Complete Summary

GUIDELINE TITLE

The role of high dose rate brachytherapy in the palliation of patients with non-small cell lung cancer: a clinical practice guideline.

BIBLIOGRAPHIC SOURCE(S)

Ung Y, Yu E, Falkson C, Haynes A, Evans WK, Lung Disease Site Group. The role of high dose rate brachytherapy in the palliation of patients with non-small cell lung cancer: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2005 Oct 25. Various p. (Evidence-based series; no. 7-16). [42 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.

COMPLETE SUMMARY CONTENT

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SCOPE

DISEASE/CONDITION(S)

Symptomatic endobronchial disease in non-small cell lung cancer

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Oncology
Pulmonary Medicine
Radiation Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To evaluate if there is a role for high dose rate endobronchial brachytherapy (HDREB) in the palliation of respiratory symptoms in patients with non-small cell lung cancer
- To evaluate what the optimal dose of high dose rate endobronchial brachytherapy is in this setting

TARGET POPULATION

Adult patients with symptomatic endobronchial disease in non-small cell lung cancer

INTERVENTIONS AND PRACTICES CONSIDERED

1. High dose rate endobronchial brachytherapy (HDREB)
2. External beam radiation therapy (EBRT)

MAJOR OUTCOMES CONSIDERED

- Response rates
- Survival rates
- Toxicity
- Symptom control

METHODOLOGY

METHODS USED TO COLLECT/SELECT 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

MEDLINE (1966 through July 2005), EMBASE (1980 through July 2005), CANCERLIT (1975 through March 2002), and the Cochrane Library (2005, Issue 4) databases were searched for evidence relevant to this practice guideline report. "Carcinoma, non-small-cell lung" (Medical subject heading (MeSH)), "Lung Neoplasms" (MeSH), and the phrase "non small cell lung" used as a text word were combined with "brachytherapy" (MeSH), "radiotherapy dosage" (MeSH) and each of the following phrases used as text words: "brachytherapy," "interstitial radiotherapy," "seed implant," "high dose," or "HDR". As the expectation was that the literature would be limited for this topic, the initial search did not include restrictions on study design. However, subsequent searches included the search terms for the following study designs and publication types: practice guidelines, systematic reviews, meta-analyses, reviews, randomized controlled trials, controlled clinical trials, clinical trials, comparative studies, follow-up studies, prospective studies, and retrospective studies.

In addition, conference proceedings of the American Society of Clinical Oncology (ASCO) (1995-2005) and the American Society for Therapeutic Radiology and Oncology (ASTRO) (2000-2005) were searched for abstracts of relevant trials. The Canadian Medical Association Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp) and the Web site of the National Guideline Clearinghouse (http://www.guideline.gov) were also searched for existing evidence-based practice guidelines.

Relevant articles and abstracts were selected and reviewed by three reviewers, and the reference lists from those sources were searched for additional trials, as were the reference lists from relevant review articles.

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if:

1. They were fully published reports of randomized controlled trials (RCTs), non-controlled prospective studies, or large retrospective studies involving more than 100 patients.
2. The treatment was of symptomatic endobronchial disease in primary non-small cell lung cancer (NSCLC).
3. At least one group in the study received high dose rate endobronchial brachytherapy (HDREB), either alone or in combination with external beam radiation therapy (EBRT), laser therapy, or photodynamic therapy (PDT).
4. The reported outcomes included symptom control, response, survival, or toxicity.

Exclusion Criteria

Articles were excluded if they were:

1. Published in a language other than English
2. Published in abstract form only
3. Letters, comments, or editorials
4. Case studies

NUMBER OF SOURCE DOCUMENTS

Six randomized controlled trials (RCTs), eighteen noncontrolled prospective studies, five large retrospective studies, and one guideline were included in this systematic review.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

As only three of the six randomized trials compared similar treatments, and all three administered different doses of high dose rate endobronchial brachytherapy (HDREB), the data were not pooled.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The Program in Evidence-based Care (PEBC) reports consist of a comprehensive systematic review of the clinical evidence on a specific cancer care topic, an interpretation of and consensus agreement on that evidence by Disease Site Groups and Guideline Development Groups, the resulting clinical recommendations and an external review by Ontario clinicians in the province for whom the topic is relevant.

