Evidence-based guideline recommendations on low-dose rate brachytherapy in patients with low- or intermediate-risk prostate cancer

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Abstract

Objective: The Genitourinary Cancer Disease Site Group (GU DSG) and Cancer Care Ontario's Program in Evidence-Based Care (PEBC) in Ontario, Canada developed a guideline on low-dose rate brachytherapy (LDR-BT) in patients with early-stage low-grade prostate cancer in 2001. The current updated guideline focuses on the research questions regarding the effect of LDR-BT alone, the effect of LDR-BT with external beam radiation therapy (EBRT) and the selection of an isotope.

Methods: This guideline was developed by using the methods of the Practice Guidelines Development Cycle and the core methodology was a systematic review. MEDLINE and EMBASE (from January 1996 to October 2011), the Cochrane Library, main guideline websites, and main annual meeting abstract websites specific for genitourinary diseases were searched. Internal and external reviews of the draft guideline were conducted.

Results: The draft guideline was developed according to a total of 10 systematic reviews and 55 full text articles that met the preplanned study selection criteria. The quality of evidence was low to moderate. The final report reflects integration of the feedback obtained through the internal review (two oncologists and a methodologist) and external review (five target reviewers and 48 professional consultation reviewers) process, with final approval given by the GU DSG and the PEBC.

Conclusion: The main recommendations are: (1) 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; and (2) I-125 and Pd-103 are each reasonable isotope options.

Introduction

The Genitourinary Cancer Disease Site Group (GU DSG) and Cancer Care Ontario's Program in Evidence-Based Care (CCO's PEBC) in Ontario, Canada, developed a guideline on low-dose rate brachytherapy (LDR-BT) in patients with early-stage low-grade prostate cancer in 2001. This guideline indicated that LDR-BT yielded promising short- and intermediate-term freedom from biochemical failure for selected patients with early-stage prostate cancer.[1] During the last decade, LDR-BT has been widely used in patients with low-risk prostate cancer and has also been increasingly prescribed in patients with intermediate- or high-risk prostate cancer.[2,3] LDR-BT is an available treatment option for low-risk patients with prostate cancer, but not for intermediate-risk patients in Ontario. To keep the CCO's guideline most relevant, current and evidence-based for the guideline end users, the CCO's PEBC and GU DSG decided to update this guideline. The target population for this new guideline are patients with newly diagnosed low- or intermediate-risk prostate cancer who require or choose active treatment and are not considering or are not suitable for active surveillance (Box 1).

Questions

1. What is the efficacy of 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 [PROs]) compared with external beam radiation therapy (EBRT) alone, or radical prostatectomy (RP) alone in the target population?
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 the 3 isotopes used for LDR-BT (I-125, Palladium-103 [Pd-103], and Cesium-131 [Cs-131]), which isotope maximizes clinical outcomes?

Box 1. Target population for this current guideline

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

Low-risk defined as:	Intermediate-risk defined as:
• PSA <10 ng/mL	• PSA ≥10 ng/mL, but <20 ng/mL
• clinical stage T1c-T2a	• or clinical stage T2b-T2c
• Gleason score <7	• or Gleason score =7

PSA: prostate-specific antigen.

Methods

This guideline developed by the CCO's PEBC and GU DSG used the methods of the Practice Guidelines Development Cycle.[4] For this project, the core methodology used to develop the evidentiary base was the systematic review. The PEBC is mandated to post its approved practice guidelines on the Cancer Care Ontario Web site (http://www.cancercare.on.ca/) for dissemination to Ontario oncologists.[5]

Literature search

The systematic review will be published separately. Briefly, MEDLINE and EMBASE (from January 1996 to October 2011), the Cochrane Library, main guideline websites, and main annual meeting abstract websites specific for genitourinary diseases (from January 2009 to October 2012) were searched for English publications or abstracts only. The preplanned study selection criteria were used to screen the literature retrieval.[5]

Internal review

Prior to the submission of this draft report for external review, the report was reviewed and approved by the PEBC Report Approval Panel, which consists of 3 members: 2 oncologists with expertise in clinical and methodology issues, and 1 methodologist.

External review

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.

Results

Literature search results

There were 5444 citations identified from the MEDLINE, EMBASE and the Cochrane Library. The reference lists of the included articles were hand-searched, and 2 further eligible papers were found. A total of 10 systematic reviews[6-15] and 55 full text articles[16-70] met the pre-planned study selection criteria. The quality of evidence from the included studies was considered to be low to moderate.[5]

DSG consensus process

The draft guideline based on the systematic review was developed by the Working Group members (the 5 main authors) and circulated for review and discussion by the GU DSG. The DSG consists of medical oncologists, radiation oncologists, surgical oncologists, a methodologist and a patient representative. The GU DSG approved the draft guideline May 2012.

Internal review

The PEBC Report Approval Panel raised these key issues:

- More should be made of the differences in acute and long-term toxicity among LDR-BT, EBRT and RP.
- 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 centre to offer this treatment.

Feedback received from the Report Approval Panel was addressed by the authors.[5]

External review

Targeted peer review

Responses were received from 5 reviewers by September 5, 2012. Key results of the feedback survey are summarized in Table 1.

