Complete Summary

GUIDELINE TITLE

The role of radiation therapy in malignant pleural mesothelioma: a clinical practice guideline.

BIBLIOGRAPHIC SOURCE(S)

Ung YC, Yu E, Falkson C, Haynes AE, Stys-Norman D, Evans WK, Lung Cancer Disease Site group. The role of radiation therapy in malignant pleural mesothelioma: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2006 Feb 6. 21 p. (Evidence-based series; no. 7-14-3). [30 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.

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SCOPE

DISEASE/CONDITION(S)

Malignant pleural mesothelioma

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Management
Treatment

CLINICAL SPECIALTY

Oncology
Pulmonary Medicine
Radiation Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To evaluate the role of radiation therapy (RT) in the management of malignant pleural mesothelioma

TARGET POPULATION

Adult patients with malignant pleural mesothelioma

INTERVENTIONS AND PRACTICES CONSIDERED

External beam radiation therapy (EBRT)

MAJOR OUTCOMES CONSIDERED

- Survival
- Toxicity and adverse effects
- Quality of life
- Impact of radiotherapy on procedure tract metastases
- 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

Evidence was identified through a systematic search of the databases MEDLINE (1966 to October 2005), EMBASE (1980 to October 2005), CANCERLIT (1975 through September 2001), and the Cochrane Library (2005, Issue 3). "Mesothelioma" (Medical Subject Heading (MeSH) and Excerpta Medica Tree (EMTREE)), "pleural neoplasms" (MeSH), "pleura mesothelioma" (EMTREE),

"malignant mesothelioma" (EMTREE), and "mesothelioma" as a text word were combined with "radiotherapy" (MeSH, EMTREE), and the following text words: "radiotherapy", "radiation", and "irradiation." Those terms were then combined with search terms for the following publication types and study designs: practice guidelines, systematic reviews, meta-analyses, reviews, randomized controlled trials, controlled clinical trials, clinical trials, multicenter studies, comparative studies, and prospective studies.

In addition, conference proceedings of the American Society of Clinical Oncology (ASCO) (1995-2005) and the American Society for Therapeutic Radiation 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 National Guidelines Clearinghouse (http://www.guideline.gov/index.asp) were also searched for existing evidence-based practice guidelines. The reference lists from those sources were searched for additional trials, as were the reference lists from relevant review articles.

Study Selection Criteria

Articles published as full reports or as abstracts were included if they focused on radiotherapy (radical, adjuvant or palliative) for patients with malignant pleural mesothelioma (MPM); reported data on survival, quality of life (QOL), or toxicity; and were:

a. Randomized trials comparing radiation therapy alone or as part of a planned combined modality regimen to no radiation therapy or best supportive care; or
b. Non-randomized prospective studies of radiation therapy, alone or as part of a planned combined modality regimen involving more than 40 patients; or
c. Meta-analyses or systematic reviews

Trials that focused on a modality other than radiation therapy, except when radiation was part of a planned combined modality regimen, were excluded. Trials published in a language other than English were also not considered.

NUMBER OF SOURCE DOCUMENTS

Three randomized trials and four non-randomized, prospective trials met the eligibility criteria for 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

Meta-Analysis of Randomized Controlled Trials
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

A post-hoc meta-analysis was conducted to explore the impact of radiotherapy on procedure tract metastases. This analysis was based on the number of patients with procedure tract metastases in each treatment arm compared with the number of patients randomized. Trials were pooled using Review Manager 4.2.7, which is available through the Cochrane Collaboration (Review Manager [RevMan] Version 4.2 for Windows. Oxford (England): The Cochrane Collaboration, 2003]. Pooled results are expressed as a relative risk ratio (RR) with 95% confidence intervals (CI) using the random effects model. The Lung Disease Site Group (DSG) did not statistically pool data for the primary outcomes of interest (survival, adverse events, and quality of life [QOL]) from the randomized trials as it was not always possible to isolate the details or effects of radiation therapy. Also, the trials spanned many years and did not use a consistent radiotherapy regimen. Pooling of data from the non-randomized prospective trials was not considered due to the heterogeneity of these trials.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

This evidence-based series was developed by the Lung Cancer Disease Site Group (Lung DSG) of Cancer Care Ontario's Program in Evidence-Based Care (CCO's PEBC). The series is a convenient and up-to-date source of the best available evidence on the role of radiation therapy in malignant pleural mesothelioma (MPM), developed through systematic review, evidence synthesis, and input from practitioners in Ontario.

Patients with malignant pleural mesothelioma (MPM) generally have a poor prognosis, and most will succumb to their disease within three to five years of diagnosis. Therefore, it is important to examine not only treatments administered with a curative intent but also those given with a palliative intent.

At the present time, there is no evidence to support the use of radical radiation therapy alone, administered with curative intent, in the management of patients with MPM. The only randomized trials of radiation therapy for patients with MPM conducted to date have investigated the use of prophylactic external beam radiation therapy (EBRT) to reduce the frequency of malignant seeding of tracts caused by thoracic drainage tubes or thoracic diagnostic procedures. One randomized trial reported a significant reduction in the frequency of malignant seeding of tracts caused by thoracic drainage tube removal and thoracic diagnostic procedures such as thoracoscopy for the EBRT group compared to the no EBRT group. However, a second randomized trial reported more procedure tract metastases in the EBRT group than the no-EBRT group (p=not reported), although these were preliminary results and were based on only 12 patients. The third randomized trial found no statistically significant differences in procedure

tract metastases. Although the frequency of procedure tract metastases after prophylactic radiation was not stated initially as an outcome of interest in this systematic review, the consensus of the authors was that the three randomized trials were the best available evidence for the use of radiation therapy for patients with MPM. Based on the consensus and the evidence analyzed in this systematic review, the authors concluded that there is insufficient evidence to definitively recommend prophylactic radiation to thoracic diagnostic tracts, and the decision to use prophylactic EBRT for patients with thoracic tracts must be based on an individualized case assessment.

