The Role of Thoracic Radiotherapy as an Adjunct to Standard Chemotherapy in Limited-Stage Small Cell Lung Cancer

Members of the Lung Cancer Disease Site Group

A Quality Initiative of the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

An assessment conducted in November 2013 put Evidence-based Series (EBS) 7-13-3 in the Education and Information section. This means that the recommendations will no longer be maintained by may still be useful for academic or other information purposes. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol).

The reviewed EBS report, consists of

Section 1: Clinical Practice Guideline
Section 2: Systematic Review
Section 3: Document Review Summary and Tool

and is available on the CCO Web site (http://www.cancercare.on.ca) PEBC Lung Cancer DSG page at: https://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/lung-ebs/

Release Date: May 16 2013

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The Role of Thoracic Radiotherapy as an Adjunct to Standard Chemotherapy in Limited-Stage Small Cell Lung Cancer: A Clinical Practice Guideline

G. Okawara, A. Gagliardi, W. K. Evans, and members of the Lung Cancer Disease Site Group

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Based on new evidence that emerged after completion of the original guideline, the Lung Cancer Disease Site Group modified the guideline recommendations in January 2003. The revised recommendations are labelled Update.

Report Date: January 2003

Guideline Question
Is there a role for thoracic radiotherapy as an adjunct to standard chemotherapy in limited-stage small cell lung cancer?

Target Population
These recommendations apply to adult patients with limited-stage small cell lung cancer.

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.

- **Update**
  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.

- **Update**
  Based on currently available data, hyperfractionated thoracic radiotherapy is NOT recommended for limited-stage small cell lung cancer outside of a clinical trial.

**Methods**

Entries to MEDLINE and CANCERLIT (through December and October 2002, respectively) 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 January 2003.

Evidence was selected and reviewed by one member of the Cancer Care Ontario Practice Guidelines Initiative’s Lung Cancer Disease Site Group and methodologists. This practice guideline has been reviewed and approved by the Lung Cancer Disease Site Group, which comprises medical and radiation oncologists, pathologists, surgeons, a respirologist, 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. The Cancer Care Ontario Practice Guidelines Initiative 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**

- **The Role of Radiotherapy with Chemotherapy**
  - **Update**
    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 Update**
  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 Update**
  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 Update**
  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 Update**
  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.

- **Adverse Effects**
  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).

Related Guidelines
Cancer Care Ontario Practice Guidelines Initiative’s Practice Guideline Reports:
- 7-13-1: *The Role of Combination Chemotherapy in the Initial Management of Limited-Stage Small Cell Lung Cancer.*
- 7-13-2: *Prophylactic Cranial Irradiation in Small Cell Lung Cancer.*

**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. The resulting practice guideline reports are convenient and up-to-date sources of the best available evidence on clinical topics, developed through systematic reviews, 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:

For the most current versions of the guideline reports and information about the PEBP, please visit the CCO website at: http://www.cancercare.on.ca
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Evidence-based Series #7-13-3: Section 2

The Role of Thoracic Radiotherapy as an Adjunct to Standard Chemotherapy in Limited-Stage Small Cell Lung Cancer: A Systematic Review

G. Okawara, A. Gagliardi, W. K. Evans, and members of the Lung Cancer Disease Site Group

A Quality Initiative of the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

Report Date: January 2003

I. QUESTION
Is there a role for thoracic radiotherapy (TRT) as an adjunct to standard chemotherapy in limited-stage small cell lung cancer (SCLC)?

II. CHOICE OF TOPIC AND RATIONALE
Combination chemotherapy is the conventional treatment modality for both limited- and extensive-stage small cell lung cancer. However, despite the systemic nature of this malignancy, thoracic control of disease remains problematic. Local failure rates of 80 to 90% have been reported in the literature (1,2). The results of trials conducted to assess the value of thoracic radiotherapy in limited-stage disease have been inconsistent. Possible explanations have been discussed by Arriagada et al (3) and include variations in treatment protocols, non-significant statistical variations and lack of sufficient statistical power. Therefore, the Lung Cancer Disease Site Group (Lung DSG) decided to review the evidence as to whether thoracic radiotherapy offers any survival benefit to patients with small cell lung cancer, when thoracic radiotherapy should be delivered with respect to the timing of chemotherapy, and at what dose.

III. METHODS
Guideline Development
This practice guideline report was developed by the Cancer Care Ontario Practice Guidelines Initiative (CCOPGI), using the methodology of the Practice Guidelines Development Cycle (1u). Evidence was selected and reviewed by one member of the CCOPGI’s Lung DSG and methodologists. Members of the Lung DSG disclosed potential conflict of interest information.
The practice guideline report is a convenient and up-to-date source of the best available evidence on the role of thoracic radiotherapy as an adjunct to standard chemotherapy in limited-stage small cell lung cancer, developed through systematic reviews, evidence synthesis, and input from practitioners in Ontario. It is intended to promote evidence-based practice. The Practice Guidelines Initiative is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

External review by Ontario practitioners was obtained through a mailed survey consisting of items that address the quality of the draft practice guideline report and recommendations, and whether the recommendations should serve as a practice guideline. Final approval of the original guideline report was obtained from the Practice Guidelines Coordinating Committee.

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.

Literature Search Strategy
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) was also searched for clinical trials using the terms [lung cancer, small cell AND radiation therapy] as was the Cochrane Library (1998, issue 2).

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

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 (PDQ), 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.

Synthesizing the Evidence
The Cancer Care Ontario Practice Guidelines Initiative’s methodologists pooled five-year survival data from four RCTs comparing early to late TRT to obtain a more precise estimate of the effect of TRT given early or late in the chemotherapy regimen. The Meta-Analyst 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 (4) was reported as the odds ratio of surviving, and in this case, a ratio greater than 1.0 favours early TRT.
IV. RESULTS

Literature Search Results

Two published meta-analyses comparing chemotherapy plus TRT with chemotherapy alone (CT) 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 (RCTs) were also eligible for review (six were fully published). Six of the nine RCTs investigated the timing of TRT delivery. The Cancer Care Ontario Practice Guidelines Initiative’s methodologists pooled published data from four RCTs examining early versus late TRT delivery. One of the nine RCTs analyzed optimal dosage of TRT delivered in conjunction with chemotherapy, while two RCTs examined single- versus twice daily TRT treatment in conjunction with chemotherapy.

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 (2u-8u).

Two of these papers led the Lung Cancer DSG to modify its recommendations in October 2000. One paper reported a trial that compared chemotherapy combined with either concurrent or alternating radiotherapy (2u). The other paper was the full report of a trial previously published in abstract form (19) that compared chemotherapy plus daily radiotherapy versus chemotherapy plus twice-daily radiotherapy (3u).

Five additional reports of randomized trials were found (4u-8u), one of which included updated results for a trial included in the original guideline report (4u).

Outcomes

Chemotherapy versus Chemo-Radiotherapy

The results of two published meta-analyses which compared chemotherapy alone with combined chemo-radiotherapy are summarized in Table 1. There was substantial overlap between the trials analyzed in each of the meta-analyses; ten of the trials cited in each meta-analysis were common to both.

Table 1. Meta-analyses examining effectiveness of thoracic radiotherapy (TRT) plus chemotherapy versus chemotherapy alone.

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<th>Reference</th>
<th>Trials Examined</th>
<th>Survival</th>
<th>Local Control</th>
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<tr>
<td>Warde (4) 1992</td>
<td>11 n=1911</td>
<td>OR 1.53* (95% CI, 1.30 to 1.76) p&lt;0.001</td>
<td>OR 3.02‡ (95% CI, 2.80 to 3.24) p&lt;0.0001</td>
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<tr>
<td>Pignon (5) 1992 individual patient data</td>
<td>13 n=2140</td>
<td>5.4% +/- 1.4%†</td>
<td>Not reported</td>
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* odds ratio for treatment effect is the odds of surviving two years among patients receiving TRT compared with the odds of patients in the control group
† absolute increase in overall survival at three years, with a standard deviation of 1.4%
‡ local control, odds ratio for treatment benefit, based on nine studies
§ relative risk of death
CI confidence interval

The Warde analysis of 11 trials reported an improvement in absolute local control of 25.3% (95% confidence interval [CI], 16.5% to 34.1%) for the combined modality group, and a benefit of TRT on two-year survival (odds ratio [OR], 1.53; 95% CI, 1.30 to 1.76; p<0.001) (4). The odds ratio for treatment effect is the odds of surviving two years among patients allocated to receive TRT compared with the odds of surviving for patients allocated to the control group.
The overall event-rate difference, i.e., the overall benefit on two year survival, was 5.4% (p<0.05; 95% CI, 1.1% to 9.7%).

The Pignon analysis of individual patient data from 13 trials showed a similar benefit in favour of the combined modality group (relative risk [RR] of death, 0.86; 95% CI, 0.78 to 0.94; p=0.001) (5) (Note the differences between Warde and Pignon in type and direction of ratios reported; Warde reported an odds ratio of survival, Pignon a relative risk of death). At three years, the absolute increase in overall survival in the group receiving both chemotherapy and thoracic radiotherapy was 5.4% ± 1.4% (standard deviation). Subgroup analysis on the basis of age indicated that the benefit from radiotherapy on mortality was greatest in patients under 55 years of age (p=0.01). The relative risk of death in favour of combination therapy was 0.72 (95% CI, 0.56 to 0.93) for patients under 55 years old and 1.07 (95% CI, 0.70 to 1.64) for patients more than 70 years old; the reductions in the risk of death were 28% ± 8% and -7%±17% respectively. The lack of a clearly significant reduction in mortality with radiotherapy found among patients over age 64 years in this subgroup analysis should be interpreted with caution given the wide confidence intervals, the general difficulty in proving a negative result, and the problems inherent in subgroup analysis.

