# Complete Summary

## GUIDELINE TITLE

The role of thoracic radiotherapy as an adjunct to standard chemotherapy in limited-stage small cell lung cancer.

## BIBLIOGRAPHIC SOURCE(S)

Lung Cancer Diseases Site Group. The role of thoracic radiotherapy as an adjunct to standard chemotherapy in limited-stage small cell lung cancer [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2003 Jan [online update]. 20 p. (Practice guideline; no. 7-13-3). [30 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)

Limited-stage small cell lung cancer

### GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Management
Treatment

### CLINICAL SPECIALTY

Oncology
Radiation Oncology

### INTENDED USERS

Physicians

### GUIDELINE OBJECTIVE(S)

To determine if there is a role for thoracic radiotherapy as an adjunct to standard chemotherapy in limited-stage small cell lung cancer (SCLC)

### TARGET POPULATION

Adult patients with limited-stage small cell lung cancer

### INTERVENTIONS AND PRACTICES CONSIDERED

1. Chemotherapy, including cisplatin, etoposide, cyclophosphamide, doxorubicin, vincristine, and vindesine, alone
2. Combined chemotherapy plus thoracic radiotherapy, including sequential, alternating, concurrent, early or late thoracic radiotherapy; high-dose or low-dose thoracic radiotherapy; or hyperfractionated radiotherapy (Note: hyperfractionated therapy is considered but not recommended)

### MAJOR OUTCOMES CONSIDERED

- Survival (median, overall two-year, overall five-year, and progression-free survival)
- Local control
- Complete response rate
- Treatment toxicity

## 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

**1999 Guideline**

A MEDLINE search was initially conducted from 1990 to July 1998 and updated to March 1999, using the terms [lung neoplasms AND carcinoma, small cell AND thoracic (tw)]. A CANCERLIT search was conducted for 1995 to July 1998 and updated to February 1999, using the same terminology. The Physician Data Query File (PDQ; U.S. National Cancer Institute) was also searched for clinical trials using the terms [lung cancer, small cell AND radiation therapy] as was the Cochrane Library (1998, Issue 2).

### 2003 Update

The original literature search has been updated using MEDLINE and CANCERLIT (through December and October 2002 respectively), and the Cochrane Library (Issue 4, 2002). The proceedings of the annual meeting of the American Society of Clinical Oncology (1998-2002) were also searched.

*Inclusion Criteria*

Articles were selected for inclusion in this systematic review of the evidence if they met the following criterion:

1. Meta-analyses or randomized controlled trials that compared chemotherapy plus radiotherapy with chemotherapy alone, early with late thoracic radiotherapy (TRT), sequential with concurrent TRT, or different doses of TRT in patients with limited-stage small cell lung cancer.

**Note**: Limited-stage small cell lung cancer is defined as a tumour confined to the hemithorax of origin, the mediastinum and the supraclavicular nodes, which can be encompassed within a "tolerable" radiotherapy port (Physician Data Query database, National Cancer Institute). Early radiation is generally defined as radiation therapy that is given within the first several cycles of chemotherapy, whereas late radiation therapy is radiotherapy started with the last scheduled course of chemotherapy or after the total course of chemotherapy is completed.)

## NUMBER OF SOURCE DOCUMENTS

### 1999 Guideline

2 published meta-analyses

9 randomized controlled trials

### 2003 Update

7 randomized controlled trials

## 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
Review of Published Meta-Analyses
Systematic Review with Evidence Tables

## DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

### 1999 Guideline

The Cancer Care Ontario Practice Guidelines Initiative's (CCOPGI) Resource Group pooled five-year survival data from four randomized controlled trials comparing early to late thoracic radiotherapy (TRT) to obtain a more precise estimate of the effect of TRT given early or late in the chemotherapy regimen. The Meta-Analyst$^{0.988}$ program provided by Dr. J. Lau, Tufts New England Medical Centre, was used to perform this analysis. Where the data were analyzed by the Cancer Care Ontario Practice Guidelines Initiative, odds ratios and 95% confidence intervals were calculated using a random effects model. Results are expressed such that a mortality odds ratio less than 1.0 favours early TRT. In contrast, the data from one published report of a meta-analysis was reported as the odds ratio of surviving, and in this case, a ratio greater than 1.0 favours early TRT.

### 2003 Update

No further evidence synthesis has been performed.

## METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

## DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

### 1999 Guideline

An initial draft of this guideline was formulated by a group member; the draft was subsequently discussed and moulded into the final form in response to both group discussions and practitioner feedback.

