Evidence-based Series 7-3 Version 2.2005 [TO BE UPDATED]

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

Management of Unresected Stage III Non-Small Cell Lung Cancer

G. Okawara. J.A. Mackay, W.K. Evans, Y.C. Ung, and the Lung Cancer Disease Site Group

Evidence-based Series 7-3 Version 2 was reviewed in 2012 and the Lung Cancer Disease Site Group (DSG) made the decision to UPDATE it on April 12, 2013. See Section 4: Document Review Summary and Tool for details.

The reviewed EBS report, consists of

Section 1: Clinical Practice Guideline [TO BE UPDATED]
Section 2: Systematic Review
Section 3: Guideline Development and External Review
Section 4: 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: July 24, 2013

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Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca

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Guideline Report History

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Management of Unresected Stage III Non-Small Cell Lung Cancer: A Clinical Practice Guideline

G. Okawara, J.A. Mackay, W.K. Evans, Y.C. Ung, and the Lung Cancer Disease Site Group

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

Report Date: May 6, 2005

The 2005 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. Please see Section 4: Document Summary and Review Tool for a summary of updated evidence published between 2005 and 2012.

Guideline Questions
1. What is the role of different schedules or doses of radiotherapy as a treatment in patients with unresected stage III non-small cell lung cancer?
2. Does chemotherapy combined with radiotherapy improve survival compared with radiotherapy alone in patients with unresected stage III non-small cell lung cancer?
3. Which sequence of radiotherapy combined with chemotherapy is most effective in improving survival for patients with unresected stage III non-small cell lung cancer?
4. Which chemotherapy regimen(s), combined with radiotherapy, is most effective in improving survival for patients with unresected stage III non-small cell lung cancer?

Target Population
These recommendations apply to adult patients with unresected, clinical or pathological, stage III non-small cell lung cancer. Unresected disease is defined as a tumour that, for either technical or medical reasons, cannot be completely resected or removed.

Recommendations
For patients with good performance status (Eastern Cooperative Oncology Group, 0-1) and minimal weight loss (usually defined as <5% in the preceding three months):

- Chemoradiation improves survival compared with radiotherapy alone and concurrent chemoradiation is recommended, with cisplatin-based chemotherapy and thoracic radiation of at least 60 Gy in 30 fractions given over a six-week period.
- Insufficient evidence exists to recommend a specific cisplatin-based regimen for use in a concurrent chemoradiation schedule. However, in the opinion of the Lung Cancer Disease Site Group, reasonable treatment options include cisplatin combined with one of etoposide, vinorelbine, or vinblastine.

For symptomatic patients with poor performance status (Eastern Cooperative Oncology Group, >1) and significant weight loss (usually defined as >10% in the preceding three months):

- Radiotherapy for symptom palliation is recommended.
- Insufficient evidence exists to determine the optimal dose or timing of radiotherapy when the goal of therapy is symptom palliation. Reasonable treatment options include 20 Gy in five fractions and 17 Gy in two fractions given one week apart. Radiotherapy administered in a single fraction of 10 Gy is not recommended based on the decreased survival and quality of life observed when compared with multifractionated radiotherapy in one Canadian trial. However, in the opinion of the Lung Cancer Disease Site Group, single fractions of radiotherapy less than 10 Gy may be appropriate in some clinical circumstances.
- Palliative chemotherapy for patients with stage III disease is not reviewed in this guideline. For guidelines on palliative chemotherapy for locally advanced (stage IIIIB) or metastatic (stage IV) disease, please visit the Cancer Care Ontario Web site.

For patients with borderline performance status or moderate weight loss (5-10%):

- Concurrent or sequential chemoradiation is an option though the quality and quantity of evidence is not as compelling as that for patients with good performance status and minimal weight loss.

Hyperfractionated radiation is not recommended outside the context of a clinical trial (see Related Guidelines section below).

Qualifying Statements

- Full dose vinorelbine (25-30 mg/m² weekly) should not be used in combination with cisplatin and concurrent radiotherapy because of toxicity concerns. The two trials of concurrent cisplatin-vinorelbine and radiotherapy reviewed in this guideline used a vinorelbine dose of 12.5-15 mg/m² generally administered weekly.
- Evidence for the use of induction chemotherapy before concurrent chemoradiation is currently limited; therefore, the Lung Cancer Disease Site Group believe that, where concurrent chemoradiation is used, the two treatment modalities should be started at the same time and as early as possible after diagnosis.
• Insufficient evidence exists to recommend for or against the use of chemotherapy as consolidation treatment after chemoradiation. However, based on the limited evidence available, if consolidation chemotherapy is used, two to three cycles could be administered.