The application of high dose rate endobronchial brachytherapy (HDREB) for lung cancer requires an adequately trained and experienced team that includes radiation oncologists, thoracic surgeons (or physicians with expertise in bronchoscopy), and medical physicists. While the aim of this evidence-based series was not to review the many technical aspects of the delivery of HDREB, the Lung Cancer Disease Site Group (DSG) recommends that rigorous quality assurance programs be in effect to ensure safety and to provide consistency in reporting dose prescriptions to facilitate comparisons of treatment results.

The analysis of the available evidence does not permit the recommendation of a standard dose or optimal fractionation for HDREB. However, a survey of the provincial cancer centres in Ontario was conducted by one of the guideline authors

(Ung) to determine common practice among centres doing HDREB. The consensus recommendation for palliation is to use a prescribed dose of 1000 cGy at 1cm from the central axis given in a single fraction. Technical factors that may influence dose reduction and the fractionation scheme include the extent of curvature causing overlap and "hot spots" of radiation dose, length of treatment, and previous external beam radiation exposure in the treatment volume.

The group of patients that may benefit from HDREB may be defined as those who have:

1. Endobronchial tumour causing symptoms of dyspnea, hemoptysis, post-obstructive pneumonitis, or intractable cough
2. Minimal extrinsic compression of the bronchi
3. Visible endoluminal disease but not complete endobronchial obstruction
4. Failed previous external beam radiation therapy (EBRT) or those who are not candidates for further external beam radiation
5. Good performance status (i.e., Eastern Cooperative Oncology Group, (ECOG) $\leq$ 2). Patients with poorer performance status caused directly by the endobronchial disease may still be suitable for HDR brachytherapy.

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

Following the review and discussion of the evidence-based series report, the Lung Cancer Disease Site Group circulated the clinical practice guideline and systematic review to clinicians in Ontario for review and feedback.

Practitioner feedback was obtained through a mailed survey of 117 practitioners in Ontario and included 35 medical oncologists, 22 radiation oncologists, 27 surgeons, 32 respirologists, and a hematologist. The survey 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 practice guideline. Written comments were invited. The practitioner feedback survey was mailed out on May 7, 2004 . Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Lung Disease Site Group (DSG) reviewed the results of the survey.

This evidence-based series reflects the integration of the draft recommendations with feedback obtained from the external review process. After being approved by the Lung Disease Site Group, the series was submitted to the Practice Guidelines Coordinating Committee. Of the 15 panel members, eight members returned ballots of the reviewed document. However, one panel member is a member of the Lung Disease Site Group and was not eligible to review the document. Six panel members approved the document and one member approved the document on condition that changes to one of the recommendations are changed due to the weak evidence supporting it.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- For patients with previously untreated, symptomatic, endobronchial non-small cell lung cancer:
    - External beam radiation therapy (EBRT) alone is more effective for palliation than high dose rate endobronchial brachytherapy (HDREB) alone.
    - The evidence does not provide conclusive results to suggest that HDREB and EBRT would provide improved symptom relief over EBRT alone.
    - For patients with complete collapse of the lung due to endobronchial obstruction, a surgical core out procedure may be needed before EBRT or EBRT with HDREB.
    - For patients previously treated by EBRT who are symptomatic from recurrent disease due to endobronchial obstruction, HDREB is recommended, providing that endobronchial brachytherapy is technically feasible.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by randomized controlled trials (RCTs), noncontrolled prospective studies, retrospective studies, and one guideline.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- One randomized trial involving 99 previously untreated patients obtained better overall palliation with external beam radiation therapy (EBRT) alone compared with high dose rate endobronchial brachytherapy (HDREB) alone (physician preference ratings for EBRT, p=0.09; patient preference ratings for EBRT, p=0.029). The incidence of fatal hemoptysis was comparable in both

groups (6% to 8%). Although survival was not a specified endpoint of that study, median survival was found to be longer (9.4 versus 8.2 months), one-year survival higher (38% versus 22%), and overall survival significantly better (p=0.04) with EBRT alone.