Quon et al (6) provide additional data bearing on the issue of treatment effects with age. The authors conducted a retrospective review of data from two previously reported Canadian randomized trials investigating combined modality therapy which included TRT. They partitioned the patients into two age groups, <70 years old and ≥70 years old. The two groups were compared with respect to baseline patient characteristics, treatment field sizes and doses, numbers of patients receiving and completing TRT, number of days required to complete TRT, toxicity, response rates and survival over the two studies. Analyses indicated that age does not appear to have an impact on the delivery, tolerance or efficacy of TRT for patients with limited-stage small cell lung cancer.

**Update**

Two additional randomized trials of chemotherapy versus chemo-radiotherapy were found during update searches (5u,6u). Johnson et al (5u) compared cyclophosphamide-doxorubicin(Adriamycin®)-vincristine (CAV) alone with CAV plus concurrent administration of split-course TRT and included a second randomization to consolidation chemotherapy (cisplatin-etoposide) or observation in responding patients. No significant differences were detected between the CAV and CAV-TRT treatment groups with respect to response rate (64% versus 67%, respectively, p=0.58) or overall survival (median, 12.8 versus 14.4 months, respectively, p=0.92 logrank). A significant advantage in two-year progression-free survival was detected for responding patients who received combined modality treatment (39% versus 15%, p=0.002). The authors noted that overall survival was longer with the combined modality treatment (two-year, 33% versus 23.5%, p=0.077; five-year, 16% versus 12%, p=0.36) and suggested that the trial may have been underpowered to detect a modest survival difference. However, the reliability of the trial results are questionable because the combined modality treatment arm was closed early due to toxicity without survival benefit; therefore, randomization was not maintained throughout the study and there was a resulting imbalance in group size (147 received combined modality treatment and 222 received chemotherapy alone).

Kraft et al (6u) administered 3 cycles of CAV as an induction regimen and then randomized 97 patients to a) prophylactic cranial irradiation alone (PCI) alone, b) PCI plus TRT at 30 Gy, or c) PCI plus TRT at 50 Gy. Three additional cycles of chemotherapy were administered after completion of TRT. Survival was significantly shorter in the treatment arm without thoracic radiotherapy compared with the two chemotherapy and thoracic radiotherapy treatment arms combined (median, 9.7 versus 12.8 months, p=0.02; two-year, 5% versus 19%, p=0.05); survival did not differ significantly according to radiotherapy dose (median, 13.5 months [30 Gy] versus 12.4 months [50 Gy]; two-year, 25% [30 Gy] versus 13% [50 Gy]). The complete response rate was also higher with the two thoracic radiotherapy treatment arms (both
47%) compared with PCI alone (26%), although the level of statistical significance was not reported.

**Toxicity of Chemotherapy versus Combined Modality Therapy**

The Pignon analysis was unable to evaluate non-lethal treatment toxicity or the incidence of toxic deaths, due to the variable reporting of toxicity by different investigators. Warde calculated the incidence of toxic deaths and found an increased risk of death in the combined modality group. The overall rate difference was 1.2% (95% CI, -0.6% to 3.0%) with a toxic mortality odds ratio (odds of treatment-related deaths in the combined modality group compared with those of the chemotherapy alone group) of 2.54 (95% CI, 1.90 to 3.18; p<0.01).

A review by Turrisi (7) acknowledged that the studies analyzed in the two meta-analyses did not employ the chemotherapy regimens most commonly used in 1995, which consisted of platinum-based chemotherapy, and that observed toxicity may have been the result of an interaction between the chemotherapy and radiotherapy.

**Update**

The combined modality regimens employed by both Johnson et al (5u) and Kraft et al (6u) included CAV, although in the former trial administration was concurrent with chemotherapy, while in the latter trial administration was sequential. Grade 4 toxicity was more common with the concurrent, combined treatment (73% versus 56% of patients, p=0.002), which also resulted in more treatment-related deaths (6 versus 3, p=0.1) (5u). Kraft et al reported generally comparable toxicities across treatment arms, although pneumonitis and dysphagia were more common with combined modality treatment even though the treatments were administered sequentially (6u).

**Timing of Radiotherapy**

Six RCTs have been published that address the issue of radiotherapy timing. One trial compared the survival of patients receiving radiotherapy either sequentially or concurrently to chemotherapy. Four trials compared the survival of patients receiving either early or late TRT concurrently or sequentially with chemotherapy. Another RCT compared early with late TRT administered twice daily. Details of these trials are summarized in Tables 2a and 2b.

**Update**

Literature review and updating activities identified four trials that addressed the issue of radiotherapy timing (2u,4u,7u,8u). One of these reports (4u) was an update of a trial previously reported in the guideline (8). Details of the trials are included in Tables 2a and 2b.

**Timing of radiotherapy – concurrent versus sequential**

Although the Pignon meta-analysis (5) examined the question of the timing of TRT (sequential, alternating and concurrent), no statistically significant differences were found among these various treatment schedules. Three out of four trials which demonstrated a significant survival advantage for combined modality therapy employed an alternating or concurrent scheme. Seven out of nine trials which did not demonstrate a survival advantage employed a sequential scheme.

Takada et al (8) randomized patients to receive either sequential thoracic radiotherapy or concurrent treatment (published as an abstract). Chemotherapy consisted of cisplatin and etoposide for a total of four cycles. Radiation was initiated after completion of the fourth cycle of chemotherapy in the sequential group, while the concurrent group started thoracic radiotherapy on day 2. The dose employed in both groups was 45 Gy given in a hyperfractionation regimen of 30 fractions over a three-week period. Median survival was 20.8 months for the sequential group and 31.3 months for the concurrent group. Significance levels were not stated. It was acknowledged by the authors that longer follow-up would be required for definitive conclusions.

**Update**
A full report of the trial by Takada et al (8) was published in 2002 (4u). Two hundred and twenty-eight eligible patients were recruited between May 1991 and January 1995. As of August 2000, median survival times were 19.7 months with sequential TRT and 27.2 months with concurrent therapy (p=0.097 logrank). A regression analysis (Cox model) adjusted for the prognostic factors of age, performance stage, and disease stage suggested a survival benefit for concurrent treatment with a mortality hazard ratio of 0.70 (95 % CI, 0.52 to 0.94, p=0.02). Objective response rates were similar at 92% for sequential treatment and 97% for concurrent treatment, although complete response rates were higher with concurrent therapy (27% versus 40%, p=0.07). In an English abstract of a paper published in Korean, Park et al reported no significant differences between concurrent or sequential chemo-radiotherapy in overall response rates (78% versus 63%, respectively, p=0.13) or survival (mean, 18.3 months versus 13.2 months, respectively, p=0.33) (7u); however, the data available in the abstract report were limited, and with only 51 patients the trial was likely underpowered to detect a survival difference.
### Table 2a. Trials examining timing of thoracic radiotherapy: Treatment regimens.