Combination chemotherapy has become accepted as part of the standard treatment for limited-stage small cell lung cancer. The Lung Cancer Disease Site Group (DSG) is in the process of developing a practice guideline on optimal chemotherapy for the initial management of limited-stage small cell lung cancer, which will be issued as Practice Guideline Report #7-13-1 titled, "The role of combination chemotherapy in the initial management of limited disease small cell lung cancer."

One concern raised during practitioner feedback was the practical feasibility of instituting radiotherapy early in the treatment course (for example, with the

second course of chemotherapy) given the limited and strained resources faced by many cancer centres in Ontario. Despite this reality, the guidelines process has been instituted in order to recommend optimal current therapy towards which the medical community should strive for the benefit of the patient population served. Because of the magnitude of the benefit observed, even some heavily strained radiotherapy treatment centres have instituted early thoracic radiotherapy through effective communication between medical and radiation oncologists and teamwork with simulation and treatment staff.

Another relevant concern related to whether treatment volumes should be based upon the pre or post chemotherapy tumour volumes. Given the recommendation for early thoracic irradiation (that is, with either the first or second course of chemotherapy), the impact of this question is significantly lessened and logic therefore dictates that radiation portals will be based upon the pre-treatment tumour volume. This is particularly highlighted by the practical situation that simulation would be performed during or conceivably even before the first course of chemotherapy in preparation for commencement of early irradiation. There is one randomized trial of 191 patients which addressed the question of treatment volume. In this study, intrathoracic recurrence rates were not statistically different between radiotherapy based upon preinduction versus postinduction chemotherapy.

There was considerable discussion within the Lung Cancer DSG about the appropriateness of recommending hyperfractionated radiotherapy to patients with limited small cell lung cancer (SCLC) on the basis of a single study, particularly as a second study, not yet fully reported, has not shown a similar survival advantage. In addition, the control arm of the Turrisi trial used a dose of radiation (45 Gy in 25 fractions) which is biologically less intense than the dose generally employed by Canadian radiation oncologists (40 Gy in 15 fractions). Furthermore, the results achieved with twice daily radiotherapy appear quite similar to those of the best arms of the Canadian trial (BR6) which showed that early radiotherapy is superior to late radiotherapy when combined with alternating cyclophosphamide, adriamycin, vincristine, cisplatin (CAV-EP) chemotherapy. Ideally, a randomized trial should compare early twice daily radiotherapy to early radiotherapy as administered in the Canadian trial (40 Gy in 15 daily fractions).

**2003 Update**

The Lung Cancer DSG continues to believe that hyperfractionated radiotherapy should not be used outside of a clinical trial for limited stage small cell lung cancer.

The new data found through the updating process provides conflicting evidence regarding the timing of radiotherapy. Although evidence regarding the use of concurrent chemoradiotherapy is conflicting, the new data from a trial evaluating concurrent versus alternating radiotherapy underscores the importance of the specific chemotherapy drugs used with the radiotherapy. Lebeau et al had more frequent and more serious lung toxicity with concurrent chemoradiotherapy compared with alternating radiotherapy. In this trial, the initial chemotherapy regimen included doxorubicin, which probably contributed to the high rate of serious pulmonary toxicity and higher mortality rate in the concurrently treated arm of the study. This observation does not negate the concept of concurrent

chemo-radiotherapy, but rather highlights the need to identify chemotherapy regimens that can be safely combined with radiotherapy. There is substantial experience with the combination of etoposide-cisplatin in combination with radiotherapy and this should be the standard outside of a clinical trial.

### 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

Practitioner feedback was obtained through a mailed survey* of 64 medical and radiation oncologists in Ontario. 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 results of the survey were reviewed by the Lung Cancer Disease Site Group.

The practice guideline recommendations reflect the integration of the draft recommendations with feedback obtained from the External Review process.

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

*Practitioner feedback was obtained using two versions of a mailed survey. One version of the questionnaire, the version traditionally used by the Cancer Care Ontario Practice Guidelines Initiative, contained nine questions. The second version, an experimental version, contained 21 questions. Practitioners eligible to participate in the survey were randomly assigned one of the two questionnaires, with the result that 33 practitioners received the experimental version and 31 practitioners, the traditional version. The two questionnaires had six questions in common; data in Table 4 of the original guideline represent practitioner responses to the six common questions, pooled across the versions of the questionnaires.