• Increased toxicity, particularly esophagitis and hematologic events, is associated with the addition of chemotherapy to radiotherapy. The results of one randomized phase II trial comparing three different cisplatin-based doublets combined with concurrent radiotherapy suggest that these toxicities occur more frequently with gemcitabine-cisplatin compared with paclitaxel-cisplatin or vinorelbine-cisplatin.

• Where single fraction radiation is used for symptom palliation, treatment volume and critical structures in the radiation field, such as the spinal cord, need to be given careful consideration in order to minimize potential toxicities.

• The patient and physician should have a full discussion of the benefits, limitations, and toxicities of therapy.

Key Evidence

• Fifteen randomized trials examined various policies or dose and schedule combinations for radiotherapy administration. Among the fully published trials, no statistically significant survival differences were detected for immediate versus delayed administration of radiotherapy (one trial) or different doses of hyperfractionated radiotherapy (one trial). Of the 11 fully published trials that compared varying doses and schedules of standard fractionated radiotherapy, three detected a statistically significant survival advantage with higher multifractionated radiation doses (20 Gy in five fractions versus 10 Gy in one fraction, \( p=0.03 \); 39 Gy in 13 fractions versus 17 Gy in two fractions, \( p=0.03 \); 30 Gy in 10 fractions versus 16 Gy in two fractions, \( p=0.03 \)). One trial detected a survival advantage for 16 Gy in two fractions compared with 20 Gy in five fractions (\( p=0.016 \)); however, the reliability of this result is limited by the size of the trial (\( n=100 \)) and the fact that survival was a secondary outcome.

• Six meta-analyses compared chemoradiation with radiation alone; three focused exclusively on trials that administered concurrent chemoradiation. There was considerable overlap in the studies included in each meta-analysis, and the results were consistent. The largest meta-analysis involved 22 studies and individual patient data from more than 3,000 patients. That meta-analysis detected a statistically significant overall survival benefit for the use of chemoradiation with a pooled hazard ratio of 0.90 (\( p=0.006 \)) or a 10% relative reduction in the risk of death, which translated into an absolute benefit of 3% at two years and 2% at five years. The survival benefit associated with chemoradiation was maintained in a subgroup analysis of 11 trials involving cisplatin-based chemoradiation (pooled hazard ratio, 0.87; 95% confidence interval, 0.79 to 0.96), increasing survival from 15% to 19% at two years (absolute benefit, 4%) and from 5% to 7% at five years (absolute benefit, 2%). Chemotherapy combinations not including cisplatin did not demonstrate a statistically significant survival benefit.

• Two of seven trials compared radiotherapy alone to radiotherapy combined with low-dose platinum-based chemotherapy used as a radiosensitizer and detected a statistically significant survival advantage for chemoradiation (estimated three-year survival: 16% versus 2%, \( p=0.009 \); 10% versus 2%, \( p=0.00001 \)). Both trials used concurrent daily cisplatin as the radiosensitizer; however, one trial also used split-course radiotherapy, which is generally considered less effective than continuous
radiotherapy because of the theoretical possibility of tumour repopulation during the rest period.

- Of seven trials that compared conventional radiotherapy alone with chemoradiation, longer survival was generally associated with the combined treatment, although the difference was statistically significant in only one small trial (n=51). Two of four small trials (32-68 patients per treatment arm) that added platinum-based chemotherapy to hyperfractionated or accelerated radiotherapy detected a statistically significant survival advantage for the combination treatment compared with radiotherapy alone (median: 18 versus 8 months, p=0.0027; 22 versus 14 months, p=0.021).

- One meta-analysis also detected a survival benefit for concurrent compared with sequential chemoradiation at two years (n=711; relative risk, 0.86; 95% confidence interval, 0.78-0.95; p=0.003).

- Three randomized trials, one reported in abstract form, comparing sequential to concurrent chemoradiotherapy detected a statistically significant survival advantage for concurrent treatment (median: 16.5 versus 13.3 months, p=0.04; 16.6 versus 12.9 months, p=0.023; 17.0 versus 14.6 months, p=0.046). Three additional trials compared sequential or concurrent chemoradiation with concurrent chemoradiation followed by consolidated chemotherapy or preceded by induction chemotherapy. In the two trials providing a statistical comparison of survival, no significant differences were detected between treatment schedules.

