Agency for Healthcare Research and Quality
Advancing Excellence in Health Care

NATIONAL GUIDELINE CLEARINGHOUSE

General

Guideline Title

Low-dose rate brachytherapy for patients with low- or intermediate-risk prostate cancer.

Bibliographic Source(s)

Rodrigues G, Yao X, Loblaw A, Brundage M, Chin J, Genitourinary Cancer Disease Site Group. Low-dose rate brachytherapy for patients with low- or intermediate-risk prostate cancer. Toronto (ON): Cancer Care Ontario (CCO); 2012 Oct 31. 55 p. (Evidence-based series; no. 3-10). [165 references]

Guideline Status

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original Guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

Recommendations

Major Recommendations

The Genitourinary Disease Site Group (DSG) and the Program in Evidence-based Care (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, low-dose rate brachytherapy (LDR-BT) alone is a treatment option as an alternative to external beam radiation therapy (EBRT) alone or radical prostatectomy (RP) alone.
- Iodine-125 (I-125) and Palladium-103 (Pd-103) are each reasonable isotope options in patients with prostate cancer.
- No recommendation can be made for or against using Cesium-131 (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.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Low- or intermediate-risk prostate cancer

Guideline Category

Assessment of Therapeutic Effectiveness

Treatment

Clinical Specialty

Family Practice

Internal Medicine

Oncology

Radiation Oncology

Surgery

Urology

Intended Users

Advanced Practice Nurses

Hospitals

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

- To evaluate the efficacy of low-dose rate brachytherapy (LDR-BT) alone for clinical outcomes
- To evaluate the efficacy of LDR-BT combined with external beam radiation therapy (EBRT) for clinical outcomes compared with LDR-BT alone, EBRT alone, or radical prostatectomy (RP) alone
- To evaluate the efficacy of three isotopes used for LDR-BT (Iodine-125 [I-125], Palladium-103 [Pd-103], and Cesium-131 [Cs-131])

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

Interventions and Practices Considered

1. Risk assessment
2. Low-dose rate brachytherapy (LDR-BT) alone
3. External beam radiation therapy (EBRT) alone
4. Radical prostatectomy (RP) alone
5. Iodine-125 (I-125) and Palladium-103 (Pd-103) isotope options
6. Participation in clinical trials

Note: Cesium-131 (Cs-131) and the combination of EBRT and LDR-BT in the target population were considered but not recommended.

Major Outcomes Considered

- Biochemical relapse-free survival
- Overall mortality
- Prostate cancer-specific mortality
- Overall survival
- Clinical recurrence-free survival rate
- Distant metastasis-free survival rate
- Time to initiation of salvage therapy
- Local control rate
- Distant control rate
- Toxicity
- Quality of life

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

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 of the original guideline document. 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 Care 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, 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, randomized controlled trials (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 low-dose rate brachytherapy (LDR-BT) with external beam radiation therapy (EBRT) alone or radical prostatectomy (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 (Iodine-125 [I-125], Palladium-103 [Pd-103], and Cesium-131 [Cs-131]).
4. Studies reported on at least one of the following clinical outcomes: overall survival/overall mortality (OS/OM), biochemical relapse-free survival (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 prostate-specific antigen [PSA] <10 ng/ml receiving LDR-BT and patients with PSA ≥10 ng/ml receiving EBRT).

Number of Source Documents

A total of 10 systematic reviews and 55 full text articles were included in this systematic review.

Data were ultimately abstracted and summarized from 36 articles.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

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.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The Evidence-Based Series (EBS) guideline developed by the Program in Evidence-based Care (PEBC) uses the methods of the Practice Guidelines Development Cycle. 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 Disease Site Group (DSG) members and one methodologist from the PEBC. 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 (see Appendix 1 in the original guideline document).

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

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

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Report Approval Panel

Prior to the submission of this evidence-based series (EBS) draft report for external review, the report was reviewed and approved by the Program in Evidence-based Care (PEBC) Report Approval Panel (RAP), which consists of three members: two oncologists with expertise in clinical and methodology issues, and a methodologist.

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.

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 Disease Site Group (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.

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).

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The recommendations are supported by randomized and non-randomized trials.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate use of low-dose rate brachytherapy (LDR-BT) as a treatment alternative to external beam radiation therapy (EBRT) alone or radical prostatectomy (RP) alone for treatment of low- or intermediate-risk prostate cancer

Potential Harms

During the six months to three years after treatment, the data suggests that low-dose rate brachytherapy (LDR-BT) is associated with less urinary incontinence and sexual impotency when compared with radical prostatectomy (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 external beam radiation therapy (EBRT), it seems that LDR-BT results in less sexual impotency and rectal morbidity in the three years after treatment.