- One randomized controlled trial evaluated HDREB in combination with EBRT to EBRT alone using biologically equivalent doses for both arms. Symptom control for cough was better in patients who were treated with EBRT alone compared to HRDEB and EBRT, and survival at one year was the same in each group. One randomized controlled trial evaluated EBRT compared to EBRT with HDREB boost. Local control was better with EBRT and HDREB, but symptom control was not evaluated.
- Two trials obtained comparable median survival (6.2 versus 6.5 months and 7.0 versus 8.5 months) and incidence of fatal hemoptysis (14% versus 19% and 13% versus 15%) for patients treated with EBRT alone or EBRT with HDREB. Combined treatment improved atelectasis in one trial (57% versus 35% of patients, respectively, p=0.009), although individual symptom scale scores were comparable for both treatments. The other trial reported a tendency toward improved local control with combined therapy (p=0.052).
- Median survival (7.4 versus 10.3 months) and incidence of fatal hemoptysis (0 versus 1 patient) were similar for neodymium-yttrium-aluminum-garnet (Nd-YAG) laser therapy alone or combined with HDREB. The symptom-free period was significantly longer with the combined treatment (8.5 versus 2.8 months, p<0.05), although toxicity and symptom palliation were not reported by treatment group.
- Eighteen prospective, non-controlled studies evaluated HDREB in doses ranging from 4 Gray (Gy) at 2cm from the source axis twice daily over two days to a single fraction of 20 Gy at 1cm from the source axis. Response rates varied between 20% and 79%, median survival between three and 28 months, and one-year survival between 7% and 78%. Hemoptysis improved for most patients, although fatal hemoptysis occurred in between 3% and 32% of patients.
- Five retrospective studies, each involving more than 100 patients, reviewed the role of HDREB alone or in combination with EBRT. Treatment intent varied from palliation to radical, using single dose or fractionated treatments. Symptom improvement ranged from 46% to 94%. The risk of fatal hemoptysis ranged from 3.6% to 21%.

POTENTIAL HARMS

- Fatal hemoptysis is a significant risk of high dose rate endobronchial brachytherapy (HDREB), with reported rates as high as 32%, while the majority of studies reported rates between 4% and 18% (see Appendix 2 of the original guideline document). The same studies reported improvement of hemoptysis in 19% to 100% of patients, while most studies reported improvement in at least 69% of patients.
- Other complications of HDREB are radiation bronchitis, bronchial or tracheal stenosis, bronchial necrosis or fistula formation, pneumothorax, and non-fatal hemorrhage.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- This guideline addresses only the use of high dose rate endobronchial brachytherapy (HDREB) for the palliation of symptomatic endobronchial disease and not its use as a radical or adjuvant treatment.
- The occurrence of fatal hemoptysis because of HDREB is a significant risk with that therapy, and occurrence rates as high as 32% of patients have been reported. However, the majority of studies report rates between 4% and 18% of patients.
- Improvement of hemoptysis as a result of HDREB ranges from 19% to 100% of patients, with most studies reporting rates of 69% and higher.
- HDREB should be provided by a team of experts that includes radiation oncologists, thoracic surgeons (or physicians with expertise in bronchoscopy), and medical physicists.
- HDREB is only possible if afterloading catheters can be inserted bronchoscopically. Patients with complete endobronchial obstruction are not suitable for HDREB.
- Treatment alternatives to HDREB include external beam radiation therapy (EBRT) (if not previously irradiated), neodymium-yttrium-aluminum-garnet (Nd-YAG) laser therapy, photodynamic therapy (PDT), and surgical core-out procedure.
- The optimal dose and fractionation for HDREB for the palliation of symptoms of airway obstruction has not yet been determined. However, commonly used doses include 1000 cGy at 1cm in a single fraction or 750 cGy at 1cm in one or two fractions.
- HDREB may be effectively combined with other endobronchial treatment modalities such as neodymium-yttrium-aluminum-garnet laser (Nd-YAG) therapy.
- Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult the practice guideline 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 their content or use or application and disclaims any for their application or use in any way.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Ung Y, Yu E, Falkson C, Haynes A, Evans WK, Lung Disease Site Group. The role of high dose rate brachytherapy in the palliation of patients with non-small cell lung cancer: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2005 Oct 25. Various p. (Evidence-based series; no. 7-16). [42 references]

ADAPTATION

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

DATE RELEASED

2005 Oct 25

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

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Provincial Lung Cancer Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

The members of the Lung Disease Site Group (DSG) disclosed potential conflicts of interest relating to the topic of this evidence-based series. No potential conflicts were declared.

GUIDELINE STATUS

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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:

- The role of high dose rate brachytherapy in the palliation of patients with non-small cell lung cancer: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO), 2005 Nov 25. Various p. (Practice guideline; no. #7-16: Section 1). Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.
- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on January 24, 2006. The information was verified by the guideline developer on February 23, 2006.

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