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<th>Treatment Groups</th>
<th>Treatment Regimens</th>
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<td><strong>Takada 1996 (8)</strong> (abstract)</td>
<td>CT + TRT (sequential)</td>
<td>cisplatin 80mg/m² day 1, etoposide 100mg/m² days 1-3 q.3-4.wks x3 1.5 Gy bid to 45 Gy over 3 wks after cycle 4</td>
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<tr>
<td><strong>Update 2002 (4u)</strong></td>
<td>CT + TRT (concurrent)</td>
<td>cisplatin, etoposide as above 1.5 Gy bid to 45 Gy over 3 wks beginning day 2, cycle 1</td>
</tr>
<tr>
<td><strong>Update Lebeau 1999 (2u)</strong></td>
<td>CT + TRT (partially concurrent)</td>
<td>cyclophosphamide 1000mg/m² day 1, doxorubicin 45mg/m² day 1, etoposide 150mg/m² days 1-2, vincristine 1.4mg/m² with vindesine (3mg/m² day 1) replacing doxorubicin for second and third courses of chemotherapy, q4wks 50 Gy in 20 fractions started immediately after second chemotherapy cycle (days 30-64)</td>
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<tr>
<td><strong>CT + TRT (alternating)</strong></td>
<td>CT as above 20 Gy in 8 fractions starting day 36 (7 days after second chemotherapy cycle) and repeated day 64; 15 Gy in 6 fractions starting day 92 (7 days after fourth chemotherapy cycle).</td>
<td></td>
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<tr>
<td><strong>Perry 1987 (9)</strong> Perry 1998 (10) Perry 1996 (11)</td>
<td>CT</td>
<td>cyclophosphamide 1000mg/m², etoposide 80mg/m², vincristine 1.4mg/m² with doxorubicin 50 mg/m² replacing etoposide in alternate cycles 7-18 q.3.wks for 18 months</td>
</tr>
<tr>
<td><strong>CT + TRT</strong></td>
<td>CT as above 4000 rad in 4 wks starting day 1, followed by 1000 rad boost after 2 wks</td>
<td></td>
</tr>
<tr>
<td><strong>CT + delayed TRT</strong></td>
<td>CT as above 4000 rad in 4 wks starting day 64 followed by 1000 rad boost after 2 wks</td>
<td></td>
</tr>
<tr>
<td><strong>Schultz 1988 (12) (abstract)</strong></td>
<td>CT + early TRT</td>
<td>cisplatin 60mg/m² day 1, etoposide 100mg/m² days 4,6,8 alternating with cyclophosphamide 1000mg/m², vincristine 1mg/m², doxorubicin 45mg/m² 40-45 Gy, 22 fractions</td>
</tr>
<tr>
<td><strong>CT + delayed TRT</strong></td>
<td>CT as above with TRT commencing in the fourth month of treatment</td>
<td></td>
</tr>
<tr>
<td><strong>Murray 1993 (13)</strong></td>
<td>CT + early TRT</td>
<td>cyclophosphamide 1000mg/m², doxorubicin 50mg/m², vincristine 2mg total dose alternating at 3-week intervals with etoposide 100mg/m², cisplatin 25mg/m² days 1-3. Each combination administered for three cycles, for a total of six chemotherapy cycles. Third cycle of cyclophosphamide-doxorubicin-vincristine delayed by one week. 40 Gy in 15 fractions over 3 wks concurrent with first cycle of etoposide-cisplatin (week 3)</td>
</tr>
<tr>
<td><strong>CT + late TRT</strong></td>
<td>CT as above 40 Gy in 15 fractions over 3 wks concurrent with last cycle of etoposide-cisplatin (week 15)</td>
<td></td>
</tr>
<tr>
<td><strong>Work 1997 (14)</strong></td>
<td>CT + early TRT</td>
<td>cisplatin 60mg/m² + etoposide 120 mg/m² for 2 x 3-week cycles followed by cyclophosphamide 1000mg/m², doxorubicin 45 mg/m² + vincristine 1.4mg/m² for 4 cycles, cisplatin-etoposide for 2 cycles, and cyclophosphamide-doxorubicin-vincristine for 2 cycles. TRT of 20 or 22.5 Gy in 11 fractions before and after the first cisplatin-etoposide cycle.</td>
</tr>
<tr>
<td><strong>CT + late TRT</strong></td>
<td>CT as above TRT as above but administered before and after the last cisplatin-etoposide cycle (week 18).</td>
<td></td>
</tr>
<tr>
<td><strong>Jeremic 1997 (15)</strong></td>
<td>CT + early Hfx TRT</td>
<td>carboplatin, etoposide 30mg each daily during RT followed by 4 sequential cycles of cisplatin 30mg/m² and etoposide 120mg/m² days 1-3 1.5 Gy bid to 54 Gy at weeks 1-4</td>
</tr>
<tr>
<td><strong>CT + late Hfx TRT</strong></td>
<td>two cycles of cisplatin and etoposide (as above) followed by RT (as above) weeks 6-9 concurrent with carboplatin and etoposide (as above) followed by two more cycles of cisplatin and etoposide</td>
<td></td>
</tr>
<tr>
<td><strong>Update Park 1996 (7u)</strong></td>
<td>CT + TRT (sequential)</td>
<td>cyclophosphamide, doxorubicin, vincristine alternating with etoposide-cisplatin q.3.wks x 6 40-50 Gy over 5-6 weeks after cycle 6</td>
</tr>
<tr>
<td><strong>CT + TRT (concurrent)</strong></td>
<td>CT as above 1.5 Gy bid to 45 Gy concurrent with cycle 1 of etoposide-cisplatin</td>
<td></td>
</tr>
<tr>
<td><strong>Update Skarlos 2001 (8u)</strong></td>
<td>CT + early Hfx TRT</td>
<td>carboplatin AUC 6 day 1 and etoposide 100mg/m² days 1-3 q.3.wks x 6 and 1.5 Gy bid to 45 Gy concurrent with cycle 1</td>
</tr>
<tr>
<td><strong>CT + late Hfx TRT</strong></td>
<td>CT as above and 1.5 Gy bid to 45 Gy concurrent with cycle 4</td>
<td></td>
</tr>
</tbody>
</table>

Notes: bid – twice daily, CT – chemotherapy, Hfx – hyperfractionated, Gy – Gray, q – every, TRT - thoracic radiotherapy, wk(s) – week(s).
Table 2b. Trials examining timing of thoracic radiotherapy: Results.

<table>
<thead>
<tr>
<th>First author, year (reference)</th>
<th>Treatment Groups</th>
<th>No. Patients*</th>
<th>Complete Response Rate</th>
<th>Median Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Takada 1996 (8)</strong>&lt;br&gt;<strong>Update 2002 (4u)</strong></td>
<td>CT + TRT (sequential)&lt;br&gt;CT + TRT (concurrent)</td>
<td>114&lt;br&gt;114</td>
<td>29.4%&lt;br&gt;37.4%</td>
<td>20.8&lt;br&gt;31.3</td>
</tr>
<tr>
<td></td>
<td>Sequential Concurrent</td>
<td>As in 1996</td>
<td>27%&lt;br&gt;40%</td>
<td>19.7&lt;br&gt;27.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p=0.07</td>
<td>Overall survival p=0.097 logrank</td>
</tr>
<tr>
<td><strong>Update</strong>&lt;br&gt;Lebeau 1999 (2u)</td>
<td>CT + TRT (partially concurrent)&lt;br&gt;CT + TRT (altering)</td>
<td>82&lt;br&gt;74</td>
<td>53%&lt;br&gt;49%</td>
<td>13.5&lt;br&gt;14.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Overall survival: p=0.15 logrank</td>
<td></td>
</tr>
<tr>
<td><strong>Perry 1987 (9)</strong>&lt;br&gt;Perry 1998 (10)&lt;br&gt;Perry 1996 (11)</td>
<td>CT&lt;br&gt;CT + TRT&lt;br&gt;CT + delayed TRT</td>
<td>128&lt;br&gt;121&lt;br&gt;141</td>
<td>36%&lt;br&gt;49%&lt;br&gt;58%</td>
<td>13.6&lt;br&gt;13.0&lt;br&gt;14.5</td>
</tr>
<tr>
<td><strong>Schultz 1988 (12)</strong>&lt;br&gt;(abstract)</td>
<td>CT + early TRT&lt;br&gt;CT + delayed TRT</td>
<td>80&lt;br&gt;78</td>
<td>48%&lt;br&gt;50%</td>
<td>10.7&lt;br&gt;12.9</td>
</tr>
<tr>
<td><strong>Murray 1993 (13)</strong></td>
<td>CT + early TRT&lt;br&gt;CT + late TRT</td>
<td>155&lt;br&gt;153</td>
<td>64%&lt;br&gt;56%</td>
<td>21.2&lt;br&gt;16.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p=0.14</td>
<td>Overall survival: p=0.008 logrank</td>
</tr>
<tr>
<td><strong>Work 1997 (14)</strong></td>
<td>CT + early TRT&lt;br&gt;CT + late TRT</td>
<td>99&lt;br&gt;100</td>
<td>59%&lt;br&gt;61%</td>
<td>10.5&lt;br&gt;12.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Overall survival: p=0.41 logrank</td>
<td></td>
</tr>
<tr>
<td><strong>Jeremic 1997 (15)</strong></td>
<td>CT + early Hfx TRT&lt;br&gt;CT + late Hfx TRT</td>
<td>52&lt;br&gt;51</td>
<td>96%&lt;br&gt;80%</td>
<td>34&lt;br&gt;26</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p=0.013</td>
<td>Overall survival: p=0.052 Wilcoxon</td>
</tr>
<tr>
<td><strong>Update</strong>&lt;br&gt;Park 1996 (7u)</td>
<td>CT + TRT (sequential)&lt;br&gt;CT + TRT (concurrent)</td>
<td>24&lt;br&gt;27</td>
<td>13%&lt;br&gt;30%</td>
<td>Mean survival: 13.2&lt;br&gt;18.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p=0.33 Wilcoxon</td>
<td></td>
</tr>
<tr>
<td><strong>Update</strong>&lt;br&gt;Skarlos 2001 (8u)</td>
<td>CT + early Hfx TRT&lt;br&gt;CT + late Hfx TRT</td>
<td>42&lt;br&gt;39</td>
<td>40.5&lt;br&gt;56.5</td>
<td>17.5&lt;br&gt;17.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p=NS</td>
<td>p=NS</td>
</tr>
</tbody>
</table>

Notes: CT – chemotherapy, Hfx – hyperfractioned, NR – not reported, NS – not statistically significant, TRT – thoracic radiotherapy.

**Timing of radiotherapy – concurrent versus alternating**

**Update**

Lebeau et al (2u) randomized patients to chemotherapy (cyclophosphamide-doxorubicin-vindesine-etoposide-vincristine) combined with either concurrent or alternating radiotherapy. The trial was terminated early, when results from the planned interim analysis indicated a statistically higher mortality rate related to lung toxicity in the concurrent radiotherapy group than in the alternating radiotherapy group (estimated two-year mortality rates, 13% and 2% respectively; p=0.05 logrank). There was no significant difference in overall survival between the groups at the time of the interim analysis.

**Timing of radiotherapy – early versus late**

In a three-armed study, Perry et al (9) compared patients receiving non-cisplatin-containing chemotherapy alone to chemotherapy combined with either early or late thoracic radiotherapy. Statistically significant advantages with respect to both local control and survival were found in the two groups receiving radiotherapy when compared with the group receiving...
chemotherapy alone. In comparing the two chemo-radiotherapy groups, there was a trend towards improved survival in the late-treatment group when compared with early treatment (p=0.078). In a ten-year update of this study (10) at a time when 95% of the enrolled patients had died, the authors reported that there was a non-significant trend in favour of late versus early radiotherapy (p=0.144). Survival rates at five years were 3% for the chemotherapy-only group, 6.6% for the early-TRT group and 12.8% for the late-TRT group (11). These results appear substantially worse than the Canadian study reported below by Murray et al (13). The difference may be attributed to: 1) the intentional reduction of chemotherapy doses in the Perry trial for those patients receiving early radiotherapy because of toxicity concerns; and 2) chemotherapy was cyclophosphamide-based in the Perry trial and cisplatin-based in the Murray trial.

