity during the three years after treatment. Given the
results from toxicity and patient-reported outcomes, the three treatment options (LDR-BT, EBRT, and RP) differ in their approaches and in their acute and long-term impacts on patients; hence, patient preference should be considered in treatment selection. For example, it may be better to choose LDR-BT rather than EBRT or RP for a patient who is concerned about his sexual function after treatment.

It seems that I-125 and Pd-103 were not different for bRFS rate at six years and for QOL at two years in patients with low-risk prostate cancer.

The 2010 Pickles et al study may provide further information regarding the first research question (84). Although this retrospective study did not meet the study inclusion criteria (i.e., the sample size from a retrospective study should be > 500), it is a relevant piece of work that fits within the Canadian context of practice. One hundred thirty-nine patients with low- or intermediate-risk prostate cancer in the LDR-BT group were matched with 139 patients in the EBRT group for PSA level, Gleason score, T stage, and the use and duration of neoadjuvant androgen deprivation therapy, but patients in the LDR-BT group were younger than those in the EBRT group. The median followed-up time was 5.5 years, and 31 patients in each group were intermediate-risk. The five-year bRFS rates in the LDR-BT group and the EBRT group were 95% versus 85% (p < 0.001) for all patients, 94% versus 88% (p < 0.001) for low-risk patients, and 100% versus 78% (p = 0.016) for intermediate-risk patients, respectively. At seven years, the bRFS rate was 95% versus 75% (p < 0.001) for all patients, respectively. Late urinary toxicity was worse in patients treated with LDR-BT, and late rectal toxicity was worse in patients treated with EBRT. Thus, this study also supports the conclusion of this systematic review that LDR-BT should be a treatment option for the target patients in addition to EBRT or RP.

When the final results of the Merrick et al and Wallner et al trials are published with the required sample size and enough follow-up time, and when the other four ongoing RCTs are completed, more evidence relevant to the research questions may become available.

This systematic review only focuses on the three stated research questions. Although the 2012 NCCN guideline (4) and the 2012 American Brachytherapy Society consensus guideline (85) are not systematic review-based, they included broader information about LDR-BT implementation in clinical practice, including patient selection for LDR-BT (absolute or relative contraindications) and details for the intraoperative procedure. Therefore, they may provide clinicians with some related and useful information about LDR-BT in prostate cancer that is beyond the scope of this guideline. On the other hand, it is well established that high-quality implants are necessary to provide optimal results in LDR-BT. However, in the eligible comparative studies and RCTs in this systematic review, no data on this issue were available.

It also should be noted that, while high-dose rate brachytherapy is another promising technique for patients with prostate cancer (86), examining this approach is beyond the scope of this guideline.

CONCLUSIONS

Some consistent evidence exists to support LDR-BT alone as a reasonable treatment alternative to EBRT alone or RP alone for patients with newly diagnosed low-or intermediate-risk prostate cancer who require or choose active treatment, and after balancing its treatment benefits and toxicities. There is insufficient evidence to recommend for or against the use of combined EBRT and BT in the target patients. I-125 and Pd-103 may not be different for bRFS and QOL in patients with newly diagnosed low-risk prostate cancer. There was no evidence that tested the efficacy of Cs-131 in the target population. Well-designed and good-quality RCTs and/or prospective comparative studies are required to investigate novel or targeted approaches in patients with low- or intermediate-risk prostate cancer.
CONFLICT OF INTEREST
The details of the authors’ conflict of interest are shown at the end of Section 3.

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- Sheila McNair and Hans Messersmith, Assistant Directors, PEBC
- Carol De Vito, Documents Manager, PEBC
- Harkanwal Randhawa, Student-Project Assistant, PEBC, for conducting the Data Audit
- Christina Lacchetti and Nofisat Ismaila, Research Coordinators, PEBC, for Internal Peer Review
Appendix 1. Members of the Working Group and the Genitourinary Cancer Disease Site Group (DSG).

Members of the Working Group

<table>
<thead>
<tr>
<th>Name</th>
<th>Position and Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>George Rodrigues - Guideline Chair</td>
<td>Radiation Oncologist, London Health Sciences Centre, London, Ontario</td>
</tr>
<tr>
<td>D. Andrew Loblaw - DSG Chair</td>
<td>Radiation Oncologist, Sunnybrook Health Sciences Centre, Toronto, Ontario</td>
</tr>
<tr>
<td>Michael Brundage</td>
<td>Radiation Oncologist, Cancer Centre of Southeastern Ontario, Kingston General Hospital, Kingston, Ontario</td>
</tr>
<tr>
<td>Xiaomei Yao</td>
<td>Research Coordinator, Program in Evidence-based Care, Cancer Care Ontario, Hamilton, Ontario</td>
</tr>
</tbody>
</table>

Members of the Genitourinary Cancer Disease Site Group

<table>
<thead>
<tr>
<th>Name</th>
<th>Position and Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sébastien Hotte - Chair</td>
<td>Medical Oncologist, Hamilton Health Sciences, Hamilton, Ontario</td>
</tr>
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<td>Neil Fleshner - Chair</td>
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<td>Charles Catton</td>
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<td>Urban Emmenegger</td>
<td>Medical Oncologist, Sunnybrook Health Sciences Centre, Toronto, Ontario</td>
</tr>
<tr>
<td>Anthony Finelli</td>
<td>Surgeon/Urologist, Princess Margaret Hospital, Toronto, Ontario</td>
</tr>
<tr>
<td>John Hastie</td>
<td>Patient representative, Simcoe, Ontario</td>
</tr>
<tr>
<td>Himu Lukka</td>
<td>Radiation Oncologist, Hamilton Health Sciences, Hamilton, Ontario</td>
</tr>
<tr>
<td>Scott Morgan</td>
<td>Radiation Oncologist, The Ottawa Hospital Cancer Centre, Ottawa, Ontario</td>
</tr>
<tr>
<td>Roanne Segal</td>
<td>Medical Oncologist, The Ottawa Hospital Cancer Centre, Ottawa, Ontario</td>
</tr>
<tr>
<td>Bobby Shayegan</td>
<td>Surgeon/Urologist, St. Joseph’s Healthcare, Hamilton, Ontario</td>
</tr>
<tr>
<td>Tom Short</td>
<td>Surgeon/Urologist, Credit Valley Hospital, Mississauga, Ontario</td>
</tr>
<tr>
<td>John Srigley</td>
<td>Pathologist, Credit Valley Hospital, Mississauga, Ontario</td>
</tr>
<tr>
<td>Padraig Warde</td>
<td>Radiation Oncologist, Princess Margaret Hospital, Toronto, Ontario</td>
</tr>
<tr>
<td>Eric Winquist</td>
<td>Medical Oncologist, London Health Sciences Centre, London, Ontario</td>
</tr>
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Appendix 2. MEDLINE search strategy (October 27, 2011).

