

Cancer Care Ontario Practice Guidelines Initiative

Sponsored By: Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care



Altered Fractionation of Radical Radiation Therapy in the Management of Unresectable Non-Small Cell Lung Cancer

Practice Guideline Report #7-12

ORIGINAL GUIDELINE: October 8, 1999
MOST RECENT LITERATURE SEARCH: September 2002
NEW EVIDENCE ADDED TO GUIDELINE REPORT: October 2000
APPENDIX UPDATED: January 2003

New evidence found between completion of the original guideline and October 2000 is consistent with the original recommendations. No new evidence has been found by update searches since October 2000.

SUMMARY

Guideline Question

Do any altered fractionation radiation schemes prolong survival in the treatment of locally advanced, unresectable stage III non-small cell lung cancer (NSCLC) compared with the North American standard of 60 Gy in 30 fractions?

Target Population

These recommendations apply to patients with locally advanced, unresectable stage III non-small cell lung cancer (NSCLC).

***Note:** The current standard treatment for unresected stage III NSCLC is combined modality therapy (Practice Guideline Report #7-3: Unresected Stage III Non-Small Cell Lung Cancer – see Appendix 1 in Full Report).*

Recommendations

Key Recommendations

- There is evidence from one randomized controlled trial demonstrating that Continuous Hyperfractionated Accelerated Radiation Therapy (CHART) improves survival over standard radiotherapy of 60 Gy in 30 fractions, in patients with locally advanced, unresectable stage III non-small cell lung cancer (NSCLC). Selected patients (with ECOG performance status ≥ 1 who do not fit the criteria for induction chemotherapy and radiotherapy or patients who prefer radiotherapy only) may be considered for CHART.

- Evidence from a comparative cohort study suggests that Hyperfractionated Accelerated Radiation Therapy (HART) also improves survival over standard radiotherapy.
- Of those trials designed to improve therapeutic ratios in patients with locally advanced, unresectable stage III NSCLC there is insufficient data of high quality to recommend hyperfractionation over standard radiotherapy of 60 Gy in 30 fractions. Further randomized controlled trials are necessary to confirm the benefits, if any, of hyperfractionation radiotherapy.
- Trials examining therapies providing greater convenience to patients with locally advanced, unresectable stage III NSCLC did not show evidence of a survival benefit for either hypofractionation or split-course radiotherapy. If symptom palliation is the main concern, patients may consider participating in clinical trials examining the role of hypofractionation or split-course radiotherapy.
- The effect of treatment on quality of life or health care costs was not reviewed in most of these trials. Therefore, if quality of life and health care costs are issues of concern, there is insufficient evidence at this time to draw any conclusions on the value of altered fractionation.

Qualifying Statements

- The main adverse effect associated with these altered fractionation treatments is acute esophagitis.

Methods

Entries to MEDLINE (through September 2002), CANCERLIT (through September 2002) and Cochrane Library (through Issue 4, 2002) databases have been searched for evidence relevant to this practice guideline. The most recent literature search was performed in October 2002.

Evidence was selected and reviewed by three members of the Cancer Care Ontario Practice Guidelines Initiative's (CCOPGI) Lung Cancer Disease Site Group (Lung DSG) and methodologists. This practice guideline has been reviewed and approved by the Lung DSG, which comprises medical and radiation oncologists, pathologists, surgeons, a psychologist, a medical sociologist and two community representatives.

External Review by Ontario practitioners was obtained through a mailed survey. Final approval of the original guideline report was obtained from the Practice Guidelines Coordinating Committee (PGCC). The 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.

Key Evidence

- One published meta-analysis, eight randomized controlled trials, one comparative cohort study and two randomized phase I/II trials evaluating altered fractionation (including continuous hyperfractionated, accelerated, CHART, HART, Continuous Hyperfractionated Accelerated Radiation Therapy Weekendless (CHARTWEL), or hypofractionated and split-course radiotherapy) were reviewed.
- The published meta-analysis demonstrated a significant survival benefit for hyperfractionated over standard radiotherapy (odds ratio, 0.69; 95% confidence interval, 0.51 to 0.95; $p=0.02$). The CCOPGI's Resource Group conducted an (unpublished) meta-analysis of the same trials as the published meta-analysis which

did not demonstrate a significant survival benefit for hyperfractionated over standard radiotherapy (odds ratio, 0.67; 95% confidence interval, 0.42 to 1.07; $p=0.091$).