Schultz (12) randomized patients to receive alternating cycles of chemotherapy consisting of cisplatin/etoposide and cyclophosphamide/doxorubicin/vincristine (published in abstract form), with thoracic radiotherapy started either on day 1 or day 120 and consisted of a dose of at least 40 Gy. Median survival for the early-TRT group was 10.7 months compared with 12.9 months for the late-TRT group. Results were not statistically significantly different between the two treatment groups.

Murray et al (13) reported results of an early versus late thoracic radiotherapy study conducted by the National Cancer Institute of Canada (NCIC). Three hundred and thirty-two patients from 22 centres were entered. Chemotherapy in this study included cisplatin. There were significant improvements in both progression-free survival (p = 0.036 logrank, 0.014 Wilcoxon) and overall survival (p = 0.008 logrank, 0.005 Wilcoxon) in the early-treatment group. Median survival times for the early and late groups were 21.2 months and 16 months respectively; five-year survival rates were 20% and 11%.

The Aarhus Lung Cancer Group published the results of a Danish study (14) which randomized 199 patients to receive early or late radiotherapy. Unlike the Canadian study, this trial did not show improvement in local control (p = 0.2) or overall survival (p = 0.4) for early TRT. Median survival times for the early and late arms were 10.5 and 12.0 months, respectively. These results are worse than the results reported by Murray et al (13) in the Canadian study, as discussed above (21.2 and 16.0 months, respectively).

The results of the Danish study may be questioned for a number of reasons. The dose of TRT was changed during the trial; patients treated before October 1984 received 40 Gy and those treated after this date received 45 Gy. In the early-TRT group, 40 Gy was the prescribed dose for 45 patients and 45 Gy was the prescribed dose for 54 patients. In the late-TRT group, 40 Gy was prescribed to 41 patients and 45 Gy was prescribed to 59 patients. In addition, TRT was prescribed in a split-course manner (two treatment periods of 20 or 22.5 Gy in 11 fractions separated by an interval of 21 days during which chemotherapy was given) which is not radiobiologically optimal. The policy on prophylactic cranial irradiation (PCI) was also modified during the course of treatment. After October 1984, all patients received PCI.

Five-year survival data from each of the above four studies comparing early with late TRT were pooled (9-14). There is no survival benefit to administering TRT early in the chemotherapy regimen (odds ratio, 1.00; 95% CI, 0.56 to 1.79; p=1.0). Figure 1 summarizes the data and presents the results of the pooled analysis.

**Update**

Upon reviewing the meta-analysis of early versus late radiotherapy in the original guideline report, two of the four trials appeared to report data from the same trial (12,14). The five-year survival data from the three distinct trials involving 777 patients (9-11,13,14) was pooled using the software package Metaview © Update Software (9u) and a similar result was obtained, indicating no survival benefit for early versus late administration of radiotherapy with chemotherapy (odds ratio, 1.04; 95% CI, 0.45 to 2.43, p=0.9). However, the utility of the pooled effect estimate is questionable since the treatment effects of the individual trials were
heterogeneous (p=0.028). Reasons for the heterogeneity of trial outcomes are discussed in the original guideline section above. The one trial that detected a significant advantage for early over late radiotherapy, alternated cyclophosphamide-doxorubicin-vincristine with cisplatin-etoposide and administered radiotherapy concurrently with cisplatin-etoposide at week 3 (early administration) or week 15 (late administration) (13). The other trial involving concurrent chemoradiation administered radiotherapy on day 1 (early administration) or day 64 (late administration) concurrently with cyclophosphamide-etoposide-vincristine given in three-weekly cycles (9-11). Work et al administered split-course radiotherapy before and after the first (week 3) and last (week 20) cycles of cisplatin-etoposide in a chemotherapy schedule that included a total of three cycles of cisplatin-etoposide and six cycles of cyclophosphamide-doxorubicin-vincristine (14). The complete chemotherapy and radiotherapy schedules are shown in Table 2a.

Figure 1. Meta-analysis examining early vs. late thoracic radiotherapy.

<table>
<thead>
<tr>
<th>Study</th>
<th>Early TRT</th>
<th>Late TRT</th>
<th>Mortality Odds Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Deaths</td>
<td>Total</td>
<td>Deaths</td>
<td>Total</td>
</tr>
<tr>
<td>Murray 1993 (13)</td>
<td>121</td>
<td>155</td>
<td>133</td>
<td>153</td>
</tr>
<tr>
<td>Perry 1996 (9/10/11)</td>
<td>113</td>
<td>121</td>
<td>123</td>
<td>141</td>
</tr>
<tr>
<td>Schultz 1988 (12)</td>
<td>67</td>
<td>80</td>
<td>65</td>
<td>78</td>
</tr>
<tr>
<td>Work 1997 (14)</td>
<td>88</td>
<td>99</td>
<td>88</td>
<td>100</td>
</tr>
<tr>
<td>TOTAL</td>
<td>389</td>
<td>455</td>
<td>409</td>
<td>472</td>
</tr>
</tbody>
</table>

Timing of radiotherapy – hyperfractionated radiotherapy

A single RCT using initial versus delayed accelerated hyperfractionated radiotherapy (Hfx TRT) was reported by Jeremic et al (15). A total of 107 patients were randomized between early thoracic radiotherapy (weeks one to four) or late radiotherapy (weeks six to nine). All patients received twice daily treatments of 1.5 Gy to a total dose of 54 Gy. Chemotherapy consisted of cisplatin and etoposide. Median and five-year survival rates were 34 months and 30% for early Hfx TRT, and 26 months and 15% for the delayed group. These results were of borderline significance on univariate analysis (p=0.05) and reached significance with multivariate analysis after controlling for factors such as sex and age (p=0.03). The early-treated group achieved a significantly higher local control rate than the delayed group (p=0.01). The frequency of grade 3 and 4 thrombocytopenia was increased with early Hfx TRT (p=0.06).

Update

A new randomized phase II trial by Skarlos et al enrolled 86 patients (8u). All patients in this study received chemotherapy (carboplatin and etoposide) plus concurrent Hfx TRT (45 Gy
given twice daily in 30 fractions) and were randomized to early (cycle one) or late (cycle four) administration of radiotherapy. There was no significant survival difference between early and late radiotherapy (median, 17.5 months versus 17.0 months, respectively).

**Doses of Radiotherapy**

Results of studies of the optimal dose of thoracic radiotherapy are inconclusive. The Danish study employed two dose levels of 40 and 45 Gy (14). The in-field recurrence rate at two years for both groups was 60 to 70%. Two-year overall survival for the 40 Gy group was 15.1% (standard error [SE], 3.8%) compared with 22.1% (SE, 3.9%) for the 45 Gy group. Five-year survival for the 40 Gy group was 9.3% (SE, 3.0%) compared with 12.8% (SE, 3.2%) for the 45 Gy group. Increasing the dose of TRT did not significantly improve overall survival (p=0.18).

The NCIC BR3 study randomized limited-stage SCLC patients to two doses of thoracic radiation of 25 and 37.5 Gy (16). Results are summarized in Table 3. There were no reported differences in overall survival or complete response rates between the two groups. Local progression-free survival was improved in the high-dose group (49 weeks, compared with 38 weeks in the low-dose group, p=0.036). Long-term follow-up results have not been reported. Neither study showed any improvement in survival at the higher dose level, but the difference in total dose in the Danish study is small and the Canadian study used doses considered low by current standards.

**Update**

The trial by Kraft et al reported in the ‘Chemotherapy versus Chemo-Radiotherapy’ section of this report also compared two different doses of radiotherapy, 30 Gy administered over three weeks versus 50 Gy administered over five weeks (6u). They detected no significant differences between the two radiotherapy doses with respect to median survival; two-year survival was 25% with the 30 Gy dose and 13% with the 50 Gy dose.

**Hyperfractionated Radiotherapy**

There are two trials that have addressed the issue of hyperfractionated radiotherapy in limited-stage SCLC (Table 3). Turrisi et al (17) published the full report of a large intergroup study, previously reported in abstract form by Johnson et al (18), in which patients were randomized to either daily thoracic irradiation to a total dose of 45 Gy in 25 fractions over five weeks or twice daily treatments of 1.5 Gy in 30 fractions over three weeks. Chemotherapy consisted of 4 cycles of cisplatin/etoposide commencing concurrently with thoracic irradiation. Median survival was 19 months for the daily treated group and 23 months for those treated twice daily. Two year survival rates were 41% and 47% respectively, and 16% and 26% at five years. These results were statistically significant (p=0.04 logrank). The observed rate of local control was higher with twice daily therapy, but this was not significant (local failure rate, 52% with once daily therapy and 36% with twice daily therapy, p=0.06). Toxicity in the form of esophagitis was significantly increased in the group receiving twice daily treatment (63% versus 44%, p<0.001). There were no cases of permanent strictures from acute esophagitis.