Several non-randomized prospective trials have shown that radical radiation therapy can be integrated into a combined modality regimen including surgery and chemotherapy. However, the same studies showed that hemithoracic radiation, without extrapleural pneumonectomy, resulted in significant toxicity including radiation pneumonitis, lung fibrosis, and bronchopleural fistula without any survival benefit.

Palliative radiation therapy may offer symptom control and increased quality of life (QOL) for these patients. Of note is the fact that no studies have included formal measures of QOL, and few studies have reported on the methods used to measure symptom control.

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

External Review by Ontario Clinicians

Following the review and discussion of Sections 1 and 2 of this evidence-based series, the Lung Disease Site Group (DSG) circulated the clinical practice guideline and systematic review to clinicians in Ontario for review and feedback.

Feedback was obtained through a mailed survey of 135 practitioners in Ontario and included medical and radiation oncologists, surgeons, and respirologists. The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations above should be approved as a practice guideline. Written comments were invited. The survey was mailed out on May 20 2005. Follow-up

reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Lung DSG reviewed the results of the survey.

Report Approval Panel

The final evidence-based series report was reviewed and approved by the Program in Evidence-based Care (PEBC) Report Approval Panel in February 2006. The Panel consists of two members, including an oncologist, with expertise in clinical and methodology issues. Key issues raised by the Panel included the following three:

1. The Panel suggested the DSG provide an explicit discussion of the value of the different levels of evidence included in the document. If a specific evidence base (e.g., retrospective studies, small prospective studies of combined modality treatment) does not inform the recommendations, the DSG should consider excluding it.
2. Given the limited and contrasting evidence for the main recommendation on prophylactic external beam radiation therapy (EBRT) for drainage tracts, a more explicit description of the DSG consensus process relating to this recommendation is important and could be included in the Discussion section of the document. The importance of the DSG consensus could also be acknowledged in the Recommendations section.
3. The DSG may want to consider conducting a meta-analysis for the three randomized controlled trials (RCTs) of tract seeding.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The lack of sufficient high-quality evidence precludes definitive recommendations being made. Instead, the Lung Cancer Disease Site Group (Lung DSG) offers the following opinions based on the evidence reviewed:

- There is limited evidence for the role of radiotherapy in the management of patients with malignant pleural mesothelioma.
- There is inconsistent evidence and no consensus among the radiation oncologist in the Lung Disease Site Group for the use of prophylactic external beam radiation therapy to tracts caused by thoracic drainage tubes or thoracic diagnostic procedures. For this reason, a recommendation could not be made for this treatment. The decision to use prophylactic external beam radiation therapy to tracts must therefore be based on an individualized case assessment.
- Radical radiation therapy alone should not be offered as a curative treatment option to patients with malignant pleural mesothelioma, based on the currently available evidence.
- Palliative radiation therapy may offer short-term symptom control in terms of chest pain; however, long-term control has not been demonstrated to date.
- Future studies including radiotherapy for the treatment of patients with malignant pleural mesothelioma should include formal measures of quality of life (QOL) and symptom control.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by randomized trials, non-randomized, prospective trials, and a meta-analysis.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Three small randomized controlled trials compared prophylactic external beam radiation therapy (EBRT) to no radiation therapy for patients with thoracic tracts caused by drainage tubes or diagnostic procedures. One randomized trial reported a significant reduction in the frequency of malignant seeding of tracts for the radiation therapy arm (0% of 20 patients) compared to the control arm (40% of 20 patients), $p<0.001$. A second randomized trial reported preliminary results from 12 patients and found more procedure tract metastases in the external beam radiation therapy arm than the control arm; however no p-value was reported. The third randomized trial did not detect a statistically significant difference in procedure tract metastases between treatment arms. A pooled analysis found no significant reduction in the frequency of procedure tract metastases. None of those trials reported any serious adverse effects due to radiation therapy.
- A poll was conducted among the radiation oncologist in the Lung Disease Site Group (DSG) to determine the pattern of practice for prophylactic radiation therapy (RT) to drainage sites. There was no consistent consensus on the use of prophylactic RT, a reflection of the lack of high-quality data from the small randomized trials available.
- Few of the identified studies reported on symptom control, and no studies included formal measures of quality of life (QOL).

POTENTIAL HARMS

Four noncomparative studies have shown that hemithoracic irradiation alone resulted in significant toxicity, including radiation-induced pulmonary fibrosis, radiation pneumonitis, and bronchopleural fistula, without any survival benefit. Median survival ranged from seven months to 17 months.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

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

End of Life Care
Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

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ADAPTATION

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

DATE RELEASED

2006 Feb 6

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) were asked to disclose potential conflicts of interest relating to the topic of this systematic review. The authors of this guideline declared that there were no conflicts of interest.

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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 radiation therapy in malignant pleural mesothelioma: a clinical practice guideline summary. Toronto (ON): Cancer Care Ontario (CCO), 2006 Feb 6. Various p. (Practice guideline; no. 7-14-3). 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 Institute on May 14, 2007. The information was verified by the guideline developer on May 23, 2007.

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