## RECOMMENDATIONS

### MAJOR RECOMMENDATIONS

- In patients with limited-stage small cell lung cancer, the addition of thoracic radiotherapy to standard combination chemotherapy improves both local control and overall survival and should be incorporated into a comprehensive treatment plan of combined modality therapy for limited-stage small cell lung cancer.
- The data from randomized trials suggest that higher doses of thoracic radiotherapy produce better local control and progression-free survival. Although the optimal dose has not yet been established, those trials that demonstrate a superior survival outcome from radiotherapy and chemotherapy over chemotherapy alone have generally used a total dose of at least 40 Gy in 15 fractions over three weeks (or a biologically equivalent dose). The radiation oncologist must assess the appropriateness and safety of this recommendation for individual patients, taking into consideration tumour field size and location, pulmonary function tests and other clinical factors. These factors are important as the improvement in overall survival occurs with an increased risk of death due to the toxicity of combined modality therapy.
- There is conflicting evidence as to the optimal timing of thoracic radiotherapy in relation to the course of chemotherapy (early or late administration of thoracic radiotherapy). The evidence is also conflicting regarding the issue of concurrent versus sequential administration of chemotherapy with radiotherapy.
- Based on currently available data, hyperfractionated thoracic radiotherapy is NOT recommended for limited-stage small cell lung cancer outside of a clinical trial.

### CLINICAL ALGORITHM(S)

None provided

## EVIDENCE SUPPORTING THE RECOMMENDATIONS

### TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

#### 1999 Guideline

Two published meta-analyses comparing chemotherapy plus thoracic radiotherapy (TRT) with chemotherapy alone were eligible for review. The first meta-analysis analyzed published results from 11 trials and the second examined individual patient data from 13 trials; there was substantial overlap between the trials analyzed in the two meta-analyses. Nine randomized controlled trials were also eligible for review (six were fully published). Six of the nine randomized controlled trials investigated the timing of TRT delivery. The Cancer Care Ontario Practice Guidelines Initiative's (CCOPGI's) Resource Group pooled published data from four randomized controlled trials examining early versus late TRT delivery. One of the nine randomized controlled trials analyzed optimal dosage of TRT delivered in conjunction with chemotherapy, while two randomized controlled trials examined single- versus twice-daily TRT treatment in conjunction with chemotherapy.

#### 2003 Update

Seven papers identified by a literature search from October 2000 to December 2002 were eligible for inclusion in the systematic review of the evidence. Two of these papers led the Lung Cancer Disease Site Group to modify its recommendations in October 2000. One paper reported a trial that compared chemotherapy combined with either concurrent or alternating radiotherapy. The other paper was the full report of a trial previously published in abstract form that compared chemotherapy plus daily radiotherapy versus chemotherapy plus twice-daily radiotherapy. Five additional reports of randomized trials were found, one of which included updated results for a trial included in the original guideline report.

## BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

### POTENTIAL BENEFITS

#### The Role of Radiotherapy with Chemotherapy

Two published meta-analyses compared chemotherapy plus thoracic radiotherapy with chemotherapy alone. The first meta-analysis analyzed published results from 11 trials and the second examined individual patient data from 13 trials; there was substantial overlap between the trials analyzed in the two meta-analyses. Both meta-analyses demonstrated positive benefits for thoracic radiotherapy in combination with chemotherapy versus chemotherapy alone. One meta-analysis demonstrated an overall benefit of thoracic radiotherapy on two-year survival [Odds Ratio, 1.53; 95% Confidence Interval, 1.30 to 1.76; p=0.001] and an absolute improvement in local control of 25.3% (95% Confidence Interval, 16.5 to 34.1). The second meta-analysis indicated a three-year overall survival benefit of 5.4% ± 1.4% (standard deviation) and a Relative Risk of death of 0.86 (95% Confidence Interval, 0.78 to 0.94; p=0.001) in favour of the combined modality group. One of two randomized trials that was not included in either meta-analysis accrued 97 patients and detected a survival benefit for combined modality treatment over chemotherapy alone. The other trial, which involved the use of split-course radiotherapy and a second randomization to consolidation chemotherapy, detected no significant difference in overall survival between treatments among 386 patients, although there was a significant advantage in two-year progression-free survival for irradiated patients. The reliability of the results of the latter trial is questionable since the combined treatment arm was closed early due to toxicity.