Bonner et al (19) published an abstract reporting a trial which randomized 253 patients to either once daily treatments to a total dose of 50.4 Gy in 28 fractions or twice daily treatments to a total dose of 48 Gy in 32 fractions given in two courses of 24 Gy each separated by a 2.5 week break. Chemotherapy consisted of six cycles of etoposide and cisplatin with irradiation starting with the fourth cycle in each arm. Median and two-year survival rates were 21 months and 43% for the two arms combined, but the authors did not report response or survival statistics for the individual treatment arms. Grade 3 or greater rates of esophagitis were shown to be significantly increased in the hyperfractionated arm (12.7% versus 4.7%, p=0.027).
Table 3. Trials which examined optimal dosage and delivery of thoracic radiotherapy.

<table>
<thead>
<tr>
<th>First author, year, (reference)</th>
<th>No. Patients</th>
<th>Treatment Groups</th>
<th>Treatment Regimen</th>
<th>Complete Response Rate</th>
<th>Median Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coy 1988 (16)</td>
<td>168 total CT + SD</td>
<td>cyclophosphamide, adriamycin, vincristine (CAV) x3 followed by VP-16, cisplatin (EP) x3 OR CAV alternating with EP for 6 cycles 25 Gy, 10 fractions, 2 wks</td>
<td>65%</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CT + HD</td>
<td>CT as above 37.5 Gy, 15 fractions, 3 wks</td>
<td>69%</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Turrisi 1999 (17)</td>
<td>206 CT + daily TRT</td>
<td>cisplatin 60mg/m², day 1 etoposide 120 mg/m² days 1-3 q 21 days x 4 18 Gy 5 days/wk x 5 wks to total dose 45 Gy</td>
<td>49%</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td></td>
<td>211 CT + twice daily TRT</td>
<td>CT as above 15 Gy bid 5 days/wk x 3 wks to total dose 45 Gy</td>
<td>56%</td>
<td>23 p=0.04 logrank</td>
<td></td>
</tr>
<tr>
<td><strong>Update</strong> Bonner 1998 (19,3u)</td>
<td>127 CT + daily TRT</td>
<td>cisplatin 30mg/m², etoposide 130 mg/m² days 1-3, q28days x6, etoposide reduced to 100mg/m² for cycles 4-6 18 Gy 5 days/wk x 5.5 wks to total dose 50.4 Gy concomitant with chemotherapy cycles 4 and 5</td>
<td>NR</td>
<td>24.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>126 CT + twice-daily TRT</td>
<td>CT as above 15 Gy bid 5 days/wk to total dose 48 Gy with a 2.5 wk break after 24 Gy</td>
<td>NR</td>
<td>23.0 Overall survival: p=0.49 logrank</td>
<td></td>
</tr>
<tr>
<td><strong>Update</strong> Kraft 1990 (6u)</td>
<td>27 CT</td>
<td>cyclophosphamide 1000mg/m², adriamycin 50mg/m², vincristine 2mg q21days x 3</td>
<td>NR</td>
<td>9.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>34 CT + 30 Gy TRT</td>
<td>Induction CT as above PCI + 30 Gy over 3wks in 2 Gy fractions starting 2wks after end of CT, then 3 further cycles of CT started 2wks after end of TRT</td>
<td>NR</td>
<td>13.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>30 CT + 50 Gy TRT</td>
<td>Regimen as above except TRT given as 50 Gy over 5wks</td>
<td>NR</td>
<td>12.4 Overall, p=0.04, CT vs. CT+TRT, p=0.02 30 Gy vs. 50 Gy, p=NS</td>
<td></td>
</tr>
</tbody>
</table>

Notes: CT - chemotherapy, Gy – Gray, HD - high dose radiotherapy, No. – number, NR - not reported, NS – not statistically significantly different, q – every, SD - standard dose radiotherapy, TRT - thoracic radiotherapy, VP-16 – etoposide, vs. – versus, wk(s) – week(s).

**Update**
The full report of the Bonner et al trial, previously published in abstract form (19), was found during reviewing and updating activities (3u) (see Table 3). Bonner et al randomized 262 patients to either once-daily treatments to a total dose of 50.4 Gy in 28 fractions or twice-daily treatments to a total dose of 48 Gy in 32 fractions given in two courses of 24 Gy each separated by a 2.5 week break (3u). Chemotherapy consisted of six cycles of etoposide and cisplatin, with irradiation starting concurrent with the fourth cycle in each arm. There was no statistically significant difference in survival between the two arms (p=0.49 logrank). Two- and three-year survival rates were 47% and 34% for the once-daily radiotherapy group and 45% and 29% for the twice-daily radiotherapy group. Rates of local progression were not significantly different between the two arms (p=0.46 logrank). The overall toxicity profile was more severe for the
twice-daily group than the once-daily group (54% versus 39% of patients with any grade 3 or greater toxicity; p=0.02 chi-square). Grade 3 or greater rates of esophagitis were significantly higher in the twice-daily arm (12.3% versus 5.3% in the once-daily arm; p=0.05 chi-square). Grade 3 or greater platelet nadirs were more frequent in patients on the once-daily than the twice-daily arm (61% versus 46%; p=0.02).

V. INTERPRETIVE SUMMARY
The Role of Radiotherapy with Chemotherapy

Two published meta-analyses (4,5) have demonstrated both survival benefit and improved local control for thoracic radiotherapy (TRT) in combination with chemotherapy compared with chemotherapy alone, indicating that combined modality therapy should be the standard of care. Toxicity was difficult to determine in both meta-analyses, as explained by Turrisi (7), because the studies in the meta-analyses did not use platinum-based chemotherapy regimens, but is likely increased with TRT.

Update

The survival advantage of chemoradiation over chemotherapy alone, identified by the two meta-analyses, was confirmed in a randomized trial involving 97 patients (6u) but was not observed in a second randomized trial involving 386 patients (5u). However, the reliability of the results reported in the latter trial is uncertain because randomization into the chemoradiotherapy treatment arm was stopped early due to toxicity (5u).

Radiotherapy Timing

Median survival was greater when TRT was administered concurrently with chemotherapy rather than sequentially, although the significance level was not reported. A meta-analysis pooling data from four RCTs (11-14) involving 927 patients did not demonstrate a difference in survival at five years when TRT was administered early compared with later in the course of chemotherapy. Theoretically, the potential sensitization of tumour cells to the effects of radiotherapy support the concurrent and early administration of TRT over concurrent and late, or sequential treatment (20). One large NCIC clinical trial did demonstrate a superior survival outcome with early radiotherapy. As well, one RCT reported by Jeremic et al demonstrated a significantly higher local control rate, median survival, and five-year survival in patients treated with Hfx TRT given early during chemotherapy (15).

Update

The results of a revised meta-analysis, involving only the three fully published trials of early versus late administration of radiotherapy were consistent with the original analysis; however, the heterogeneous nature of the trial outcomes suggest that the trial results may be better considered individually. Two of the trials (one involving concurrent and one sequential administration of chemoradiotherapy) did not detect a difference between early and late radiotherapy; the third trial, involving concurrent chemoradiotherapy, detected a significant survival advantage in favour of early administration of radiation.

Two new randomized trials compared concurrent with sequential administration of radiotherapy and chemotherapy (4u,7u). Neither trial detected a statistically significant survival difference between treatments, although the larger trial, previously reported in abstract form, detected a survival benefit for concurrent treatment when the analysis was adjusted for prognostic factors. The results of the other small trial were reported in an English abstract of a Korean publication and provided limited data (7u).

In contrast to the one RCT in the original guideline that compared early with late administration of hyperfractionated radiotherapy, one recent trial reported by Skarlos detected no significant differences between groups with respect to response rate or survival (8u). However, the radiotherapy and chemotherapy regimens were different in the two trials and this may partially account for the discrepancy in the outcomes (see Tables 2a and 2b).
Radiotherapy Dosage

One RCT examining dosage reported no significant survival benefit of high dose over low dose TRT, although there was an improvement in local control at higher doses (16). There is currently insufficient evidence to recommend an optimum dose of irradiation. The data from randomized trials suggest that higher doses produce better local control, and the consensus of the Lung DSG was that the dose should be at least 40 Gy in 15 fractions over three weeks (or a biologically equivalent dose).

Update

One new but small RCT detected no difference in survival for two doses of radiotherapy in a combined modality regimen (6u), which was consistent with the results of the one RCT reported in the original guideline (16).

Hyperfractionated Radiotherapy

Two RCTs have been reported which investigated the use of hyperfractionated (twice-daily) irradiation versus once daily treatment. The one fully published RCT demonstrated a significant survival advantage for hyperfractionation (17). Based on the one large study, the Provincial Lung Cancer DSG believes that hyperfractionated TRT administered concurrently with chemotherapy early in the chemotherapy treatment course may offer a superior survival outcome for patients with limited-stage SCLC, but that a confirmatory trial is necessary. Furthermore, a direct comparison to the best arms of the Canadian BR6 trial (13) would clarify whether hyperfractionated radiotherapy is superior to current Canadian practice.

Update

There are now two fully published RCTs which have investigated the use of hyperfractionated (twice-daily) radiotherapy versus once-daily treatment. One of the RCTs demonstrated a statistically significant survival advantage for hyperfractionation (17) and the other did not (3u). Both studies demonstrated a significant increase in toxicity, especially grade 3 esophagitis.

The second RCT (3u) randomized patients following assessment of response to three cycles of chemotherapy. Patients were excluded if their tumour had progressed to a degree which the radiation oncologist considered could not be safely encompassed in an acceptable field (of the 311 assessable patients enrolled in the study, 262 were ultimately randomized). The first trial (17) stipulated that both the once daily and twice daily groups begin their irradiation concurrently with the first cycle of chemotherapy. Given the uncertainty of the superiority of early TRT over later TRT, the second study may have excluded those patients who would have benefited most from hyperfractionated TRT. This result therefore does not exclude the possibility of a potential survival benefit for hyperfractionated TRT. However, the Provincial Lung Cancer DSG continues to believe that an appropriately conducted confirmatory trial is necessary before hyperfractionated TRT could be recommended as standard treatment.