- Of six fully published trials that compared different chemotherapy regimens or schedules within a combined modality treatment approach, three involved older or non-standard chemotherapy regimens combined with split-course radiotherapy, one involved hyperfractionated chemoradiation with or without weekend chemotherapy and detected no statistically significant survival differences between groups, one compared concurrent with sequential chemoradiation involving two different chemotherapy regimens, and one involved three newer platinum-based chemoradiation combinations, but that trial was not designed to compare survival across treatment groups.

- Clinical experience suggests that the toxicity resulting from chemotherapy and/or radiotherapy in the treatment of unresected stage III NSCLC is largely confined to neutropenic-related infection, weight loss, and vomiting. Weight loss and serious infections requiring hospitalization are more prevalent with chemoradiation (sequential or concurrent) compared to radiation alone. Patients receiving concurrent combined chemoradiation or radiation alone are at risk for radiation pneumonitis and esophagitis, and meta-analyses indicate that severe acute esophagitis is more frequently associated with concurrent chemoradiation compared with radiation alone. Toxicities commonly reported in clinical trials include hematologic toxicity and nausea and vomiting, both associated with combined chemoradiation. Symptom control and quality of life were mainly assessed in trials comparing different radiotherapy schedules and doses, with few reporting a statistically significant difference between schedules.

**Related Guidelines**


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Evidence-based Series #7-3 Version 2.2005: Section 2

Management of Unresected Stage III Non-Small Cell Lung Cancer: A Systematic Review

G. Okawara, J.A. Mackay, W.K. Evans, Y.C. Ung, and the Lung Cancer Disease Site Group

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

The 2005 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. Please see Section 4: Document Summary and Review Tool for a summary of updated evidence published between 2005 and 2012.

QUESTION(S)
1. What is the role of different schedules or doses of radiotherapy as a treatment in patients with unresected stage III non-small cell lung cancer (NSCLC)?
2. Does chemotherapy combined with radiotherapy improve survival compared with radiotherapy alone in patients with unresected stage III NSCLC?
3. Which sequence of radiotherapy combined with chemotherapy is most effective in improving survival for patients with unresected stage III NSCLC?
4. Which chemotherapy regimen(s), combined with radiotherapy, is most effective in improving survival for patients with unresected stage III NSCLC?

Unresected stage III NSCLC is defined as clinical or pathological stage III disease with tumours that, for either technical or medical reasons, cannot be completely resected. Survival was selected as the primary outcome of interest, although quality of life (QOL) was also considered an important outcome and toxicity was a secondary outcome of interest.

INTRODUCTION
Of the approximately 21,700 new cases of lung cancer expected in Canada in 2004 (1), 75 to 80% will be of the non-small cell type, and most of those will be locally advanced (stage
III) or metastatic (stage IV) (2). When the Tumour Nodes Metastases staging system developed by Mountain was applied to a large database, the five-year survival for locally advanced disease was approximately 15% for stage IIIA and 5% for stage IIIB (3). Until recently, the generally accepted standard therapy for patients with locally advanced, unresectable NSCLC was radiation therapy (2).

Radiotherapy commonly relieves the symptoms of locally advanced NSCLC, and there is a small percentage (approximately 5%) of long-term survivors following radical radiotherapy. Attempts to improve survival with high-dose radiotherapy have been reported in numerous studies. However, controversy has existed as to whether radiotherapy should be immediate or delayed and uncertainty remains as to what the total radiotherapy dose should be. Until 1990, randomized controlled trials had demonstrated no survival benefit for patients who received immediate radiotherapy alone, delivered with modern megavoltage equipment, compared with patients who were given radiotherapy only when they became symptomatic.

The use of systemic treatment in combination with radiation (chemoradiation) has been investigated because of evidence of tumour regression and a small survival benefit with chemotherapy in metastatic NSCLC. A large meta-analysis published in 1995 demonstrated a survival benefit for patients treated with chemoradiation (combined modality therapy) compared with radiotherapy alone (4); however, the results of individual studies have been conflicting. The administration of chemotherapy and radiotherapy within a chemoradiation regimen may be sequential, where one modality is followed by the other modality, or concurrent, where the two modalities are administered at the same time. In addition, chemoradiation may be preceded by a course of chemotherapy (induction) or followed by a course of chemotherapy (consolidation). The relative effectiveness of different chemoradiation regimens and schedules remains undefined.

Because of continued controversies over the most effective therapy for stage III disease, the Lung Cancer Disease Site Group (Lung DSG) chose to prioritize a complete revision of their previous practice guideline report on this topic (5).

