Complete Summary

GUIDELINE TITLE

Prophylactic cranial irradiation in small cell lung cancer.

BIBLIOGRAPHIC SOURCE(S)

Lung Cancer Disease Site Group. Kotalik J, Yu E, Markman BR, Evans WK. Prophylactic cranial irradiation in small cell lung cancer [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2003 Nov [online update]. 16 p. (Practice guideline report; no. 7-13-2). [15 references]

GUIDELINE STATUS

This is the current release of the guideline.

The FULL REPORT, initially the full original Guideline or Evidence Summary, 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

SCOPE

DISEASE/CONDITION(S)

Brain metastases of small cell lung cancer

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Prevention
Treatment

CLINICAL SPECIALTY

Oncology
Radiation Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To make recommendations about the role of prophylactic cranial irradiation (PCI) in patients with small cell lung cancer who have achieved complete response/remission
- To make recommendations about what dose and fractionation schedules of prophylactic cranial irradiation are optimal
- To make recommendations about whether the use of prophylactic cranial irradiation in patients with small cell lung cancer in complete remission affects quality of life

TARGET POPULATION

Adult patients with limited- or extensive-stage small cell lung cancer who have achieved complete remission in response to induction therapy (chemotherapy or chemoradiotherapy)

INTERVENTIONS AND PRACTICES CONSIDERED

Prophylactic cranial irradiation

MAJOR OUTCOMES CONSIDERED

- Disease-free survival
- Overall survival
- Quality of life
- Cognitive functioning

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

2000 Guideline

MEDLINE (1985 through December 1999), CANCERLIT (1985 through October 1999) and the Cochrane Library (1999, Issue 4) databases were systematically searched. "Carcinoma, small cell" (Medical subject heading [MeSH]) was combined with "cranial irradiation" (MeSH), and each of the following phrases used as text words: "prophylactic cranial irradiation", "whole brain irradiation", "elective brain irradiation", "prophylactic brain irradiation", "prophylactic whole brain irradiation", "whole brain radiation". These terms were then combined with the search terms for the following study designs: practice guidelines, systematic reviews or meta-analyses, reviews, randomized controlled trials, and controlled clinical trials. In addition, the Physician Data Query (PDQ) clinical trials database (U.S. National Cancer Institute), was searched for reports of new or ongoing trials. Relevant articles and abstracts were selected and reviewed by three reviewers and the reference lists from these sources were searched for additional trials, as were the reference lists from relevant review articles.

November 2003 Update

The original literature search has been updated using MEDLINE (through October 2003), CANCERLIT (through October 2002), EMBASE (1980 through 2003, week 34), the Cochrane Library (2003, Issue 4), and the conference proceedings of the 1997 to 2003 annual meetings of the American Society of Clinical Oncology (ASCO). The Physicians Data Query (PDQ) clinical trials database (U.S. National Cancer Institute) was also searched for reports of new or ongoing trials.

Inclusion Criteria

Articles were selected for inclusion in this overview of the evidence if they were the following:

1. Meta-analyses or individual randomized controlled trials that compared the administration of prophylactic cranial irradiation (PCI) with no administration of prophylactic cranial irradiation to patients with small cell lung cancer (SCLC) who had achieved complete response to induction therapy (chemotherapy or chemoradiotherapy).
2. Abstracts of meta-analyses or trials were also considered.

Exclusion Criteria

1. Phase I and II studies were not considered for inclusion in this report because of the availability of randomized controlled trials.
2. Papers published in a language other than English were not considered.

NUMBER OF SOURCE DOCUMENTS

2000 Guideline

7 studies (6 randomized controlled trials [described in 8 reports], 1 meta-analysis of individual patient data, and 1 additional unpublished study)

2003 Update

One additional meta-analysis was reviewed.

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

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

It was decided not to pool the results of the individual randomized controlled trials because of the availability of an up-to-date, published meta-analysis that included the most recent randomized trials comparing prophylactic cranial irradiation (PCI) with no prophylactic cranial irradiation in patients with small cell lung cancer who had achieved complete response to induction chemotherapy or chemoradiotherapy.

The information obtained from the original guideline report remains current for the 2003 Update. No new information has emerged.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

2000 Guideline

Based on strong evidence that patients with small call lung cancer (SCLC) who achieve a complete remission after induction therapy (chemotherapy or chemoradiotherapy) have a substantial decrease in the frequency of brain metastases and improved disease-free survival, and on an individual patient data meta-analysis demonstrating an improvement in overall survival, the Lung Disease Site Group (DSG) felt confident to recommend the use of prophylactic cranial irradiation (PCI) in this situation.