Database(s): Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1948 to Present

Search Strategy:

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The addition of Cs-131 to the MEDLINE literature search (May 16, 2012).

Database(s): Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present

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Appendix 3. EMBASE search strategy (October 27, 2011).

Database(s): Embase 1996 to 2011 Week 42
Search Strategy:

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The addition of Cs-131 to the EMBASE literature search (May 16, 2012).

Database(s): Embase 1996 to 2012 Week 19
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</table>
### Appendix 4. Ongoing trials (checking on March 20, 2012).

**1. I-125 Versus Pd-103 for Medium Risk Prostate Cancer**
- **Phase:** Phase III
- **Type:** Treatment
- **Status:** Active
- **Age:** 40 to 90
- **Sponsor:** Other
- **Protocol IDs:** 02-4407-V04, NCT00486499
- **Estimated sample size:** 660
- **Study start date:** March 2003

**Summary**
The shorter half-life of Pd-103 versus I-125, will increase the rate of tumor eradication. A total of 660 patients with AJC clinical stage T1c-T2a prostatic carcinoma (Gleason grade 7 to 9 and/or PSA 10-20 ng/ml) will be randomized to implantation with I-125 (144 Gy) versus Pd-103 (124 Gy).

**2. Pd-103 Dose De-Escalation for Early Stage Prostate Cancer: A Prospective Randomized Trial**
- **Phase:** Phase III
- **Type:** Treatment
- **Status:** Active
- **Age:** No age specified
- **Sponsor:** Other
- **Protocol IDs:** 05-8-3, NCT00247312
- **Estimated sample size:** 600
- **Estimated primary completion date:** October 2008

**Summary**
The purpose of this study is to determine the most appropriate radiation implant dose for palladium-103 monotherapy. Radiation dose is related to potential cure. From previously published studies, it appears that the prescribed radiation dose can be reduced by 14-20% without any difference in potential cure (in this study, the dose is being decreased 10%). Although most patients tolerate brachytherapy well, complications to appear to be related to radiation exposure to normal structures (i.e. urethra, rectum and proximal penis). By reducing the prescribed dose, it is conceivable that fewer patients will experience side effects and complications.

**3. Low Dose Supplemental External Radiation With Pd-103 Versus Pd-103 Alone for Prostate Cancer**
- **Phase:** Phase III
- **Type:** Treatment
- **Status:** Active
- **Age:** 40 to 80
- **Sponsor:** Other
- **Protocol IDs:** 04-8-10, NCT00241384
- **Estimated sample size:** 300
- **Estimated primary completion date:** September 2010

**Summary**
The primary purpose of this study is to evaluate two treatment regimens for prostate cancer, prostate implant with 20 Gy of external beam radiation therapy versus prostate implant with 0 Gy of external beam radiation therapy. Patients diagnosed with intermediate risk prostate cancer between the ages of 40 and 80 who have chosen brachytherapy with or without external beam radiation therapy as their intended treatment will be eligible and will be offered participation.

**4. Implant Radiation Therapy or Surgery in Treating Patients With Prostate Cancer**
- **Phase:** Phase III RCT
- **Type:** Educational/Counseling/Training, Treatment
- **Status:** Active
- **Age:** Adult
- **Sponsor:** Other
- **Protocol IDs:** CDR0000668741, USCTU-SABRE1, ISRCTN88144169, EU-21018, CRUK-CTAAC-C328/A8692, EU-21018, CRUK-CTAAC-C328/A8692, NCRN-11061813, US-SABRE1, NCT01098331
- **Estimated sample size:** 400
Summary
PURPOSE: This randomized clinical trial is studying implant radiation therapy to see how well it works compared with surgery in treating patients with low- or intermediate-risk prostate cancer.

### 5. Androgen Suppression Combined With Elective Nodal and Dose Escalated Radiation Therapy

**Phase:** Phase III  
**Type:** Treatment  
**Status:** Active  
**Age:** 18 and over  
**Sponsor:** Other  
**Protocol IDs:** R04-0050, NCT00175396  
**Estimated sample size:** 400  
**Estimated primary completion date:** December 2012

**Summary**
The purpose of this trial is to compare two similar treatments for patients diagnosed with prostate cancer. The two treatment arms being compared are: (Standard Arm) hormone therapy, which will prevent the production of the male hormone, testosterone, by the testicles, and pelvic external beam radiation therapy (EBRT) followed by a high-dose, conformal EBRT boost versus (Investigational Arm) hormone therapy and pelvic EBRT followed by permanent 125-Iodine brachytherapy boost (implantation of radioactive iodine sources or "seeds" into the prostate). Patients must have histologically-proven prostate cancer stage T1c - T3a (UICC 1997). Patients with clinically organ-confined disease must meet the Canadian consensus definition of intermediate risk disease (i.e any one or more of: CS = T2b [UICC1997 = bilateral palpable intra-capsular disease], GS = 7, or iPSA >10 and 20). Patients with Gleason sum 8 and/or PSA > 20 must have a CT pelvis, and nuclear medicine bone scan showing no evidence of nodal (N0) or distant metastases (M0).

### 6. A Phase III Study Comparing Combined External Beam Radiation And Transperineal Interstitial Permanent Brachytherapy With Brachytherapy Alone For Selected Patients With Intermediate Risk Prostatic Carcinoma

**Phase:** Phase III  
**Type:** Treatment  
**Status:** Active  
**Age:** 18 and over  
**Sponsor:** Other  
**Protocol IDs:** RTOG-0232  
**Estimated sample size:** 586  
**Status:** Closed to Accrual  
**Estimated primary completion date:** Unknown

**Summary**
To determine whether combined external beam radiation and transperineal interstitial permanent brachytherapy will result in better freedom from progression for 5 years compared to brachytherapy alone among selected patients with intermediate risk prostatic carcinoma.
REFERENCES


Evidence-Based Series 3-10 Version 2: Section 3

A Quality Initiative of the Program in Evidence-Based Care, Cancer Care Ontario

Low-Dose Rate Brachytherapy for Patients with Low- or Intermediate-Risk Prostate Cancer: Development Methods, Recommendations Development and External Review Process

G. Rodrigues, X. Yao, A. Loblaw, M. Brundage, J. Chin, and the Genitourinary Cancer Disease Site Group

Report Date: October 31, 2012

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, termed Disease Site Groups (DSGs), as well as other groups or panels called together for a specific topic, all mandated to develop the PEBC products. These panels are comprised of clinicians, other health care providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based guidelines, known as Evidence-based Series (EBS) reports, using the methods of the Practice Guidelines Development Cycle (1,2). The EBS report consists of an evidentiary base (typically a systematic review), an interpretation of and consensus agreement on that evidence by our Groups or Panels, the resulting recommendations, and an external review by Ontario clinicians and other stakeholders in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each document, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original guideline information.