METHODS

This systematic review was developed by Cancer Care Ontario’s Program in Evidence-based Care (PEBC) using the methods of the Practice Guidelines Development Cycle (6). Evidence was selected and reviewed by two members of the PEBC Lung DSG and methodologists.

This systematic review is a convenient and up-to-date source of the best available evidence on the management of unresected, stage III NSCLC. The body of evidence in this review is primarily comprised of mature randomized controlled trial data. That evidence forms the basis of a clinical practice guideline developed by the Lung DSG. The systematic review and companion practice guideline are intended to promote evidence-based practice in Ontario, Canada. The PEBC is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

A practice guideline report on unresected stage III NSCLC was originally completed by the Lung DSG in 1997 and published in Cancer Prevention & Control 1997;1:249-59 (5). Given the volume of new, published data on this topic since 1997, the DSG decided to reorganize and rewrite the 1997 guideline. This document replaces the 1997 report.

Literature Search Strategy

Literature searches were conducted in MEDLINE (1966 through November 2005), EMBASE (1980 through 2005, week 46), the Cochrane Library (2005, Issue 4), and the Cochrane Central Register of Controlled Trials (2005, issue 4) using the following search terms as MEDLINE or EMBASE subject headings “carcinoma, non-small-cell lung”, “lung carcinogenesis”, “lung adenocarcinoma”, “lung alveolus cell carcinoma”, “lung, non small cell...
cancer”, “lung squamous cell carcinoma”, “radiotherapy” and “cancer radiotherapy”, combined with the text words “non small cell lung”, “radiotherapy”, “radiation therapy”, “chemoradiation”, “inoperable”, or “unresectable”, and the following publication types and study designs: practice guidelines, systematic reviews or meta-analyses, randomized controlled trials, and controlled clinical trials.

In addition, conference proceedings of the annual meetings of the American Society of Clinical Oncology (ASCO, 1999 through 2005) and the American Society for Therapeutic Radiology and Oncology (ASTRO, 1999 through 2004) were searched for abstracts of relevant trials. The Canadian Medical Association Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp) and the National Guidelines Clearinghouse (http://www.guideline.gov/index.asp) were searched for existing, evidence-based practice guidelines published since 2000.

Relevant articles and abstracts were selected and reviewed by two reviewers, and the reference lists from those sources were searched for additional trials as were the reference lists from relevant review articles.

**Inclusion Criteria**

Articles were included in this systematic review if they were fully published reports or abstract of meta-analyses or randomized trials (phase II or III) comparing the following in patients with unresectable stage III NSCLC:

1. Different schedules or doses of radiotherapy as a single modality treatment; or
2. Radiotherapy alone versus the same radiotherapy regimen combined with chemotherapy; or
3. Different chemoradiation regimens that differ only in the radiation regimen used; or
4. Different chemoradiation regimens that differ only in the chemotherapy regimen used; or
5. Timing of radiotherapy and chemotherapy administration within a chemoradiation treatment approach.

In addition, evidence-based practice guidelines or systematic reviews were eligible, which addressed radiotherapy-based treatment for unresectable stage III NSCLC and included recommendations published since 2000.

**Exclusion Criteria**

The following were not considered:

1. Trials evaluating any of the following treatment options or comparisons: older radiotherapy equipment (e.g., equipment that antedated Cobalt-60), 3D conformal radiotherapy, bronchial artery infusion chemotherapy, split-course radiotherapy when compared with another radiotherapy schedule, or conventional compared with altered fractionation radiotherapy (see Related Guidelines section of this report).
2. Trials of chemoradiation involving a non-platinum chemotherapy combination and published prior to 1995. Meta-analyses have shown a survival advantage for chemoradiation over radiation alone for platinum-based chemotherapy but not other chemotherapies (4,7).
3. Trials randomizing only patients that had responded to, or did not progress on, induction chemotherapy.
4. Trials that did not report the required outcomes by treatment group. For trials with palliative intent, required outcomes included symptom control or QOL; for other trials, survival data were required.
5. Letters and editorials reporting trial data.
6. Papers published in a language other than English.

**Synthesizing the Evidence**

The DSG decided not to statistically pool data from randomized controlled trials for the following reasons:
There were no consistent radiotherapy dose/schedule comparisons among trials of palliative radiotherapy;
Several meta-analyses comparing chemoradiation with radiation alone have already been conducted although no consistent chemotherapy regimens or radiotherapy schedules or doses have been compared across trials;
Trials comparing the timing of chemoradiation administration have primarily been published in abstract form to date and provide limited data for statistical pooling.