Meta-analyses provide an estimate of the overall magnitude of a treatment effect for a body of available evidence. However, meta-analyses should be carefully assessed before relying on them as the basis for a treatment recommendation in the absence of a large, definitive trial. Because of concern about the robustness of the meta-analysis, the modest value of p=0.01 and the absence of randomized trial data supporting PCI-improved overall survival, the authors of this practice guideline report and the members of the Lung DSG advise caution in the interpretation of these data. However, there is strong evidence from four published randomized controlled trials that PCI decreases the frequency of brain

metastases and increases the disease-free survival rate in patients with SCLC who achieve complete responses after induction chemotherapy or chemoradiation therapy.

Members of the Lung DSG discussed whether those patients with extensive disease who achieve complete remission should receive PCI, particularly as their overall survival is shorter than the survival of patients with limited disease and there are virtually no long-term survivors. The Lung DSG concluded that, as the randomized trials included patients with extensive disease who had achieved complete response and there was an overall benefit in terms of disease-free survival, patients with extensive disease should not be denied the potential benefit of reduced risk of central nervous system metastases. This recommendation also takes into account the fact that staging of lung cancer may not be accurate and that the presence of extensive disease may not have been proven by biopsy. Although Lung DSG members acknowledged that central nervous system metastases can be treated when they occur, the psychological and physical consequences of brain metastases are grave, the neurological sequelae of the metastases often resolve incompletely after treatment, and survival is generally short once central nervous system metastases occur. For these reasons, the Lung DSG concluded that it was reasonable to offer PCI to those patients with extensive disease who achieve a complete response, in an effort to extend disease-free survival and maintain a good quality of life for the patient for as long as possible.

The widespread adoption of PCI following the achievement of a complete response to treatment in SCLC has been inhibited by concerns about acute and late neurological sequelae. These concerns arose from early small reports of acute neurological deterioration of cognitive and other neurological functions when radiotherapy was given in large fractions, high total dose and in combination with chemotherapy drugs, particularly nitrosoureas. Concerns about these potential neurological consequences and American concerns about medical-legal actions strongly influenced care providers against using PCI. Recent trials of PCI have carefully assessed the cognitive functioning of patients before, during, and after treatment. It is noteworthy that cognitive functioning, at least as measured by psychometric instruments, is commonly impaired prior to the administration of PCI and has shown no deterioration during PCI relative to those who do not receive PCI. Therefore, most investigators have concluded that serious acute neurotoxicity is not a major concern when the doses of radiotherapy recommended in this report are used. Although not commented on in the studies reviewed, Lung DSG members felt that short-term somnolence following PCI was a common side effect.

Most studies have not followed patients for more than several years. However, Lung DSG members have observed individual patients who have survived five or more years who have developed dementia. Whether this is directly related to PCI or to other factors is unknown, but it remains a concern and follow-up studies of long-term survivors are needed to inform this issue.

There is insufficient evidence available to comment on the optimal timing of PCI in relation to the administration of chemotherapy. The Lung DSG felt that PCI should not be concurrent with chemotherapy because of the potential interaction of the drugs and radiation on the brain vasculature or neural tissue, which might

increase the risk of late neurotoxicity. Members of the Lung DSG felt that it should be given as soon as possible after completion of chemotherapy in complete responders.

In an attempt to obtain additional information about possible dose-response relationships, the Lung DSG considered a review of PCI versus no PCI for patients with SCLC which did not meet the inclusion criteria for this systematic review. Suwinski et al published a review based on a total of 40 trials of PCI versus no PCI, including 11 randomized and 12 nonrandomized trials, most of which involved patients with SCLC who had not achieved complete response to induction therapy. Two of the six randomized controlled trials cited above were included in the Suwinski analysis. The authors reported that a dose range of 30 to 35 Gy in 2 to 3 Gy fractions reduced the incidence of brain metastases within the remaining lifetime of the patients by 80%. They also suggested that PCI be administered early (within 60 days of starting induction therapy) which would mean that many patients would receive cranial irradiation concurrently with chemotherapy and would not have achieved complete remission. The toxicity resulting from concurrent administration of PCI and chemotherapy was not discussed.