The Evidence-Based Series

Each EBS is comprised of three sections:

- **Section 1: Guideline Recommendations.** Contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the Group or Panel involved and a formalized external review in Ontario by review participants.
Section 2: Evidentiary Base. Presents the comprehensive evidentiary/systematic review of the clinical and scientific research on the topic and the conclusions reached by the Group or Panel.

Section 3: EBS Development Methods and External Review Process. Summarizes the EBS development process and the results of the formal external review of the draft version of the EBS.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES
Development and Internal Review
This EBS was developed by the Genitourinary Cancer DSG of the CCO PEBC. The series is a convenient and up-to-date source of the best available evidence on the comparison among LDR-BT, EBRT, and RP for clinical outcomes in patients with newly diagnosed low- or intermediate-risk prostate cancer, developed through a review of the evidentiary base, evidence synthesis, and input from external review participants in Ontario. During the discussion, three key issues were raised by Genitourinary Cancer DSG members below, followed by the bulleted responses made by the Working Group:

1. The different definitions of PSA failure as part of the measurement of bRFS outcome were used in the studies that compared LDR-BT with RP.
   - For LDR-BT, most publications before 2006 used the 1996 American Society for Therapeutic Radiology and Oncology (ASTRO) definition: three consecutive rising PSA values each obtained at least three months apart (3). After 2006, most publications followed the 2005 ASTRO definition (PSA should be higher than nadir plus 2 ng/ml) (4) because of “benign PSA bounces”, defined as patients who met the criteria for biochemical relapse using the Phoenix PSA definition of failure but who had a subsequent decrease in PSA level without intervention to a new nadir of ≤ 0.5 ng/ml (5). The 1996 ASTRO definition may underestimate the effect of LDR-BT. For RP, the failure of PSA was mostly defined as PAS value ≥ 0.2 ng/ml, > 0.3 ng/ml, or >0.4 ng/ml among the included studies. Using the ASTRO 2005 definition for PSA failure creates a bias favoring LDR-BT when compared with RP, but adequate follow-up will reduce this bias (4). For this reason bRFS at ≥ 5 years was analysed and interpreted in this guideline as a key outcome. Additionally, there was no significant difference between LDR-BT and RP for the outcome of PCSM/OM at ≥10 years.

2. For intermediate-risk patients, we should look at the results of EBRT with > 76 Gray versus LDR-BT in matched patients.
   - Before 2000, most publications on EBRT alone used dose of 63-70 Gray; after 2000, most publications on EBRT used dose of 70-81 Gray. What the appropriate dose is for EBRT alone is beyond the scope of this guideline. However, low-dose EBRT before 2000 may underestimate the effect of EBRT. Since most of the publications before 2001 used the 1996 ASTRO definition for PSA failure for LDR-BT, which would underestimate the effect of LDR-BT when it was compared with RP or EBRT, that would balance the underestimation of low-dose EBRT, as in the 1998 D'Amico et al study (6).

3. Low-intermediate and high-intermediate populations should be separated.
   - At the beginning of this project, the working group decided to classify the low-risk and intermediate-risk patients with prostate cancer by using the definition in the Genitourinary Radiation Oncologists of Canada guideline (7) and the NCCN clinical practice guideline (8). In addition, no included study used the terms of low-intermediate-risk patients and high-intermediate-risk patients, but if it proves necessary, we will consider these risk terms when updating this guideline.
Report Approval Panel

Prior to the submission of this EBS draft report for external review, the report was reviewed and approved by the PEBC Report Approval Panel (RAP), which consists of three members: two oncologists with expertise in clinical and methodology issues, and a methodologist. The key issues raised by the RAP are below, followed by the bulleted modifications and/or responses made by the guideline authors:

1. More should be made of the differences in acute and long-term toxicity as the data really do not show any difference in survival. It is the difference in therapeutic approach and the toxicity (acute and chronic) that should be the determinants of whether one treatment is used in preference to other by patients. The authors should highlight some of the side effects that are important to patients. As which prostate treatments to receive is now coming down to patient choice what is involved in treatment by way of procedures, discomfort, hospital stay, acute and late toxicities needs to be laid out in a clear way that enables patients to make decisions. Of course their physicians need to understand these differences also and this document does not do that at all well.
   • We have added more details of the differences between LDR-BT, EBRT, and RP in Section 1. Justification for Recommendation, and we have also added more description of the different side effects for the different treatment options in Section 2. Discussion.

2. The discussion does not provide any direction about how the recommendations can be put into practice and specifically what needs to be in place at a cancer center in order to offer this treatment. Also it does not describe what information clinicians need to present to patients so they can make informed choices.
   • Based on the original three research questions, how to put the recommendations into practice and what information clinicians would need to present them to patients are beyond the scope of this guideline. However, we have added a qualifying statement that 2012 NCCN guideline and 2012 American Brachytherapy Society consensus guideline may provide clinicians with broader information about LDR-BT implementation in clinical practice, including patient selection for LDR-BT (absolute or relative contraindications) and details for the intraoperative procedure, which are beyond the scope of this guideline.

3. There could be a brief description of what resources need to be in place in order to deliver low dose rate brachytherapy in a cancer center.
   • Again, based on the original three research questions, this topic is beyond the scope of this guideline.

4. It's not clear why active surveillance is not a comparison. Even if a patient wanted treatment or a clinician wanted to offer treatment, the treatments under consideration in this guideline should demonstrate that they superior to nothing. A statement about why active surveillance was not included is required.
   • We have added one sentence under in Section 1. Introduction and Section 2. Introduction to explain why active surveillance was not considered among the options in this guideline. The issue of active surveillance will be addressed in a separate guideline, EBS 17-9, currently under development at the PEBC and scheduled to be published in 2013.