RESULTS

Literature Search Results

Forty-seven randomized trials (phase II and phase III) and six meta-analyses met the eligibility criteria for this systematic review and are summarized in Table 1. Of those, 46 were fully published reports, and seven were in abstract or brief report form only. Data from slide presentations associated with abstract trial reports were included if the presentations were publicly available on meeting Web sites. In addition, five relevant evidence-based practice guidelines and systematic reviews were identified (8-12). Randomized trials of conventional radiotherapy that were included in published meta-analyses of chemoradiation versus radiation alone are not reported separately in this guideline report, with the exception of trials involving chemotherapy used as a radiosensitizer, which were included because none of the meta-analyses examined this form of treatment administration separately.

The following trials were initially considered for inclusion in the guideline but were excluded by two reviewers for the reasons indicated:
1. A trial comparing immediate radiotherapy with delayed radiotherapy or chemotherapy did not report the data for the delayed radiotherapy treatment arm separately and the chemotherapy administered was not platinum-based (13).
2. In one abstract report of a trial comparing chemoradiation with radiation alone, it was unclear if the survival data reported by treatment group were median or mean data, and the group data were inconsistent with the data reported in the ‘Discussion’ section of the abstract report (14).
3. One small trial of 72 patients that compared two different chemotherapy regimens combined with split-course radiotherapy did not clearly describe the treatment regimens (15).
4. A randomized phase I trial comparing radiotherapy with or without paclitaxel in 45 patients administered different radiotherapy doses in the two treatment arms (63 Gy and 59.4 Gy, respectively) (16).

Table 1. Summary of meta-analyses and randomized trials (phase II and phase III) included in this practice guideline report.

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<td>1</td>
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<td>Conventional radiotherapy dose and schedule comparisons</td>
<td>11</td>
<td>1</td>
<td>(19-30)</td>
<td>2</td>
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<tr>
<td>Hyperfractionated radiotherapy dose and schedule comparisons</td>
<td>1</td>
<td>0</td>
<td>(31)</td>
<td>2</td>
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<tr>
<td>Chemoradiation vs. radiation alone</td>
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<td></td>
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</tr>
<tr>
<td>Meta-analyses</td>
<td>5</td>
<td>1</td>
<td>(4,7,32-36)</td>
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In addition, published trial data could not be located for two trials reported in the National Cancer Institute (NCI) clinical trials database as closed to accrual (Web site address: http://www.cancer.gov/search/clinical_trials/search_clinicaltrialsadvanced.aspx):


Practice Guidelines and Systematic Reviews
During the development of this practice guideline report, three evidence-based guidelines on treatment for NSCLC and two systematic reviews that included guidance on the use of radiotherapy in NSCLC were published (8-12). All the guidelines and reviews were reasonably well-conducted and were based on searches of a variety of literature sources (including MEDLINE and Cochrane Library) searched through mid-2001 (9-11) or late 2002 (12). However, only the Cochrane systematic review specified the research question of interest, provided full details on the search strategies used, and clearly described the criteria and methods for study selection and the results of the evaluation of study quality (8). Two guidelines were funded through an unrestricted educational grant from Bristol-Myers Squibb (10,11). Overall, the conclusions reached by each of the guidelines and systematic reviews were supported by the evidence that was reviewed. The focus of each report differed to some extent, although the relevant recommendations and guidance from the documents are generally consistent with each other (Appendix A). In particular, the reports agree that combined platinum-based chemoradiation is the appropriate treatment for patients with unresectable locally advanced NSCLC of good performance status (PS) (9-12). Most of the reports also agree that palliative radiotherapy alone can provide symptom relief in selected patients with symptomatic, unresectable NSCLC (8,9,12).

There is considerable overlap in the studies reviewed in each of the guidelines and systematic reviews reported above; however, the Lung DSG also identified additional studies, including some recent publications, which were relevant to the current topic. In addition, the Lung DSG felt that a separate review of some treatment approaches would be of value (e.g., low-dose chemotherapy used as a radiosensitizer within a combined modality treatment regimen). Therefore, the Lung DSG agreed to continue with the development of a practice guideline addressing the four guideline questions described above.

Outcomes
None of the trials included in this guideline reported blinding of treatment administration for patients or trial clinicians. Blinding can limit measurement bias, particularly for the subjective outcomes used in palliative radiotherapy trials, such as QOL and symptom control (71). Missing data is also of concern with QOL assessments (72) and few trials discuss how this issue is addressed. These factors should be taken into account when considering the results of subjective outcome assessments. Randomized phase II trials are included in this guideline.
report. Although those trials are generally designed to explore the efficacy and toxicity of a specific treatment rather than to compare the effectiveness of different treatments, they do provide relevant data on treatment toxicities and supporting data for the comparative randomized trials.