Alternating versus concurrent chemo-radiotherapy

Update

The trial investigating alternating versus concurrent TRT (2u) was terminated early due to pulmonary toxicity in the concurrent group. No survival advantage was demonstrated. The increased toxicity of concurrent treatment may have resulted from an interaction between the particular chemotherapeutic agents used and the high daily fractionated dose of radiotherapy. The median survival of patients on the two arms of the study (13.5 months and 14.0 months) is below that which would be expected with platinum-based chemotherapy for limited-stage small cell lung cancer. Based on these results, neither alternating thoracic irradiation nor concurrent thoracic radiation in combination with the drugs employed in this study is recommended.
VI. ONGOING TRIALS

<table>
<thead>
<tr>
<th>Protocol IDs</th>
<th>Title and details of trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>LLCG-TR8SCLC, EU-98011</td>
<td>Phase III randomized study of timing of thoracic radiotherapy in patients with limited stage small cell lung cancer who are receiving combination chemotherapy. All patients receive cyclophosphamide, doxorubicin, and vincristine by IV bolus alternating with 3 days of daily etoposide IV infusion over 60-120 minutes and cisplatin IV infusion over 30 minutes. This treatment alternates every 3 weeks for six courses. Patients are randomized to have thoracic radiotherapy either with course 2 (arm I) or with course 6 (arm II) of chemotherapy. Patients in arm I are given 1 week of rest between radiotherapy and the second course of chemotherapy. Outcomes: Survival, local recurrence, distant metastases. Projected accrual: 398 patients. Status: Closed. Summary last updated: 05/2002.</td>
</tr>
</tbody>
</table>

VII. DISEASE SITE GROUP CONSENSUS PROCESS

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 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 (Working title: The role of combination chemotherapy in the initial management of limited disease small cell lung cancer).

One concern raised during practitioner feedback (please see section VIII) 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 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 (21). 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 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 (17) 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 arm of the Canadian trial (BR6) which showed that early radiotherapy is superior to late radiotherapy.
when combined with alternating 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).

**Update**

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

The new data found through the updating process provides conflicting evidence regarding the timing of RT. Although evidence regarding the use of concurrent chemo-radiotherapy 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 chemo-radiotherapy compared with alternating radiotherapy (2u). 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.

**VIII. EXTERNAL REVIEW OF THE PRACTICE GUIDELINE REPORT**

This section describes the external review activities undertaken for the original guideline report.

**Draft Recommendations**

Based on the evidence described in the original report above, the Lung DSG drafted the following recommendations:

**Target Population**

These recommendations apply to adult patients with limited-stage small cell lung cancer.

**Draft Recommendations**

- In patients with limited-stage small cell lung cancer, thoracic radiotherapy (TRT) improves both local control and overall survival and should be incorporated into a comprehensive treatment plan of combined modality therapy for limited small cell lung cancer (SCLC).
- The total dose should be 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 taking into consideration tumour field size and location, pulmonary function tests and other clinical factors.
- There is conflicting evidence as to the optimal timing of TRT in relation to the course of chemotherapy (early or late administration of TRT). Recent evidence and theoretical considerations favour the early administration of TRT. Evidence supports the administration of chemotherapy concurrent with TRT over sequential chemotherapy-radiotherapy administration. Although hyperfractionated TRT has been employed, the toxicity associated with this form of treatment has been shown to be significantly increased over standard fractionation without clear clinical benefits. Therefore, at the present time, the use of hyperfractionated TRT should be limited to a clinical trial setting.

**Practitioner Feedback**

Based on the evidence contained in the original report and the draft recommendations presented above, feedback was sought from Ontario clinicians.
Methods
Practitioner feedback was obtained through a mailed survey\(^1\) 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 above 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.

Results
Key results of the practitioner feedback survey of the original draft guideline report are summarized in Table 4. Fifty (82%) surveys were returned. Forty-two (84%) respondents indicated that the practice-guideline-in-progress report was relevant to their clinical practice and they completed the survey.

Summary of Written Comments
Practitioners commented on the difficulty of gaining access to radiotherapy machines in a timely fashion in order to give early radiotherapy. There were positive comments on rigour, comprehensiveness, and value of the literature review.

Table 4. Practitioner responses to six items on the practitioner feedback survey.

<table>
<thead>
<tr>
<th>Item</th>
<th>Strongly agree or agree Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>The rationale for developing a clinical practice guideline, as stated in the “Choice of Topic” section of the report, is clear.</td>
<td>41 (97.6)</td>
</tr>
<tr>
<td>There is a need for a clinical practice guideline on this topic.</td>
<td>38 (90.5)</td>
</tr>
<tr>
<td>The results of the trials described in the report are interpreted according to my understanding of the data.</td>
<td>40 (95.2)</td>
</tr>
<tr>
<td>I agree with the draft recommendations as stated.</td>
<td>37 (88.1)</td>
</tr>
<tr>
<td>This report should be approved as a practice guideline.</td>
<td>36 (85.7)</td>
</tr>
<tr>
<td>If this report were to become a practice guideline, how likely would you be to make use of it in your own practice?</td>
<td>Very likely or likely 38 (90.5)</td>
</tr>
</tbody>
</table>

Modifications/Actions
On the basis of comments from practitioners, changes in wording were made to the draft recommendations, concerning the evidence used to support the recommendation for early rather than late administration of TRT. A suggested change in wording in section II. CHOICE OF TOPIC AND RATIONALE of the guideline report was made.

Approved Practice Guideline Recommendations
These practice guideline recommendations reflect the integration of the draft recommendations with feedback obtained from the External Review process. They have been approved by the Lung DSG and the Practice Guidelines Coordinating Committee.

This practice guideline applies to patients with limited-stage small cell lung cancer.

\(^1\) 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 represent practitioner responses to the six common questions, pooled across the versions of the questionnaires.
In patients with limited-stage small cell lung cancer, the addition of thoracic radiotherapy (TRT) 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 (SCLC).

The data from randomized trials suggest that higher doses of TRT 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 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 TRT in relation to the course of chemotherapy (early or late administration of TRT). Recent evidence from a large National Cancer Institute of Canada (NCIC) trial favours the early administration of TRT (5-year survival, 20% for early TRT versus 11% for late TRT). Evidence supports the administration of chemotherapy concurrent with TRT over sequential chemotherapy-radiotherapy administration.

Hyperfractionated TRT has been shown in one large, fully published study to increase the long-term survival of patients with limited SCLC (5-year survival, 26% with hyperfractionated TRT versus 16% with once daily radiotherapy). This was achieved with an increased rate of short-term grade 3 esophagitis. Based on the currently available evidence from a single study, hyperfractionated TRT administered concurrently with chemotherapy early in the chemotherapy treatment course may provide a superior survival outcome in patients with limited stage SCLC, but confirmatory trials are needed.

Update
The third and final bullets of the recommendations were changed, to read as follows:

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.

IX. PRACTICE GUIDELINE
This practice guideline reflects the most current information reviewed by the Lung DSG.

Target Population
These recommendations apply to adult patients with limited-stage small cell lung cancer.

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.

- **Update**
  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.

- **Update** Based on currently available data, hyperfractionated thoracic radiotherapy is NOT recommended for limited-stage small cell lung cancer outside of a clinical trial.

**Related Guidelines**
Cancer Care Ontario Practice Guidelines Initiative’s Practice Guideline Reports:
- 7-13-1: *The role of combination chemotherapy in the initial management of limited-stage small cell lung cancer*
- 7-13-2: *Prophylactic cranial irradiation in small cell lung cancer*

**X. JOURNAL REFERENCE**

**XI. ACKNOWLEDGEMENTS**
The Lung DSG would like to thank Drs. Gordon Okawara and William K. Evans for taking the lead in drafting, revising and updating this practice guideline report. The Lung DSG would also like to thank Ms. Toni Newman, Ms. Lubna Baig, Ms. Anna Gagliardi, Ms. Barbara R. Markman, and Ms. Jean Mackay for assistance in the development and updating of this practice guideline report.

*For a complete list of Lung DSG members, please visit the CCO website at: http://www.cancercare.on.ca/*
REFERENCES


**Update**

This section includes all references obtained from the review and updating activities.


Evidence-based Series #7-13-3: Section 3

The Role of Thoracic Radiotherapy as an Adjunct to Standard Chemotherapy in Limited-Stage Small Cell Lung Cancer

Review Date: September 24, 2012

The 2003 guideline recommendations require an UPDATE

This means that the DSG/GDG will rewrite the guideline at the earliest opportunity. Until then the recommendations remain of some use in clinical decision making

OVERVIEW

The original version of this guidance document was released by Cancer Care Ontario’s Program in Evidence-based Care in 1999, and updated in 2003.

In September 2011, this document was assessed in accordance with the PEBC Document Assessment and Review Protocol and was determined to require a review. As part of the review, a PEBC methodologist conducted an updated search of the literature. A clinical expert (GO) reviewed and interpreted the new eligible evidence and proposed the existing recommendations require an update. The Lung Cancer Disease Site Group (DSG) agreed to update the recommendations found in Section 1 (Clinical Practice Guideline) in September 2012.

DOCUMENT ASSESSMENT AND REVIEW RESULTS

Question Considered

Is there a role for thoracic radiotherapy (TRT) as an adjunct to standard chemotherapy in limited-stage small cell lung cancer (SCLC)?