5. The 10 systematic reviews were ultimately not used or eligible, correct? Where did they go?
   • We have added an explanation in Section 2. Literature Search Results as to where the 10 systematic reviews were and why they were not discussed further.
6. There is a list of names in Appendix 1 for guideline development group, but it is unclear what their discipline is or who they represent.
• We have added participant disciplines to Section 2. Appendix 1.

External Review by Ontario Clinicians and Other Experts

The PEBC external review process is two-pronged and includes a targeted peer review that is intended to obtain direct feedback on the draft report from a small number of specified content experts and a professional consultation that is intended to facilitate dissemination of the final guidance report to Ontario practitioners.

Following the approval of the document at Internal Review, the Genitourinary Cancer DSG circulated the draft document with recommendations modified as noted under Internal Review, above, to external review participants for review and feedback.

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<th>BOX 1:</th>
<th>DRAFT RECOMMENDATIONS (approved for external review July 11, 2012)</th>
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<td>TARGET POPULATION</td>
<td>Patients with newly diagnosed low- or intermediate-risk prostate cancer (low-risk patients are defined as having a PSA &lt; 10 ng/ml, clinical stage T1c-T2a, and Gleason score &lt; 7; intermediate-risk patients are defined as having a PSA greater than or equal to 10 ng/ml but less than 20 ng/ml or a clinical stage T2b-T2c or a Gleason score = 7) who require or choose active treatment and are not considering or are not suitable for active surveillance.</td>
</tr>
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<td>QUESTIONS</td>
<td>4. What is the efficacy of low-dose rate brachytherapy (LDR-BT) alone for clinical outcomes (i.e., biochemical relapse-free survival [bRFS], overall survival [OS] or overall mortality [OM], prostate cancer-specific mortality [PCSM], negative biopsy rate, salvage treatment rate, toxicity, or patient-reported outcomes including quality of life [QOL]) compared with external beam radiation therapy (EBRT) alone, or radical prostatectomy (RP) alone?</td>
</tr>
<tr>
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<td>5. What is the efficacy of LDR-BT combined with EBRT for clinical outcomes compared with LDR-BT alone, EBRT alone, or RP alone?</td>
</tr>
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<td>6. Among three isotopes used for LDR-BT (Iodine-125 [I-125], Palladium-103 [Pd-103], and Cesium-131 [Cs-131]), which isotope maximizes clinical outcomes?</td>
</tr>
<tr>
<td>INTENDED USERS</td>
<td>Radiation oncologists, urological surgeons, and other clinicians who provide care for patients defined by the target population.</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>In 2001, the Genitourinary DSG and the PEBC in Ontario, Canada, developed a guideline on LDR-BT in patients with early-stage low-grade prostate cancer (EBS 3-10 The Use of Brachytherapy in T1 or T2 Prostate Cancer) (1). Since the main evidence in the 2001 guideline was from single-arm studies and stronger levels of evidence such as comparative studies or randomized controlled trials (RCTs) have become available during the last decade, an updated guideline has been deemed necessary. To date, three isotopes are available for LDR-BT in patients with prostate cancer: I-125, Pd-103, and Cs-131, which each has different half-life times: 59.4 days, 17.0 days, and 9.7 days, respectively (2). It is unclear which isotope maximizes clinical outcomes when used in...</td>
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patients with newly diagnosed low- or intermediate-risk prostate cancer. This current updated guideline focuses on the above three research questions regarding LDR-BT alone, LDR-BT with EBRT, and the selection of an isotope. As noted in the questions, the target patients for this guideline are those who require or choose active treatment and not patients who are considering and are suitable for active surveillance. A separate guideline (EBS 17-9 Active Surveillance for the Management of Localized Low-Risk Prostate Cancer) is being developed by the PEBC and will be available on the CCO website in 2013.

RECOMMENDATIONS AND KEY EVIDENCE

The Genitourinary DSG and the PEBC offer the following recommendations based on the current evidence assessed in conjunction with this systematic review:

- For patients with newly diagnosed low-risk or intermediate-risk prostate cancer who require or choose active treatment, LDR-BT alone is a treatment option as an alternative to EBRT alone or RP alone.
- I-125 and Pd-103 are each reasonable isotope options in patients with prostate cancer.
- No recommendation can be made for or against using Cs-131 or the combination of EBRT and LDR-BT in the target patient population.
- Patients should be encouraged to participate in clinical trials to test novel or targeted approaches in this disease.

Qualifying Statement

- The following LDR-BT doses were suggested from the included studies when LDR-BT was used alone: 140-160 Gray for I-125, or 108-125 Gray for Pd-103.
- The following EBRT doses were suggested from the included studies when EBRT was used alone after 2001: 70-81 Gray (Determining the appropriate dose for EBRT alone is beyond the scope of this guideline).
- Patient preference should be considered in treatment selection due to the different approaches involved with these three treatments (LDR-BT, EBRT, and RP) and their different acute and long-term impacts on patients.
- Not all patients with intermediate-risk disease may be appropriate for LDR-BT monotherapy. Patients with multiple risk factors (PSA > 10 ng/ml, Gleason score 7, Gleason primary pattern 4, T2c disease, and high positive core positivity), may be more appropriately treated with other modalities (or combinations of modalities). The exact definition for high-intermediate disease has not yet appeared in the literature or been agreed upon by other consensus approaches.
- The 2012 National Comprehensive Cancer Network (NCCN) guideline (3) and 2012 American Brachytherapy Society consensus guideline (4) may provide clinicians with broader information about LDR-BT implementation in clinical practice beyond the scope of this guideline, including patient selection for LDR-BT (absolute or relative contraindications) and details of the intraoperative procedure.

Key Evidence

- There were 10 systematic reviews (5-14) and 55 study articles (15-69) included in this guideline; 36 articles summarized in Tables 2-4 in Section 2 were the primary evidence-base on which recommendations were made. Among them, six articles reported on three RCTs, 14 on prospective studies, and 16 on retrospective studies. The quality of evidence from the included studies was considered to be low to
- For bRFS at ≥ 5 years:
  - LDR-BT compared with EBRT: Three retrospective studies with 1560 patients showed there were no significant differences between the two groups (20, 25, 60). One of these retrospective studies showed p > 0.25 in low-risk patients (25); another one showed the bRFS rate was 90% for LDR-BT and 86% for EBRT (p = 0.969) in intermediate-risk patients (60); the third one showed a hazard ratio (HR) of 1.04 (95% confidence interval [CI], 0.56-1.94; p = 0.900) in mixed low-, intermediate- and ≤20% of high-risk patients (20).
  - LDR-BT compared with RP: One RCT with 200 low-risk patients (LDR-BT = 92% versus [vs.] RP = 91%) (31) and one retrospective study with 927 low-risk patients (risk ratio [RR], 1.1; CI, 0.3-3.6) (25) showed no statistical difference between two groups; two retrospective studies showed that LDR-BT led to a higher bRFS rate than did RP in 578 intermediate-risk patients (90% vs. 60%-80%) (60) and in 674 mixed low-, intermediate- and ≤20% of high-risk patients (HR, 0.44; CI, 0.25-0.77) (20), respectively.
  - LDR-BT, I-125 compared with Pd-103: One RCT with 263 low-risk patients showed no significant differences between the two groups (bRFS 96.8% vs. 99.2%, p = 0.149) (41).