Professional consultation

The notification email was sent July 19, 2012 and the consultation period ended August 30, 2012. Sixty (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 2.

Practice guideline

This report reflects integration of the written comments obtained through the external review process, with final approval given by the GU DSG and the Report Approval Panel of the PEBC.

Table 1. Responses to items on the targeted peer reviewer questionnaire

Survey item	Reviewer ratings (n=5)				
	Lowest quality (1)	(2)	(3)	(4)	Highest quality (5)
Rate the guideline development methods.	0	0	1	1	3
Rate the guideline presentation.	0	0	2	1	2
Rate the guideline recommendations.	0	0	2	2	1
Rate the completeness of reporting.	0	0	1	4	0
Does this document provide sufficient information to inform your decisions? If not, what areas are missing?	0	0	2	2	1
Rate the overall quality of the guideline report.	0	0	1	3	1
	Strongly disagree (1)	(2)	(3)	(4)	Strongly agree (5)
I would make use of this guideline in my professional decisions.	0	1	0	2	2
I would recommend this guideline for use in practice.	0	1	0	2	2

Recommendations

- For patients with newly diagnosed low-risk or intermediate-risk prostate cancer who require or choose active treatment, LDR-BT alone is 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 (prostate-specific antigen [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[71] and the 2012 American Brachytherapy Society consensus guideline[72] 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

- For bRFS at ≥5 years:
  - *LDR-BT compared with EBRT:* Three retrospective studies with 1529 patients showed there were no significant differences between the 2 groups.[21,26,61] One of these retrospective studies reported $p > 0.25$ in low-risk patients;[26] another one reported the

Table 2. Responses to items on the professional consultation survey

Survey item	Number (%)				
	Lowest quality (1)	(2)	(3)	(4)	Highest quality (5)
Rate the overall quality of the guideline report.	1 (2)	0 (0)	6 (13)	23 (48)	18 (37)
	Strongly disagree (1)	(2)	(3)	(4)	Strongly agree (5)
I would make use of this guideline in my professional decisions.	2 (4)	1 (2)	5 (11)	16 (33)	24 (50)
I would recommend this guideline for use in practice.*	2 (4)	1 (2)	2 (4)	21 (44)	21 (44)

*One reviewer did not rate the third item.

bRFS rate as 90% for LDR-BT and 86% for EBRT ($p = 0.969$) in intermediate-risk patients;[61] 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 ≤20% of high-risk patients.[21]

  - *LDR-BT compared with RP:* One randomized controlled trial (RCT) with 200 low-risk patients (LDR-BT 92% vs. RP 91%)[32] and 1 retrospective study with 927 low-risk patients (risk ratio [RR], 1.1; CI, 0.3 to 3.6)[26] showed no statistical difference between the 2 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%)[61] and in 674 mixed low-, intermediate- and ≤20% of high-risk patients (HR, 0.44; CI, 0.25 to 0.77),[21] respectively.
  - *LDR-BT, I-125 compared with Pd-103:* One RCT with 263 low-risk patients showed no significant differences between the 2 groups (bRFS 96.8% vs. 99.2%, $p = 0.149$).[42]
- For PCSM/OM at ≥10 years:
  - *LDR-BT compared with RP:* One retrospective study with 41 395 mixed low- and intermediate-risk patients reported no statistical difference between the 2 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.[60]
- 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 2 groups.[69] 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 ≤20% of high-risk patients.[16]
- For PROs:
  - *LDR-BT compared with EBRT:* Two prospective studies showed no difference between the 2 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).[28,46]
  - *LDR-BT compared with RP:* Three prospective studies showed that urinary incontinence and sexual potency favoured LDR-BT, while urinary irritation favoured RP; for bowel PROs, one study favoured RP, but 2 other studies found no difference (low- and intermediate-risk patients together).[22,33,46] In an RCT in low-risk patients, results were consistent with the above observational studies at 1 year, but these differences for PROs were not sustained at 5 years.[32]
  - *I-125 compared with Pd-103:* One RCT reported that Pd-103 resulted in worse overall PROs than I-125 at 1 month, and I-125 resulted in worse overall PROs than Pd-103 at 6 months, but there was no difference between the 2 groups at 1 and 2 years.[34]

Discussion

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. 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 low-, or intermediate-risk prostate cancer (studies were allowed to include ≤20% of high-risk patients).

When considering toxicity and PROs, 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 EBRT. During the 6 months to 3 years after treatment, the data suggest 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 first 3 years after treatment. Patient preference should be considered in the treatment selection due to the different approaches involved with these 3 treatments (LDR-BT, EBRT and RP) and their different acute and long-term impacts on patients.

It should be noted that high-dose rate brachytherapy is another promising technique for patients with prostate cancer,[73] but its study is beyond the scope of this guideline.

Updating

This document will be reviewed in 3 years to determine if it is still relevant to current practice and to ensure that the recommendations are based on the best available evidence. If new evidence that will result in changes to these recommendations becomes available before the 3-year mark, an update will be initiated as soon as possible.

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This paper has been peer-reviewed.

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