- Three of four randomized controlled trials demonstrated a survival benefit for hyperfractionation compared with standard radiotherapy, although not all results were statistically significant [data from one of the three trials were not statistically significant; data from the second trial demonstrated a three year survival rate of 22% for hyperfractionated versus 0% for standard radiotherapy, but no significance level was reported; and the third trial demonstrated a statistically significant two-year survival benefit ($p<0.05$)].
- With respect to hyperfractionated accelerated radiotherapy: one randomized controlled trial which compared CHART with standard radiotherapy demonstrated an advantage with CHART for two-year survival rates (30% versus 21%) and five-year survival rates (20% versus 13%) (hazard ratio, 0.78; 95% confidence interval, 0.65 to 0.94; $p=0.008$). One comparative cohort study demonstrated a three-year survival benefit for HART of 28% versus 6% for standard radiotherapy ($p<0.001$). No survival data were cited in the full report of one phase I/II study of CHARTWEL; the authors state that there was no survival difference between the two groups at 18 months after radiotherapy.
- One randomized controlled trial showed that hypofractionation improved three-year survival (19% versus 9% for standard radiotherapy) but no significance was reported. Acute treatment toxicity was reduced in the hypofractionation patients (30% experienced no esophagitis compared with 70% of standard radiotherapy patients).
- Hyperfractionation, CHART and hypofractionated radiotherapy demonstrated no significant differences in late toxicity compared with standard radiotherapy. Esophagitis was more severe ($p=0.004$) and of longer duration ($p<0.0001$) in patients receiving accelerated radiotherapy compared to the standard radiotherapy group. Esophagitis was experienced by 87% of HART patients versus 44% of standard radiotherapy patients ($p<0.05$). Accelerated radiotherapy was shown to increase acute toxicity over standard radiotherapy. It is unclear whether toxicity was monitored for split-course radiotherapy.

Prepared by the Lung Cancer Disease Site Group

For further information about this practice guideline report, please contact Dr. William K. Evans, Chair, Lung Cancer Disease Site Group, Cancer Care Ontario, 620 University Avenue, Toronto ON M5G 2L7; TEL (416) 971-5100 ext. 1650; FAX (416) 217-1235.

PREAMBLE: About Our Practice Guideline Reports

The Cancer Care Ontario Practice Guidelines Initiative (CCOPGI) is a project supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care, as part of the Program in Evidence-based Care. The purpose of the Program is to improve outcomes for cancer patients, to assist practitioners to apply the best available research evidence to clinical decisions, and to promote responsible use of health care resources. The core activity of the Program is the development of practice guidelines by multidisciplinary Disease Site Groups of the CCOPGI using the methodology of the Practice Guidelines Development Cycle.¹ The resulting practice guideline reports are convenient and up-to-date sources of the best available evidence on clinical topics, developed through systematic review, evidence synthesis and input from a broad community of practitioners. They are intended to promote evidence-based practice.

This practice guideline report has been formally approved by the Practice Guidelines Coordinating Committee, whose membership includes oncologists, other health providers, community representatives and Cancer Care Ontario executives. Formal approval of a practice guideline by the Coordinating Committee does not necessarily mean that the practice guideline has been adopted as a practice policy of CCO. The decision to adopt a practice guideline as a practice policy rests with each regional cancer network that is expected to consult with relevant stakeholders, including CCO.

Reference:

1. 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.

For the most current versions of the guideline reports and information about the CCOPGI and the Program, please visit our Internet site at:

<http://www.cancercare.on.ca/ccopgi/>

For more information, contact our office at:

Phone: 905-525-9140, ext. 22055

Fax: 905-522-7681

Copyright

This guideline is copyrighted by Cancer Care Ontario; the guideline and the illustrations herein may not be reproduced without the express written permission of Cancer Care Ontario. Cancer Care Ontario reserves the right at any time, and at its sole discretion, to change or revoke this authorization.

Disclaimer

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 judgement in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation nor warranties of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.