- For PCSM/OM at ≥ 10 years:
  - LDR-BT compared with RP: One retrospective study with 41,395 mixed low-risk and intermediate-risk patients reported no statistical difference between two groups for PCSM or OM, regardless of age. For men < 60 years old, PCSM was 0.5% vs. 1.3% (p = 0.380) and OM was 7.9% vs. 7.8% (p = 0.908), respectively; for men ≥ 60 years old, PCSM was 5.3% vs. 3.8% (p = 0.595) and OM was 37.1% vs. 27.4% (p = 0.625), respectively (59).

- For toxicity:
  - LDR-BT compared with EBRT: One retrospective study with 729 low-risk patients reported that LDR-BT may lead to more late grade 2 genitourinary and gastrointestinal toxicities but less impotence than EBRT and that there may be no difference for the late grade 3 genitourinary and gastrointestinal toxicities between two groups (68). Another retrospective study reported that LDR-BT might lead to less second primary cancers at 2.8-5.3 years than might EBRT in 58,623 mixed low-, intermediate-, and ≤ 20% of high-risk patients (15).

- For patient-reported outcomes:
  - LDR-BT compared with EBRT: Two prospective studies showed no difference between the two groups for urinary domains, but LDR-BT led to less sexual and rectal problems than did EBRT (low- and intermediate-risk patients were both included) (27, 45).
  - LDR-BT compared with RP: Three prospective studies showed that urinary incontinence and sexual potency favored LDR-BT, while urinary irritation favored RP; for bowel patient-reported outcomes, one study favored RP but two other studies found no difference (low- and intermediate-risk patients together) (21, 32, 45). In an RCT in low-risk patients, results were consistent with the above observational studies at one year, but these differences for patient-reported outcomes were not sustained at five years (31).
  - For LDR-BT, I-125 compared with Pd-103: One RCT reported that Pd-103 resulted in worse overall QOL than did I-125 at one month, and I-125 resulted in worse overall QOL than did Pd-103 at six months, but there was no difference between
the two groups at one and two years (33).

**Justification for Recommendation**

Many included studies in this guideline are retrospective studies. Retrospective studies may have more biases than prospective studies and RCTs and may overestimate the effects of the treatments. For this reason, a high criterion for sample size in retrospective studies of greater than or equal to 500 subjects was used. Although the quality of evidence from included studies is low to moderate in this guideline, the evidence across the eligible studies consistently supports the conclusion that there is no difference in efficacy between LDR-BT and EBRT, or between LDR-BT and RP in patients with favourable risk prostate cancer (predominately low-, or intermediate-risk, but studies were allowed to include < 20% of high-risk prostate cancer). From clinical experience, LDR-BT does have advantages over EBRT and RP for convenience and recovery: only one outpatient treatment visit is required for LDR-BT compared to 35-44 treatment visits for EBRT; recovery is significantly shorter for LDR-BT (generally within a few days) than that for RP (one to four weeks depending on the procedures).

When considering toxicity and patient-reported outcomes, including QOL, the evidence consistently supports the conclusion that LDR-BT does not cause more toxicity than do EBRT or RP, and LDR-BT may lead to less second primary cancers at 2.8 to 5.3 years than may EBRT. During the six months to three years after treatment, the data suggests that LDR-BT is associated with less urinary incontinence and sexual impotency when compared with RP, and RP leads to less urinary irritation and less rectal morbidity than does LDR-BT. However, these differences may diminish over time. When LDR-BT was compared with EBRT, it seems that LDR-BT results in less sexual impotency and rectal morbidity in the three years after treatment. Patient preference should be considered in treatment selection due to the different approaches involved with these three treatments (LDR-BT, EBRT, and RP) and their different acute and long-term impacts on patients.

Hence, after balancing treatment benefit and harm, for patients with newly diagnosed low-risk prostate cancer, LDR-BT should continue to be a treatment option in Ontario (the alternatives being EBRT or RP alone), as there is insufficient evidence to support that one of the three treatment options is more effective than the others, and all have comparable effects on patient-reported outcomes (albeit in different domains). For patients with newly diagnosed intermediate-risk prostate cancer, since EBRT and RP are already treatment options in Ontario, LDR-BT should become a treatment option as well, based on the above evidence.

One RCT showed that I-125 and Pd-103 were not different for bRFS at six years and for QOL at two years in patients with low-risk prostate cancer. Thus, I-125 and Pd-103 are each reasonable isotope options for prostate cancer patients.

It should be noted that high-dose rate brachytherapy is another promising technique for patients with prostate cancer (70), but its study is beyond the scope of this guideline. Costing outcomes were also outside the scope of this work.

**FUTURE RESEARCH**

A search of the National Cancer Institute (NCI) clinical trials database (http://www.cancer.gov/clinicaltrials) for the ongoing trials on March 20, 2012 resulted in five ongoing RCTs that met the selection criteria for this guideline. The two RCTs are already included in this guideline (41,63), but the results of preplanned full sample size analyses have not been published. The third ongoing trial compares LDR-BT plus 20 Gy EBRT with LDR-BT alone in patients with intermediate-risk prostate cancer. The fourth trial investigates the effect of LDR-BT versus RP in patients with low- or intermediate-risk prostate cancer.
prostate cancer. The fifth trial tests neo-adjuvant hormonal therapy (neo-HT) plus concurrent and adjuvant androgen suppression (adj-HT) plus elective pelvic nodal irradiation (EPNI) plus high dose conformal EBRT, against neo-HT plus adj-HT plus EPNI plus I-125 in patients with intermediate- or high-risk prostate cancer. This guideline has highlighted the fact that many important questions remain potential subjects of further investigation, such as the effect of Cs-131 and the effect of the combination of EBRT and LDR-BT on the target patient population. Well-designed and good-quality RCTs and prospective comparative studies are required to answer these research questions in patients with low- or intermediate-risk prostate cancer.