Radiotherapy Alone

Fifteen randomized trials addressed the role of radiotherapy alone (Table 2). Two trials compared immediate with delayed radiotherapy (17,18), 12 compared different schedules or doses of conventional radiotherapy (19-30), and one compared different schedules or doses of hyperfractionated radiotherapy (31). Two trials were reported in abstract form and provided limited methodological detail (17,26). Of the 13 fully published trials, all but two (20,25) were conducted across multiple sites, with the majority in either the United Kingdom (U.K.) and Ireland (18,21,22,24) or North America (19,27,31). Randomization in most trials was centralized and conducted by telephone, although three trials used a sealed envelope system (20,23,25), and three trials did not report the method of randomization (27,29-31). Seven trials described how the required sample size was determined (18,23-25,27-30), including one trial designed as an equivalence trial (29), with four failing to reach the specified target (18,23,28,30). Of the trials reporting survival data, only one trial included less than 96% of randomized patients in the survival analysis (19), although two trials did not clearly report the number of patients included in the analyses (20,23). Two trials specified that linear accelerators were used to deliver radiotherapy (20,27), most described treatment as palliative (18,20-25,27-30), and two included survival as the primary outcome of interest (23,24). Of the 13 trials, only two reported good PS (0-2) as an inclusion criteria (23,24).

Immediate versus delayed radiotherapy

Two randomized trials, including one reported in abstract form, compared immediate administration of radiotherapy with delayed treatment administered when symptomatic control became necessary (17,18). In the trial by Falk et al, radiotherapy was given to 90% of patients assigned to immediate treatment and 42% assigned to delayed treatment (18). Neither trial detected a statistically significant survival difference between treatments, although this was a secondary outcome in the fully published trial (18), and the results in the abstract report were based on preliminary data (17).

Variable doses and schedules of conventional radiotherapy

Twelve trials, including one reported in abstract form, compared different doses or schedules of radiation given in a conventional manner (19-30). Radiotherapy given at a dose of 17 Gy in two fractions over one week was the most frequently examined schedule, used in four U.K. trials (21,22,24,25) and one Norwegian trial (28). Treatment in most trials was described as palliative or could be inferred as palliative from the radiotherapy dose and schedule used, although therapy in one trial was intended as radical (19). However, it is recognized that the definition of a palliative dose of radiation varies across countries. In Canada, doses greater than 30 Gy would generally be considered radical in nature. Thus, treatment in some of the trials reported in Table 2 (20,23,24,28) would be considered as radical, despite their palliative intent. Limitations in the conduct of four trials were noted. In the trial by Teo et al, there was an imbalance in the number of patients allocated to each treatment, 18 patients (6%) were also excluded from the analyses because they did not complete treatment, and 36 patients (12%) were not evaluable for symptom improvement (20). Two of the five centres in the trial by Sundstrøm et al refused to enroll patients in the 50 Gy treatment arm in the last year of the study due to an inadequate capacity for radiotherapy, resulting in a lower patient recruitment in that treatment arm (28). The primary outcome measure in the trial by Kramer et al was based on an unvalidated adaptation of the Rotterdam Symptom Checklist (29) and the Polish trial.
closed prematurely because of decreasing accrual, after enrolling only 100 of the planned 321 patients (30).
Table 2. Randomized trials of radiotherapy alone.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Disease Stage</th>
<th>RT Regimen</th>
<th>Number Randomized (Analyzed)</th>
<th>CR&amp;PR, %</th>
<th>Median, Months</th>
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<th>Symptom Control / QOL, % of Patients</th>
<th>Toxicity, % of Patients</th>
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<td><strong>Immediate vs. delayed radiotherapy</strong></td>
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<tr>
<td>Alberti, 1990</td>
<td>Limited disease</td>
<td>Delayed RT, 52-56Gy</td>
<td>63 total (17)</td>
<td>NA (17)</td>
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<td>78 (18)</td>
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<td>76 (17)</td>
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<td>Falk, 2002</td>
<td>Locally advanced disease +/- metastasis</td>
<td>Immediate RT, 17Gy, 2fx, 2wks OR 10Gy, 1fx recommended</td>
<td>115 (115)</td>
<td>NA (17)</td>
<td>11</td>
<td>78 (18)</td>
<td>15</td>
<td>76 (17)</td>
<td>19</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reference</th>
<th>Disease Stage</th>
<th>RT Regimen</th>
<th>Number Randomized (Analyzed)</th>
<th>CR&amp;PR, %</th>
<th>Median, Months</th>
<th>Survival Rate, %</th>
<th>Overall</th>
<th>Symptom Control / QOL, % of Patients</th>
<th>Toxicity, % of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Comparisons of different doses and schedules of conventional radiotherapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perez, 1982</td>
<td>III</td>
<td>20Gy X 2, split-course</td>
<td>254 (201)</td>
<td>46 (51)</td>
<td>NR (17)</td>
<td>10 (2-yr)</td>
<td>NS (18)</td>
<td>NR (17)</td>
<td>NR (18)</td>
</tr>
<tr>
<td>Macbeth, 1996</td>
<td>Advanced, non-metastatic disease</td>
<td>17Gy, 2fx, 1wk</td>
<td>255 (255)</td>
<td>7 (31)</td>
<td>NR (17)</td>
<td>1-yr/2-yr</td>
<td>HR 0.82 (95% CI, 0.69-0.99, p=0.03 Mantel-Cox)</td>
<td>Patient-reported symptom palliation© at 2 months generally better with 17 Gy, particularly energy levels (44% vs. 30%) and sleep difficulties (67% vs. 48%).</td>
<td></td>
</tr>
</tbody>
</table>