Literature Search and New Evidence

The new search (January 2003 to February 2012) yielded 20 references representing 4 clinical practice guidelines, 7 systematic reviews and meta-analyses and 7 RCTs found evaluating aspects of thoracic radiotherapy as an adjunct to chemotherapy in limited-stage small cell lung cancer. Two on-going studies, comparing twice-daily to once-daily thoracic radiotherapy were identified from clinicaltrials.gov. Brief results of these studies are shown in the Document Review Tool.

Impact on Guidelines and Its Recommendations

There needs to be some modifications to the current recommendations due to the current evidence available. Hence, the Lung Cancer DSG decided that the 2003 recommendations on the role of thoracic radiotherapy as an adjunct to standard chemotherapy in limited-stage small cell lung cancer require an UPDATE.
Document Review Tool

| Number and title of document under review | 7-13-3 The Role of Thoracic Radiotherapy as an Adjunct to Standard Chemotherapy in Limited-Stage Small Cell Lung Cancer |
| Current Report Date | January 2003 |
| Clinical Expert | Dr. Gordon Okawara |
| Research Coordinator | Lesley Souter |
| Date Assessed | September 2011 |
| Approval Date and Review Outcome (once completed) | 24 Sept 2012 [UPDATE] |

Original Question(s):
Is there a role for thoracic radiotherapy (TRT) as an adjunct to standard chemotherapy (CT) in limited-stage small cell lung cancer?

Target Population:
Adult patients with limited-stage small cell lung cancer

Study Section Criteria:
Articles were selected for inclusion in this systematic review of the evidence if they met the following criteria:

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

Search Details:

- January 2003 to February 2012, week 8 (Medline + Embase)
- January 2003 to April 2012 (clinicaltrial.gov)

Brief Summary/Discussion of New Evidence:
Of 956 total hits from Medline + Embase and 321 total hits from clinicaltrial.gov, 20 references representing 4 clinical practice guidelines, 7 systematic reviews and meta-analyses and 7 RCTs were found evaluating aspects of thoracic radiotherapy as an adjunct to chemotherapy in limited-stage small cell lung cancer. Two on-going studies, comparing twice-daily to once-daily thoracic radiotherapy were identified from clinicaltrials.gov.

Systematic Reviews

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Literature Search Date</th>
<th>Brief Results</th>
<th>References</th>
</tr>
</thead>
</table>
| Any regimen of TRT given concurrently or not, with any CT regimen. Analysis | Cochrane Central Register of Controlled Trials – 2009 issue 1; | • Overall survival not different between early and late TRT  
• Trend towards increased overall survival in early TRT with platinum chemotherapy | Pijls-Johannesma et. al., 2010 |
stratified according to total treatment time of TRT and administration, or not, of concurrent chemotherapy
- Outcomes: survival, local control, toxicity, compliance

<table>
<thead>
<tr>
<th>Early (less than 30 days after start of CT) TRT vs. late TRT and overall TRT treatment time</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCTs analyzed to determine whether timing of TRT influenced survival, local tumour control, toxicity and compliance</td>
</tr>
<tr>
<td>Cochrane Central Register of Controlled Trials - 2006 issue 3; MEDLINE – 1966 to present (at time of publication); EMBASE – 1974 to present (at time of publication); CINAHL – 1982 to present (at time of publication)</td>
</tr>
<tr>
<td>When overall treatment time less than 30 days, trend towards increased overall survival for early TRT</td>
</tr>
<tr>
<td>No significant effect on local tumour control for early vs late TRT</td>
</tr>
<tr>
<td>Trend towards higher severe pneumonitis for early TRT</td>
</tr>
<tr>
<td>Trend towards higher severe oesophagitis for early TRT</td>
</tr>
<tr>
<td>Severe leucopenia significantly more frequent in patients receiving early TRT</td>
</tr>
<tr>
<td>Severe thrombocytopenia risk not significantly different between early and late TRT</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>1) total RT dose; 2) treatment time of TRT; 3) early vs late RT; 4) the time from start of any treatment to end of TRT (SER); 5) concurrent vs sequential RT and CT; 6) equivalent RT dose in 2-Gy fractions corrected for the overall treatment time of TRT (EQD&lt;sup&gt;2&lt;/sup&gt;,&lt;sub&gt;T&lt;/sub&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase III trials. Interventions analyzed for the influence on local tumour control, survival, esophagitis and pneumonitis.</td>
</tr>
<tr>
<td>Cochrane Central Register of Controlled Trials - 2003, issue 4; MEDLINE – 1966 to present (at time of publication); EMBASE – 1974 to present (at time of publication); CINAHL – 1982 to present (at time of publication)</td>
</tr>
<tr>
<td>SER was the most important predictor of outcome</td>
</tr>
<tr>
<td>Higher 5-year survival rate in the shorter SER arm</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1) CT regimen; 2) induction treatment that led to complete response; 3) start date of induction treatment; 4) overall treatment time of TRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCTs analyzed to determine whether timing of TRT influenced local tumour control</td>
</tr>
<tr>
<td>Cochrane Central Register of Controlled Trials - 2003, issue 4; MEDLINE – 1966 to present (at time of publication); EMBASE – 1974 to present (at time of publication); CINAHL – 1982 to present (at time of publication)</td>
</tr>
<tr>
<td>2-year survival better with early TRT</td>
</tr>
<tr>
<td>Post-hoc analysis excluding trial with non-platinum CT concurrently with TRT</td>
</tr>
<tr>
<td>5-year survival higher with early TRT</td>
</tr>
<tr>
<td>Short overall treatment time may also improve survival</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1) Same RT scheme, given early vs. late; 2) split-course RT, given alternately with CT vs. continuous-course RT given concurrently; 3) RT,</th>
</tr>
</thead>
<tbody>
<tr>
<td>PubMed Jan 2004</td>
</tr>
<tr>
<td>Small therapeutic advantage of early RT in combination with concurrent CT</td>
</tr>
<tr>
<td>For simultaneous RT-CT, 2&lt;sup&gt;nd&lt;/sup&gt; generation CT schedules should be used</td>
</tr>
<tr>
<td>Sequential RT after CT led to worse results than</td>
</tr>
</tbody>
</table>

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Pijls-Johannesma et. al., 2007

De Ruysscher et. al., 2006

De Ruysscher et. al., 2006

Stuschke and Pottgen, 2004
given with altered fractionation and the same concurrent CT

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Name of trial (phase)</th>
<th>Population</th>
<th>Outcomes</th>
<th>Brief Results</th>
<th>References</th>
</tr>
</thead>
</table>
| 1) early TRT vs. 2) late TRT delivery relative to chemotherapy | MEDLINE and CANCERLIT 1985 to present (at time of publication) | • Meta-analysis  
• Survival benefit at 2 years with early delivery vs. late TRT | Fried et. al., 2004 |
| 1) early concurrent TRT and chemotherapy vs. 2) sequential or delayed alternating TRT and chemotherapy | MEDLINE and Cochrane Database 1966 to March 2003 | • Meta-analysis  
• Most published RCT are underpowered  
• Early concurrent TRT results in superior survival than delayed or split-course TRT | Huncharek and McGarry, 2004 |

### RCTs: Timing of Radiotherapy – early versus late

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Name of trial (phase)</th>
<th>Population</th>
<th>Outcomes</th>
<th>Brief Results</th>
<th>References</th>
</tr>
</thead>
</table>
| 1) early TRT concurrently with first cycle of CT (week 3) vs. 2) late TRT concurrently with sixth cycle of CT (week 15) | Phase III (not specified in study) | CT and RT naïve patients with limited disease small cell lung cancer under the age of 75, n=325 | Survival, tumour response, toxicity | • More patients withdrawn due to toxicity with early TRT  
• Survival rates not different between early and late TRT  
• Tumour response was not different between early and late TRT  
• No difference in proportion of patients who experienced brain relapse  
• Fewer patients in early TRT arm experienced relapse in chest and spine  
• Higher rate of nonhematologic toxicity in early TRT arm but no difference in hematologic toxicities | Spiro et. al., 2006 |
| 1) once daily vs. 2) split-course twice-daily TRT AND 3) younger patients (less than 70 years old) vs. 4) older patients (over 70 years old) | NCTTG, phase III | Patients with LD-SCLC, n=263 | Survival and toxicity | • Both once-daily and twice-daily TRT associated with acceptable rates of late radiation related toxicity  
• Older patients showed more weight loss, poorer performance status, increased pulmonary toxicity and more deaths due to treatment  
• Long-term survival was not different between age groups | Faivre-Finn et. al., 2011 |
| 3) Split-course twice-daily vs. 2) once-daily TRT | NCCTG 89-20-52, Phase III | Patients with LS-SCLC, n=310 | Long-term survival | • No difference in 5-year survival rates, tumour progression rates, intrathoracic failure, in-field failure, or distant failure between TRT fractionation patterns | Schild et. al., 2004 |