Qualifying Statements

Qualifying Statements

- The following low-dose rate brachytherapy (LDR-BT) doses were suggested from the included studies when LDR-BT was used alone: 140 to 160 Gray for Iodine-125 (I-125) or 108 to 125 Gray for Palladium-103 (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, external beam radiation therapy [EBRT], and radical prostatectomy [RP]) and their different acute and long-term impacts on patients.
- The 2012 National Comprehensive Cancer Network (NCCN) guideline and the 2012 American Brachytherapy Society consensus guideline 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.
- Care has been taken in the preparation of the information contained in this report. Nonetheless, any person seeking to apply or consult the report is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding the report content or use or application and disclaims any responsibility for its application or use in any way.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Quick Reference Guides/Physician Guides

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Rodrigues G, Yao X, Loblaw A, Brundage M, Chin J, Genitourinary Cancer Disease Site Group. Low-dose rate brachytherapy for patients with low- or intermediate-risk prostate cancer. Toronto (ON): Cancer Care Ontario (CCO); 2012 Oct 31. 55 p. (Evidence-based series; no. 3-10). [165 references]

Adaptation

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

Date Released

2012 Oct 31

Guideline Developer(s)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

Guideline Developer Comment

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

Source(s) of Funding

The Program in Evidence-based Care (PEBC) is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from the Ontario Ministry of Health and Long-Term Care.

Guideline Committee

Genitourinary Cancer Disease Site Group

Composition of Group That Authored the Guideline

Members of the Working Group: George Rodrigues (*Guideline Chair*), Radiation Oncologist, London Health Sciences Centre, London, Ontario; D. Andrew Loblaw (*Disease Site Group [DSG] Chair*), Radiation Oncologist, Sunnybrook Health Sciences Centre, Toronto, Ontario; Michael Brundage, Radiation Oncologist, Cancer Centre of Southeastern Ontario, Kingston General Hospital, Kingston, Ontario; Joseph Chin, Surgeon/Urologist, London Health Sciences Centre, London, Ontario; Xiaomei Yao, Research Coordinator, Program in Evidence-based Care, Cancer Care Ontario, Hamilton, Ontario

Members of the Genitourinary Cancer DSG: Sébastien Hotte (*Chair*), Medical Oncologist, Hamilton Health Sciences, Hamilton, Ontario; Neil Fleshner (*Chair*), Surgeon/Urologist, Princess Margaret Hospital, Toronto, Ontario; Jack Barkin, Surgeon/Urologist, Humber River Regional Hospital, Toronto, Ontario; Glenn Bauman, Radiation Oncologist, London Health Sciences Centre, London, Ontario; Rodney Breau, Surgeon/Urologist, The Ottawa Hospital, Ottawa, Ontario; Christina Canil, Medical Oncologist, The Ottawa Hospital Cancer Centre, Ottawa, Ontario; Charles Catton, Princess Margaret Hospital, Toronto, Ontario; Urban Emmenegger, Medical Oncologist, Sunnybrook Health Sciences Centre, Toronto, Ontario ; Anthony Finelli , Surgeon/Urologist, Princess Margaret Hospital, Toronto, Ontario; John Hastie, Patient representative, Simcoe, Ontario; Himu Lukka, Radiation Oncologist, Hamilton Health Sciences, Hamilton, Ontario; Scott Morgan, Radiation Oncologist, The Ottawa Hospital Cancer Centre, Ottawa, Ontario; Roanne Segal, Medical Oncologist, The Ottawa Hospital Cancer Centre, Ottawa, Ontario; Bobby Shayegan, Surgeon/Urologist, St. Joseph's Healthcare, Hamilton, Ontario; Tom Short, Surgeon/Urologist, Credit Valley Hospital, Mississauga, Ontario; John Srigley, Pathologist, Credit Valley Hospital, Mississauga, Ontario; Padraig Warde, Radiation Oncologist, Princess Margaret Hospital, Toronto, Ontario; Eric Winquist, Medical Oncologist, London Health Sciences Centre, London, Ontario

Financial Disclosures/Conflicts of Interest

In accordance with the Program in Evidence-based Care (PEBC) Conflict of Interest (COI) Policy, the guideline authors, the Genitourinary Cancer Disease Site Group (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. 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 Report Approval Panel (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.

Guideline Status

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Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

Availability of Companion Documents

The following are available:

- Low-dose rate brachytherapy for patients with low- or intermediate-risk prostate cancer. Summary. Toronto (ON): Cancer Care Ontario (CCO); 2012 Oct 31. 12 p. Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.
- Program in Evidence-based Care handbook. Toronto (ON): Cancer Care Ontario (CCO); 2012. 14 p. Available in PDF from the Cancer Care Ontario Web site.

Patient Resources

None available

NGC Status

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