© Patient-reported symptom palliation at 2 months generally better with 17 Gy, particularly energy levels (44% vs. 30%) and sleep difficulties (67% vs. 48%).
<table>
<thead>
<tr>
<th>Study, Year</th>
<th>Stage</th>
<th>Dose, Gy, fx, wk</th>
<th>Total, Evaluable</th>
<th>Percent Complete Response</th>
<th>Log Rank, p-value</th>
<th>Table 1</th>
<th>Table 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rees, 1997 (25)</td>
<td>III-IV</td>
<td>17Gy, 2fx, 1wk</td>
<td>111 (111)</td>
<td>NR</td>
<td>1.27 (95% CI, 0.57-1.75)</td>
<td>Tendency toward improvement with 17 Gy (patient report) but NS on any symptom.</td>
<td>Dysphagia more frequent with 17 Gy: 50% vs. 38% after start of treatment; 28% vs. 15%, p=0.06, 2wks after treatment.</td>
</tr>
<tr>
<td>Senkus, 2005 (29)</td>
<td>III-IV</td>
<td>16Gy, 2fx, 1wk</td>
<td>149 (149)</td>
<td>NR</td>
<td>0.03</td>
<td>Average total symptom score similar by treatment with (p=0.299) and without (p=0.22) adjustment for initial symptom score.</td>
<td>Severe acute dyspnea, malaise and/or nausea for 30 Gy vs. 16 Gy: 3% vs. &lt;1%. No myelopathy occurred. Early dysphagia, 30-40%.</td>
</tr>
<tr>
<td>Senkus-Konefka, 2005 (30)</td>
<td>Locally advanced / metastatic</td>
<td>16Gy, 2fx</td>
<td>45 (45)</td>
<td>29</td>
<td>0.016</td>
<td>For 58 evaluable patients: no significant group differences on symptomatic response up to 8 wks.</td>
<td>16 Gy vs. 20Gy: esophagitis, 24% vs. 12%, p=0.3 pneumonitis, chest pain, and skin reactions, all 4% vs. 3%, p=1.0.</td>
</tr>
</tbody>
</table>