### RCTs: Fractionation

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Name of trial (phase)</th>
<th>Population</th>
<th>Outcomes</th>
<th>Brief Results</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) early concurrent twice-daily TRT vs. 2) high dose once-daily TRT</td>
<td>Phase II</td>
<td>n=38, patients with LS-SCLC</td>
<td>Long-term toxicity</td>
<td>• Both once-daily and twice-daily TRT associated with acceptable rates of late radiation related toxicity</td>
<td>Faivre-Finn et. al., 2011</td>
</tr>
</tbody>
</table>
| 1) once-daily vs. 2) split-course twice-daily TRT AND 3) younger patients (less than 70 years old) vs. 4) older patients (over 70 years old) | NCTTG, phase III | Patients with LD-SCLC, n=263 | Survival and toxicity | • Older patients showed more weight loss, poorer performance status, increased pulmonary toxicity and more deaths due to treatment  
• Long-term survival was not different between age groups | Schild et. al., 2005 |
| 3) Split-course twice-daily vs. 2) once-daily TRT | NCCTG 89-20-52, Phase III | Patients with LS-SCLC, n=310 | Long-term survival | • No difference in 5-year survival rates, tumour progression rates, intrathoracic failure, in-field failure, or distant failure between TRT fractionation patterns | Schild et. al., 2004 |
1) Once-daily vs. 2) twice-daily TRT

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Name of trial (phase)</th>
<th>Population</th>
<th>Outcomes</th>
<th>Brief Results</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) 54 Gy vs. 2) 58 Gy vs. 3) 62 Gy TRT delivered once-a-day</td>
<td>Phase I</td>
<td>Patients with LS-CLC, n=18 (6 per dose level)</td>
<td>Rate of acute RT toxicity rates</td>
<td>Maximum tolerated hypofractionated TRT dose was 58 Gy in 25 daily fractions</td>
<td>Yee et. al., 2010</td>
</tr>
<tr>
<td>1) 50Gy TRT in 2.0Gy fractions continuously concurrent with first 2 CT cycles vs 2) 50Gy TRT split course in 2.5Gy fractions concurrent with first 3 CT cycles</td>
<td>Phase III</td>
<td>Patients with LS-SCL, n=114</td>
<td>Survival</td>
<td>Interdigitating split-course TRT was tolerable in LS-SCLC patients, but did not improve survival</td>
<td>Blackstock et. al, 2005</td>
</tr>
</tbody>
</table>

## On-going RCTS

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Name of trial (phase)</th>
<th>Population</th>
<th>Outcomes</th>
<th>Brief Results</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concurrent 1) once-daily (66-70 Gy) vs. 2) twice-daily (45 Gy in 30 fractions in 3 weeks) TRT</td>
<td>CONVERT, phase III</td>
<td>Plan to recruit 532 patients with LS-SCLC over 4 years, n=278 at time of abstract</td>
<td>Overall survival</td>
<td>Only reports on recruitment so far. Plan to fill by March 2013</td>
<td>Faivre-Finn and Falk, 2012</td>
</tr>
</tbody>
</table>
| Concurrent TRT with 1) first cycle or 2) third cycle of CT | Phase III | Patients with LS-SCLC, n=219 | Survival | Abstract presented at ASCO 2012<br>
Late (3rd cycle start) TRT showed comparable survival outcomes and complete response rates as early (1st cycle start) TRT<br>
Late TRT showed lower frequency of febrile neutropenia | Park et. al., 2012 |
| 1) High dose (once daily for 16 days followed by twice daily for 9 days) vs. 2) twice-daily (45Gy in 3 weeks) TRT | CALG 30610/RTOG 0538, phase III | Plan to recruit 712 patients with LS-SCLC | Overall survival | No results published yet | Slotman, 2011 |

## Practice Guidelines

<table>
<thead>
<tr>
<th>Title</th>
<th>Organization</th>
<th>Year of search</th>
<th>Summary of recommendations</th>
<th>Reference</th>
</tr>
</thead>
</table>
| Small cell lung cancer: Clinical practice guidelines in oncology | National Comprehensive Cancer Network (NCCN) | Guideline published in 2011, date of literate search not given | Radiotherapy should be delivered as either 1.5 Gy twice daily (total dose of 45 Gy) or 2 Gy once daily (total dose of 60-70 Gy) <br>
Radiotherapy should start concurrent with chemotherapy cycle 1 or 2 | Kalemkerian et. al., 2011 |
<p>| Small-cell lung | European | Guideline published in | First-line treatment should include thoracic | Sorensen et. al., |</p>
<table>
<thead>
<tr>
<th>Cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up</th>
<th>Society for Medical Oncology (ESMO)</th>
<th>2010, date of literature search not given</th>
<th>Radiotherapy (TRT)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Early TRT concurrent with platinum-based chemotherapy is superior to late radiotherapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• No recommendation on whether twice-daily fractionation is superior to once-daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Optimal dose of TRT has not been established</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Patients should be treated with combined concurrent chemoradiotherapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Patients eligible for early concurrent chemoradiotherapy should be treated with accelerated hyperfractionated radiation therapy concurrently with platinum-based chemotherapy</td>
</tr>
<tr>
<td>Small cell lung cancer</td>
<td>American College of Chest Physicians (ACCP)</td>
<td>Guideline published in 2003, date of literature search not given</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Patients should be referred to a radiation oncologist and a medical oncologist for chemotherapy and radiation therapy</td>
</tr>
</tbody>
</table>

1. Does any of the newly identified evidence, on initial review, contradict the current recommendations, such that the current recommendations may cause harm or lead to unnecessary or improper treatment if followed? Answer Yes or No, and explain if necessary, citing newly identified references:

1. No

If Yes, the document will be immediately removed from the PEBC website, and a note as to its status put in its place. Go to 2.

2. On initial review,
   a. Does the newly identified evidence support the existing recommendations?
   b. Do the current recommendations cover all relevant subjects addressed by the evidence, such that no new recommendations are necessary?

   Answer Yes or No to each, and explain if necessary:

2. a. Yes
   b. Yes

If both are Yes, the document can be ENDORSED. If either is No, go to 3.

3. Is there a good reason (e.g., new stronger evidence will be published soon, changes to current recommendations are trivial or address very limited situations) to postpone

3. NA
<table>
<thead>
<tr>
<th>Updating the Guideline? Answer Yes or No, and explain if necessary:</th>
<th>If Yes, a final decision can be DELAYED up to one year. If No, go to 4.</th>
</tr>
</thead>
<tbody>
<tr>
<td>4. Do the PEBC and the DSG/GDG responsible for this document have the resources available to write a full update of this document within the next year?</td>
<td>4. NA</td>
</tr>
</tbody>
</table>

If Yes, the document needs an UPDATE. It can be listed on the website as IN REVIEW for one year. If a full update is not started within the year, it will be automatically ARCHIVED. If NO, go to 5.

5. If Q2, Q3, and Q4 were all answered NO, this document should be ARCHIVED with no further action.

<table>
<thead>
<tr>
<th>Review Outcome</th>
<th>UPDATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSG/GDG Approval Date</td>
<td>September 24, 2012</td>
</tr>
<tr>
<td>DSG/GDG Commentary</td>
<td></td>
</tr>
</tbody>
</table>

New References Identified (alphabetical order):


**Literature Search Strategy:**

**Medline**
1. meta-Analysis as topic/
2. meta analysis.pt.
3. (meta analy$ or metaanaly$).tw.
4. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative syntheses or quantitative overview).tw.
5. (systematic adj (review$ or overview?)).tw.
6. (exp Review Literature as topic/ or review.pt. or exp review/) and systematic.tw.
7. or/1-6
8. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
9. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual seach$).ab.
10. (selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
11. (study adj selection).ab.
12. 10 or 11
13. review.pt.
14. 12 and 13
15. exp randomized controlled trials as topic/ or exp clinical trials, phase III as topic/ or exp clinical trials, phase IV as topic/
16. (randomized controlled trial or clinical trial, phase III or clinical trial, phase IV).pt.
17. random allocation/ or double blind method/ or single blind method/
18. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
19. or/15-18
20. (phase II or phase 2).tw. or exp clinical trial/ or exp clinical trial as topic/
21. (clinical trial or clinical trial, phase II or controlled clinical trial).pt.
22. (20 or 21) and random$.tw.
23. (clinical$ adj trial$1).tw.
24. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
25. placebos/
26. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
27. (allocated adj2 random).tw.
28. or/23-27
29. practice guidelines/
30. practice guideline?.tw.
31. practice guideline.pt.
32. or/29-31
33. 7 or 8 or 9 or 14 or 19 or 22 or 28 or 32
34. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.
35. 33 not 34
36. limit 35 to english
37. animal/
38. human/
39. 37 not 38
40. 36 not 39
41. *carcinoma, small cell/rt
42. carcinoma, small cell/
43. small cell lung.tw.
44. 42 or 43
45. exp radiotherapy, adjuvant/
46. radiotherap:.tw.
47. thoracic radiotherap:.tw.
48. radiation therap:.tw.
49. thoracic radiation:.tw.
50. 45 or 46 or 47 or 48 or 49
51. (44 and 50) or 41
52. non small cell lung.ti.
53. 51 not 52
54. 40 and 53

Embase
1. exp meta analysis/ or exp systematic review/
OUTCOMES DEFINITION

1. **ARCHIVE** – An archived document is a document that will no longer be tracked or updated but may still be useful for academic or other informational purposes. The document is moved to a separate section of our website, each page is watermarked with the phrase “Archived document, not for use in clinical decision making.”

2. **ENDORSEMENT** – An endorsed document is a document that has been reviewed by the DSG for currency and relevance, and the DSG believes it is still useful as guidance for clinical decision making. A document may be endorsed because the DSG feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. **DEFERRAL** – A Deferral means that the clinical reviewers feel that the document is still useful and the decision has been made to postpone further action due to a number of reasons. The reasons for deferral should be found in the DART form and on the document.

4. **UPDATE** – An Update means that the DSG/GDG recognizes that there is new evidence that makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The DSG/GDG will rewrite the guideline at the earliest opportunity to reflect this new evidence. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making.