**Methods**

**Targeted Peer Review:** During the guideline development process, 10 targeted peer reviewers from Ontario and other provinces considered to be clinical and/or methodological experts on the topic were identified by the Genitourinary Cancer DSG. Several weeks prior to completion of the draft report, the nominees were contacted by email and asked to serve as reviewers. Six reviewers agreed and the draft report and a questionnaire were sent via email for their review. The questionnaire consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a guideline. Written comments were invited. The questionnaire and draft document were sent out on July 19, 2012. Follow-up reminders were sent at two weeks (email) and at four weeks (telephone call). The Genitourinary Cancer DSG reviewed the results of the survey.

**Professional Consultation:** Feedback was obtained through a brief online survey of health care professionals who are the intended users of the guideline. All the clinicians in the PEBC database who were searched out by using “genitourinary” were contacted by email to inform them of the survey. Participants were asked to rate the overall quality of the guideline (Section 1) and whether they would use and/or recommend it. Written comments were invited. Participants were contacted by email and directed to the survey website where they were provided with access to the survey, the guideline recommendations (Section 1) and the evidentiary base (Section 2). The notification email was sent on July 19, 2012. The consultation period ended on August 30, 2012. The Genitourinary Cancer DSG reviewed the results of the survey.

**Results**

**Targeted Peer Review:** Responses were received from five of six reviewers by September 5, 2012: RH, MM, JM, and TP from Vancouver British Columbia, and DD from London Ontario. Key results of the feedback survey are summarized in Table 1. Summary of main written comments from targeted peer reviewers and the working group’s modifications/actions taken in response are summarized in Table 2.
Table 1. Responses to nine items on the targeted peer reviewer questionnaire.

<table>
<thead>
<tr>
<th>Question</th>
<th>Reviewer Ratings (n=5)</th>
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<tbody>
<tr>
<td></td>
<td>Lowest Quality (1)</td>
</tr>
<tr>
<td>1. Rate the guideline development methods.</td>
<td>0</td>
</tr>
<tr>
<td>2. Rate the guideline presentation.</td>
<td>0</td>
</tr>
<tr>
<td>3. Rate the guideline recommendations.</td>
<td>0</td>
</tr>
<tr>
<td>4. Rate the completeness of reporting.</td>
<td>0</td>
</tr>
<tr>
<td>5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?</td>
<td>0</td>
</tr>
<tr>
<td>6. What are the barriers or enablers to the implementation of this guideline report?</td>
<td>Financial. Funding of seeds by CCO. Appropriate referrals of patients to providers (may get surgery w/o having a brachytherapy consult). Treatment resources - most Ontario institutions do not have enough OR / anaesthesia time to handle more cases. Canadian Cancer centres may lack infrastructure to immediately offer LDR-BT. Also LDR-BT expertise is not universal amongst Canadian radiation oncologists. Hence infrastructure work will be required. Due to the outcome dependence on quality, appropriate training and quality-assessment infrastructure will be necessary for the existing and new LDR-BT programs. Leading examples of excellence exist within Ontario and in other provinces.</td>
</tr>
<tr>
<td>7. Rate the overall quality of the guideline report.</td>
<td>Lowest Quality (1)</td>
</tr>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>8. I would make use of this guideline in my professional decisions.</td>
<td>Strongly Disagree (1)</td>
</tr>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>9. I would recommend this guideline for use in practice.</td>
<td>0</td>
</tr>
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</table>

Table 2. Modifications/actions/responses regarding main written comments from targeted peer reviewers.

<table>
<thead>
<tr>
<th>Main written comments</th>
<th>Modifications, actions, or responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The guideline authors did a systematic review, but they have left out a number of important studies including all the publications from our centre which has the largest LDR-PB program in Canada with more than 4000 implants to date and some 50 peer reviewed articles. At our centre LDR-PB is regarded as having clearly superior biochemical outcomes to EBRT, but comparisons with RP are compromised by different biochemical endpoints.</td>
<td>Among the 11 citations that the reviewer provided in his survey, four articles were published after October 27, 2011 (which was our literature search date), and other 7 articles did not meet our preplanned study selection criteria. Among the four articles that were published after October 27, 2012, one did not meet our study selection criteria, two have not been indexed in Medline by September 11, 2012, and the fourth one was a systematic review paper and all its analysed papers were included in our literature search. If new evidence that would result in changes to these recommendations becomes available, an update of literature search for this guideline will be initiated as soon as possible.</td>
</tr>
<tr>
<td>2. Two papers need to be included: (1). Grimm P, Billiet I, Bostwick D, Dicker</td>
<td>The first paper was the systematic review that we just mentioned above that all its analysed papers</td>
</tr>
</tbody>
</table>


were included in our literature search. Although it was published in February 2012, its literature search date was from 2000 to 2010.

The second paper was a retrospective study with a sample size of 278 that did not meet our preplanned study selection criteria (i.e., the sample size from a retrospective study should be >500). However, the guideline authors thought it was a relevant piece of work that fit within the Canadian context of practice. Thus, one paragraph on page 28 in Section 2 described this study and also stated that “this study also supports the conclusion of this systematic review that LDR-BT should be a treatment option for the target patients in addition to EBRT or RP”.

3. The recommendations are clinically sound, but lack any compelling arguments to favour LDR-BT, this is a strategic error in this reviewer’s opinion.

Without high-quality comparative studies or RCTs, we are unable to make a strong conclusion that LDR-BT is greater than other treatment options.

4. (1). It is unclear which intermediate risk patients are unsuitable (just says those with multiple factors). This leaves a lot open to interpretation.

(2). The document does not conclude whether it is or is not suitable to combine EBRT, and Brachytherapy, that is, should it be done or not done or is standard of care in US and current RTOG trials, (OBIS, 0924)

(1). There is not clear evidence to let us make very clear recommendations for the intermediate-risk patients. Thus, under Qualify statement on Page 2 in Section 1, we stated that “Patients with multiple risk factors (PSA >10 ng/ml, Gleason score 7, Gleason primary pattern 4, T2c disease, and high positive core positivity), may be more appropriately treated with other modalities (or combinations of modalities). The exact definition for high-intermediate disease has not yet appeared in the literature or been agreed upon by other consensus approaches.”