#### Radiotherapy Timing--Concurrent versus Sequential or Alternating Administration

Three randomized controlled trials compared concurrent chemo-radiotherapy with either sequential or alternating chemo-radiotherapy. One trial demonstrated a non-significant increase in overall survival for patients receiving thoracic radiotherapy concurrently with chemotherapy versus sequentially following chemotherapy (p=0.097 logrank). However, a regression analysis adjusted for prognostic variables detected a significant survival benefit for concurrent treatment (Hazard Ratio, 0.70; 95% Confidence Interval, 0.52 to 0.94, p=0.02). Another small trial available only in abstract form reported no survival benefit for concurrent over sequential administration of radiotherapy (p=0.33). One randomized controlled trial which compared concurrent chemo-radiotherapy with

chemotherapy alternating with thoracic radiotherapy showed no significant difference between the two treatment arms (p=0.15 logrank).

### Radiotherapy Timing--Early versus Late Administration

Five randomized controlled trials investigated early versus late thoracic radiotherapy delivery. Methodologists working with the Lung Cancer Disease Site Group conducted a meta-analysis of published data involving 777 patients from three of the randomized controlled trials that examined early versus late daily thoracic radiotherapy delivery. Two of these trials administered chemotherapy concurrently with the radiotherapy and one administered it sequentially. Results of the meta-analysis indicated that there was no survival benefit to administering thoracic radiotherapy early in relation to the chemotherapy administration schedule (Odds Ratio, 1.04; 95% Confidence Interval, 0.45 to 2.43; p=0.9), although the treatment effects detected in the three trials were heterogeneous. Only one of these trials obtained a significant result: the National Cancer Institute of Canada detected a survival advantage for early, concurrent administration of thoracic radiotherapy compared with late, concurrent administration (5-year survival, 20% versus 11%, respectively, p=0.008 log rank). In addition, two randomized controlled trials compared early administration of hyperfractionated thoracic radiotherapy (concurrent with the first course of chemotherapy) to late administration (given concurrently with cycle three or four of chemotherapy). In one of those trials, early administration achieved a significantly higher local control rate and an improvement in survival that was close to statistical significance. In the other trial, there were no differences between administration schedules in complete response rate or survival.

### Radiotherapy Dosage

Two randomized controlled trials examining radiotherapy dosage reported no significant survival benefit of high dose over low dose thoracic radiotherapy; although in one trial, there was an improvement in local control at higher doses.

### Hyperfractionated Radiotherapy

Hyperfractionated thoracic radiotherapy has been shown in one large, fully published study (417 patients) to significantly increase the long-term survival of patients with limited small cell lung cancer (5-year survival, 26% with hyperfractionated thoracic radiotherapy versus 16% with once daily radiotherapy, p=0.04 logrank). This was achieved with an increased rate of short-term grade 3 esophagitis. A second large randomized trial (262 patients) has recently been fully published and has not detected a survival advantage for hyperfractionated thoracic radiotherapy (3-year survival, 29% with hyperfractionated thoracic radiotherapy versus 34% with once daily radiotherapy, p=0.49). Grade 3 esophagitis was again significantly more frequent in the hyperfractionated arm.

## POTENTIAL HARMS

One meta-analysis demonstrated an increased risk of toxic death in the combined chemotherapy-radiotherapy group compared with the chemotherapy alone group (Odds Ratio, 2.54; 95% Confidence Interval, 1.90 to 3.18; p<0.01). In one trial,

grade 3 and 4 thrombocytopenia was increased in the early hyperfractionated radiotherapy group compared with late hyperfractionated radiotherapy (p=0.062).

## 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 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
Safety

## IDENTIFYING INFORMATION AND AVAILABILITY

### BIBLIOGRAPHIC SOURCE(S)

Lung Cancer Diseases Site Group. The role of thoracic radiotherapy as an adjunct to standard chemotherapy in limited-stage small cell lung cancer [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2003 Jan [online update]. 20 p. (Practice guideline; no. 7-13-3). [30 references]

### ADAPTATION

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

### DATE RELEASED

1999 Oct 8 (updated online 2003 Jan)

## 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 and Health Long-Term Care

## GUIDELINE COMMITTEE

Lung Cancer Disease Site Group

## COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of 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.

## 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 is available:

- The role of thoracic radiotherapy as an adjunct to standard chemotherapy in limited-stage small cell lung cancer. Summary. Toronto (ON): Cancer Care Ontario (CCO) 1999 Oct 8 (updated online 2003 Jan)

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

### 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 on August 6, 2003. The updated information was verified by the guideline developer on September 2, 2003.

### COPYRIGHT STATEMENT



## DISCLAIMER

### NGC DISCLAIMER

Readers with questions regarding guideline content are directed to contact the guideline developer.



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