Members of the Lung DSG expressed concern that too low a dose of radiation is probably ineffective. The radiation dose recommendation is 30 to 36 Gy in 2 to 3 Gy fractions or the biological equivalent.

2003 Update
As a result of feedback received during the peer review process prior to the publication of this guideline, the Lung DSG amended the description of Suwinski et al from "meta-analysis" to "review" and revised the last paragraph of this section as follows:

Members of the Lung DSG expressed concern that too low a dose of radiation is probably ineffective. The Lung DSG concluded that there is some indication that 30 to 36 Gy in 2 to 3 Gy per fraction or a biologically equivalent dose may produce a better outcome than a lower dose or less aggressive fractionation regimen.

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

2000 Guideline

Practitioner feedback was obtained through a mailed survey of 88 practitioners in Ontario (38 medical oncologists, 22 radiation oncologists and 28 surgeons). 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. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Lung Disease Site Group reviewed the results of the survey.

Final approval of the original guideline report was obtained from the Practice Guidelines Coordinating Committee.

The Cancer Care Ontario Practice Guidelines Initiative (CCOPGI) has a formal standardized process to ensure the currency of each guideline report. This consists of periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

2003 Update

After the practice guideline was approved by the Practice Guidelines Coordinating Committee, a reformatted version was submitted for publication. As part of its peer-review process, the journal had the manuscript reviewed, and the comments of the external reviewers were sent to the guideline authors. As a result of the reviewers' comments, the authors modified the guideline recommendations. The revisions were reviewed and approved by the members of the Lung Disease Site Group and sent to the Practice Guidelines Coordinating Committee for information.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

For patients who have achieved complete response after induction therapy, prophylactic cranial irradiation (PCI) is recommended. There is insufficient evidence to make a definitive recommendation with respect to dose. There is some indication that 30 to 36 Gy in 2 to 3 Gy per fraction or a biologically equivalent dose may produce a better outcome than a lower dose or less aggressive fractionation regimen.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by randomized controlled trials and meta-analyses.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

There is strong evidence to recommend prophylactic cranial irradiation (PCI) for patients who have achieved complete remission following chemotherapy or chemoradiotherapy. Data from randomized controlled trials demonstrate that prophylactic cranial irradiation decreases the frequency of brain metastases and increases disease-free survival in these patients. Two meta-analyses conducted on an overlapping set of studies report increased overall survival, and one reports increased disease-free survival with prophylactic cranial irradiation.

POTENTIAL HARMS

There is insufficient evidence to comment on the long-term effects of prophylactic cranial irradiation on quality of life.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- The radiotherapy schedule commonly used in Canada is 25 Gy in 10 fractions over two weeks. Data from further research, including a trial currently ongoing that compares 25 Gy in 10 fractions with 36 Gy in 18 fractions, will be required to determine optimal dose of prophylactic cranial irradiation.
- There is insufficient evidence to make recommendations concerning the optimal timing of prophylactic cranial irradiation in relation to the administration of chemotherapy. Lung Cancer Disease Site Group members generally felt that it should be given as soon as possible after completion of chemotherapy.
- Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult these guidelines 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 warranties of any kind whatsoever regarding their content or use or application and disclaims any responsibility 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)

Lung Cancer Disease Site Group. Kotalik J, Yu E, Markman BR, Evans WK. Prophylactic cranial irradiation in small cell lung cancer [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2003 Nov [online update]. 16 p. (Practice guideline report; no. 7-13-2). [15 references]

ADAPTATION

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

DATE RELEASED

2000 Mar 22 (updated online 2003 Nov)

GUIDELINE DEVELOPER(S)

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

GUIDELINE DEVELOPER COMMENT

The Practice Guidelines Initiative (PGI) is the main project of the Program in Evidence-based Care (PEBC), 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

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

Members of the Lung Cancer Disease Site Group disclosed potential conflict of interest information.

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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:

- Prophylactic cranial irradiation in small cell lung cancer. Summary. Toronto (ON): Cancer Care Ontario (CCO), 2003 Nov. Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.
- Browman GP, Levine MN, Mohide EA, Hayward RS, 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 June 5, 2002. The information was verified by the guideline developer as of July 8, 2002. This summary was updated by ECRI on January 27, 2003. The information was verified by the guideline developer on February 24, 2003. This summary was updated by ECRI on April 19, 2004. The information was verified by the guideline developer on April 29, 2004.

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