(2). There is insufficient evidence to recommend for or against the use of combined EBRT and BT in the target patients up to date. In the ongoing trial of RTOG-0924 RTOG-0924, NCT01368588, they mixed high-dose rate brachytherapy and LDR-BT together and also their target patients include high-risk patients. Thus, this ongoing trial beyond this guideline scope and is not listed under ONGOING TRIALS in Section 2.

5. (1). The second paragraph on Page 12: “with ERT and RP” reference to RP is inappropriate here as no radiation is used with RP.

(2). The third paragraph from bottom on Page 16: “bRFS rates at greater than” should read “less than”.

We have revised them based on the reviewer’s comments.

Professional Consultation: Sixty of 192 (31%) responses were received. Twelve stated that they did not have interest in this area or were unavailable to review this guideline at this moment. The key results of the feedback survey from 48 doctors are summarized in Table 3.
The main comments from the professional consultants and the working group’s modifications/actions taken in response are summarized in Table 4.

### Table 3. Responses to four items on professional consultation survey.

<table>
<thead>
<tr>
<th>Question</th>
<th>Lowest Quality</th>
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<th></th>
<th>Highest Quality</th>
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<tbody>
<tr>
<td></td>
<td>(1)</td>
<td>(2)</td>
<td>(3)</td>
<td>(4)</td>
<td></td>
</tr>
<tr>
<td>1. Rate the overall quality of the guideline report.</td>
<td>2%</td>
<td>0%</td>
<td>13%</td>
<td>48%</td>
<td>38%</td>
</tr>
<tr>
<td></td>
<td>Strongly Disagree</td>
<td></td>
<td></td>
<td></td>
<td>Strongly Agree</td>
</tr>
<tr>
<td>2. I would make use of this guideline in my professional decisions.</td>
<td>4%</td>
<td>2%</td>
<td>10%</td>
<td>33%</td>
<td>50%</td>
</tr>
<tr>
<td>3. I would recommend this guideline for use in practice.</td>
<td>4%</td>
<td>2%</td>
<td>4%</td>
<td>45%</td>
<td>45%</td>
</tr>
</tbody>
</table>

4. What are the barriers or enablers to the implementation of this guideline report?

- Availability of LDR-BT by site - local expertise, and cost issue.
- Scarcity of Phase III Trials.
- 1). Informing practitioners of the guidelines and options. Usually there is a lag of about a year until guidelines filter to the rank and file. A significant proportion of patients in Northern Ontario communities will seek treatment advice from their family doctors because access to specialists (urologists etc…) is a challenge. 2). Timely access to brachytherapy, surgery or EBRT. Resources are limited and for a significant proportion of patients accessing treatment is very disruptive given the winter weather conditions, travelling great distances, isolation from support system etc. The result is sometimes the patient and treating urologist would opt for an option that is most available closer to home and less disruptive rather than the patient having the opportunity of choosing.
- Patient education is the key. Many prostate cancer patients needing treatment are well educated in respect to the alternatives. As urologists, we can help in the decision making.
- It is unreasonable not to offer LDR-BT as a viable option. Physician education (lack of) is a significant barrier.
- Enablers: multidisciplinary counselling of prostate cancer patients early in their course. Barriers: provider bias in treatment suggestions.
- The barriers are probably the low number of radiation oncologists trained in Brachytherapy. The enablers are the data which shows that in the selected cases, brachytherapy is either equal or better than RP or EBRT. However, by educating urologists and Radiation-Oncologists in this new development, I am sure that the barriers will drop: 1) No Surgery 2) One treatment 3) Little or no incontinence 4) Little or no increased sexual problems 5) High chance of cure. It takes some men a great leap of faith to go on a watchful waiting program. This type of patient who cannot cope with the idea of a cancer in his body would undoubtedly benefit from this new treatment.
- It would facilitate patient entry into these trials if access to brachytherapy were available at the Carlo Fidani site at Credit Valley Hospital given the logistics of travel to downtown Toronto.
- More RCTs are required, and so LDR-BT for intermediate-risk prostate cancer should only be offered on an investigational basis or as part of a RCT.
- Few centres offer brachytherapy. Travel may be an issue for patients.
- Barrier: recommendations/conclusions are not new. There will be no change to current practice. Those who don't currently recommend LDR-BT will probably not change based on this document. Enablers: With updated studies and data perhaps it will lend some credibility to the treatment.
- It is not going to change practice in Ontario unless there is a commitment from the MOHLTC to fund the seeds for intermediate risk patients.
I think this need to be implemented quickly across the province; many centres don't have the expertise but can be learned from centres that routinely practice brachytherapy. This is a much awaited guidelines which will enable the caregivers to provide optimal care to prostate cancer patients in Ontario. LDR brachytherapy alone is used widely across the globe in low and intermediate risk prostate cancer with excellent results for more than a decade. There is increasing evidence in the use of brachytherapy (both LDR and HDR) in combination with external radiation in high risk prostate cancer. This need to be addressed soon as well.

Table 4. Modifications/actions/responses regarding main written comments from professional consultants.

<table>
<thead>
<tr>
<th>Summary of main written comments</th>
<th>Modifications, actions, or responses</th>
</tr>
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<tbody>
<tr>
<td>1. Absurd to suggest that any radiotherapy modality influences the second malignancy ratio at 2.8 - 5.3 years!!</td>
<td>In the Abdel-Wahab 2008 study, it reported that LDR-BT may lead to less second primary cancers at 2.8-5.3 years than might EBRT in 58,623 mixed low-, intermediate- and ≤20% of high-risk patients. EBRT is one of the treatment options in Ontario. Since LDR-BT can lead to less second primary cancers than EBRT, we think LDR-BT can be another treatment option for the target patients.</td>
</tr>
<tr>
<td>2. One randomized phase III trial that seeks to answer the second question (RTOG 0232, A Phase III Study Comparing Combined External Beam Radiation And Transperineal Interstitial Permanent Brachytherapy With Brachytherapy Alone For Selected Patients With Intermediate Risk Prostatic Carcinoma) appears to be overlooked and not mentioned.</td>
<td>For the PEBC guidelines, we usually only search the NCI clinical trials database (<a href="http://www.cancer.gov/clinicaltrials">http://www.cancer.gov/clinicaltrials</a>) for the ongoing clinical trials. The RCT that the reviewer mentioned is not in the NCI database. Since it is related to our research questions, we have added it under ONGOING TRIALS in Section 2 and we also have searched the Radiation Therapy Oncology Group website (<a href="http://www.rtog.org/ClinicalTrials">http://www.rtog.org/ClinicalTrials</a>) and no further eligible ongoing trials have been found.</td>
</tr>
<tr>
<td>3. One item lacking from the analysis is mention of implant quality, which is a major deficiency in the 1998 JAMA paper of D'Amico. Poor quality implants with incomplete coverage of the prostate as in this paper should not be considered to provide similar outcome to modern higher quality procedures. Implant quality is therefore an unacknowledged confounder. Another point is that although it is not possible to recommend one form of radiation over another, is there not a consistent trend for higher disease control rates with high quality implants compared with EBRT?</td>
<td>This is a good point, but in the eligible comparative studies in this guideline, no data on this issue were available. We have added two sentences to clarify this point under DISCUSSION in Section 2 on page 29.</td>
</tr>
<tr>
<td>4. Concerned that LDR-BT will be used and justified in inappropriate patients with intermediate - high risk prostate cancer.</td>
<td>The high-risk patients with prostate cancer are not the target population in this guideline. For intermediate-risk patients, we stated under Qualifying Statement in Section 1:“Not all patients with intermediate-risk disease may be appropriate for LDR-BT monotherapy. Patients with multiple risk factors (PSA &gt;10 ng/ml, Gleason score 7, Gleason primary pattern 4, T2c disease, and high positive core positivity), may be more appropriately treated with other modalities (or combinations of modalities). The</td>
</tr>
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</table>
exact definition for high-intermediate disease has not yet appeared in the literature or been agreed upon by other consensus approaches”.

5. (1). As expected, available data was scant. The guideline appears to support use of brachytherapy for low and intermediate risk patients, although (I think) most oncologists would agree that a patient with GS 6, PSA 10.5 is different from GS 7, PSA 19 with respect to risks of ECE and positive seminal vesicles. For instance, the Pickles paper only include low-tier intermediate risk patients, so caution should be used about statements regarding the full spectrum of intermediate risk disease.

(1). We agree with the reviewer’s comments on this point. Just because of insufficient evidence, we made some statements under Qualifying Statement in Section 1: “Not all patients with intermediate-risk disease may be appropriate for LDR-BT monotherapy. Patients with multiple risk factors (PSA >10 ng/ml, Gleason score 7, Gleason primary pattern 4, T2c disease, and high positive core positivity), may be more appropriately treated with other modalities (or combinations of modalities). The exact definition for high-intermediate disease has not yet appeared in the literature or been agreed upon by other consensus approaches”.

(2). Comparison in that study should be used with caution since external beam doses were quite low compared with standard doses used today (max 72 Gy, median 68 Gy).

(2). We discuss this point under DISCUSSION part in Section 2: “Before 2000, most publications on EBRT alone used a dose of 63 to 70 Gray; after 2000, most used a dose of 70 to 81 Gray. What the appropriate dose is for EBRT alone is beyond the scope of this guideline; however, the low-dose EBRT before 2000 may underestimate the effect of EBRT.”

(3). Some of the text does not read very well. For example, in the EBS document: pg 16 “bRFS rates at greater than five years were not analyzed”. Did the authors mean “less than”? pg 27 reads as if a patient can have a 20% high-risk prostate cancer. Whereas studies were performed on patient groups containing up to 20% of cases with high-risk prostate cancer. pg 28 "one median of 5.5 years” and “late urinary toxicity were” read very awkwardly and distract from the flow of the document.

We have revised the corresponding parts that the reviewer mentioned.

6. To make it more practical, there should be more about patient selection criteria.

We wish we could do that if we could find more good-quality evidence from the medical literature. All the PEBE guidelines will be updated every three years if possible. We wish we could add more patient selection criteria in the next updated version. Also, if new evidence that would result in changes to these recommendations becomes available before three years have elapsed, an update will be initiated as soon as possible.

Conclusion

This EBS report reflects the integration of feedback obtained through the external review process with final approval given by the Genitourinary Cancer DSG, and the working group. The final guideline draft was sent to the Genitourinary Cancer DSG members on October 5, 2012 for their approval. Among the 18 Genitourinary Cancer DSG members (except for the working group members), 16 voted, and the response rate was 89% with an approval rate of 100%, which met the new PEBC requirement established in August 2012 (i.e., for each PEBC guideline, it is required a response rate and an approval rate of 75% from the DSG members, respectively).
CONFLICT OF INTEREST

In accordance with the PEBC Conflict of Interest (COI) Policy, the guideline authors, the Genitourinary Cancer DSG members, and the internal and targeted external reviewers were asked to disclose potential COI. Among the five guideline authors, GR declared that he published a commentary on intensity-modulated radiotherapy for prostate cancer in *The Canadian Journal of Urology* (9). The other four guideline authors declared they had no financial and/or professional conflicts of interests.

Among 18 Genitourinary Cancer DSG members, four declared conflicts. GB declared that he received a Canadian Institutes of Health Research grant for conducting an image guideline in patients with prostate cancer within the past five years, and his professional income will increase by substantially more than $10,000 if he has one patient more per month accept brachytherapy than before; HL declared that he was the head of his department, his department received more than $5000 in a single year from a relevant business entity, and he was one of the authors of the previous EBS 3-10 guideline (*The Use of Brachytherapy in T1 or T2 Prostate Cancer*); SM declared that if this guideline led to expanded Ontario Health Insurance for brachytherapy, then the proportion of cases of low and intermediate-risk prostate cancer treated with EBRT at his centre might fall, which might decrease his professional income by more than $10,000; CC declared that he owned the Charles Catton Professional Corporation having income from the radiotherapy treatment of patients with prostate cancer.

The PEBC Assistant Director (HM) and two Research Coordinators (CL and NI) declared that they had no conflicts of interest.

The three RAP members (WE, LE, and MB) declared that they had no conflicts of interest.

Three of five target external reviewers (MM, RH, and DD) declared that they had no conflicts of interest. JM declared being a principal investigator on two RCTs of prostate brachytherapy that were sponsored by Oncura Corporation, published a point-counterpoint opinion in the journal Brachytherapy with other co-authors, and gave a lecture to a special ASTRO symposium in 2010. TP declared receiving travel support from GE/Oncura and grant funding from Oncura as a co-investigator in an RCT about brachytherapy in prostate cancer in the past five years, and also declared publishing two papers in 2010 and 2011, respectively, about brachytherapy in prostate cancer.

The COIs declared above did not disqualify any individuals from performing their designated role in the development of this guideline, in accordance with the PEBC COI Policy. To obtain a copy of the policy, please contact the PEBC office by email at ccopgi.mcmaster.ca.
REFERENCES