**Comparisons of different doses and schedules of hyperfractionated radiotherapy**

<table>
<thead>
<tr>
<th>Study, Year</th>
<th>Stage</th>
<th>Dose, Gy, fx, wk</th>
<th>Total, Evaluable</th>
<th>Percent Complete Response</th>
<th>Log Rank, p-value</th>
<th>Table 1</th>
<th>Table 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cox, 1990 (31)</td>
<td>II-IV</td>
<td>All BID</td>
<td>884 total</td>
<td>NR</td>
<td>0.83</td>
<td>Primary symptoms up to 54 wks: dyspnea, cough, hemoptysis, p=NS. No consistent differences on other QOL or clinician-evaluated measures.</td>
<td>Clinician assessed dysphagia less frequent with 50 Gy at 2wks (p=0.05). Spinal toxicity: 4 patients (2 each with 17 Gy and 50 Gy) including 3 with temporary symptoms.</td>
</tr>
<tr>
<td>Randomized</td>
<td>60Gy, 25fx, 5wks</td>
<td>NR (83)</td>
<td>9.2</td>
<td>39 / 16</td>
<td>0.012</td>
<td>Induction CT: vindesine 3 mg/m² days 1 and 3 and cisplatin 80 mg/m² day 2 every 4 weeks for 3 courses. No significant differences in grade 3 or 4 acute (7-14%) or late (7-13%) toxicities.</td>
<td></td>
</tr>
<tr>
<td>phase I/II</td>
<td>64.8Gy, 27fx, 6wks</td>
<td>NR (127)</td>
<td>6.3</td>
<td>33 / 14</td>
<td>0.012</td>
<td>Assessed using a standardized scale: Rotterdam Symptom Checklist (18,24); Lung Cancer Symptom Scale (27,28); European Organization for Research and Treatment of Cancer (27). One trial evaluated symptom control using an unvalidated adaptation of the Rotterdam Symptom Checklist (29) and one trial developed their own 4-point scale (30).</td>
<td></td>
</tr>
<tr>
<td>RTOG 83-11</td>
<td>69.6Gy, 29fx, 6wks</td>
<td>NR (220)</td>
<td>10.0</td>
<td>44 / 20</td>
<td>0.012</td>
<td>Total 206 entered and eligible patients split between groups; RT 20 Gy X 2 and RT 40 Gy. Complete response rate for the split-course radiotherapy regimen was lower than for the other regimens (p=0.02).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>74.4Gy, 31fx, 7wks</td>
<td>NR (211)</td>
<td>8.7</td>
<td>40 / 15</td>
<td>0.012</td>
<td>Method of symptom assessment was not clearly described.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>79.2Gy, 33 fx, 7wks</td>
<td>NR (207)</td>
<td>10.5</td>
<td>45 / 20</td>
<td>0.012</td>
<td>The intention-to-treat tumour response rate is reported in the table. The rate reported in the paper was based on 47 evaluable patients: 20 Gy vs. 16 Gy, 52% vs. 54%, p=0.99.</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BID – twice daily, CI – confidence interval, CR – complete response, CT – chemotherapy, fx – fraction(s), Gy – gray(s), HR – hazard ratio, MRC – Medical Research Council, NA – not applicable, NR – not reported, NS – not statistically significant, PR – partial response, QOL – quality of life, RT – radiotherapy, RTOG – Radiation Therapy Oncology Group, SCLC – small cell lung cancer; vs. – versus, wk(s) – week(s), yr – year.
a Induction CT: vindesine 3 mg/m² days 1 and 3 and cisplatin 80 mg/m² day 2 every 4 weeks for 3 courses.
b Assessed using a standardized scale: Rotterdam Symptom Checklist (18,24); Lung Cancer Symptom Scale (27,28); European Organization for Research and Treatment of Cancer (27). One trial evaluated symptom control using an unvalidated adaptation of the Rotterdam Symptom Checklist (29) and one trial developed their own 4-point scale (30).
c Total 206 entered and eligible patients split between groups; RT 20 Gy X 2 and RT 40 Gy.
d Complete response rate for the split-course radiotherapy regimen was lower than for the other regimens (p=0.02).
e Method of symptom assessment was not clearly described.
f The intention-to-treat tumour response rate is reported in the table. The rate reported in the paper was based on 47 evaluable patients: 20 Gy vs. 16 Gy, 52% vs. 54%, p=0.99.
Only four of the 12 trials detected a statistically significant survival difference between radiotherapy schedules. In three of those trials, longer survival was associated with higher doses of radiotherapy delivered more frequently; however, no single dose or schedule was consistently superior (24,27,29). The reliability of the results in the other trial was limited because survival was a secondary outcome and accrual was halted early (30). Among the four fully published U.K. trials, only the trial that focused exclusively on patients with a good to moderate PS (0-2) detected a significant survival difference between radiotherapy treatments (24). Similarly, an exploratory subgroup analysis of the multicentre Canadian trial by Bezjak et al suggested that the survival benefit associated with a multifractionated compared with a single-fractionated regimen was specific to patients with locally advanced disease and good PS (Eastern Cooperative Oncology Group [ECOG], 0-1) (27).

Perez et al found that local recurrence rates were inversely related to the radiotherapy dose, with a rate of 35% following 60 Gy, 42% after 50 Gy, and 51% following 40 Gy (p=0.006) (19). In contrast, two trials detected no significant difference between radiation doses on local control (hazard ratio, [HR], 0.86; 95% confidence interval [CI], 0.68 to 1.09 (24); p=0.64 (28)). In one trial, distant metastases occurred earlier among patients receiving the lower dose radiation (HR, 0.69; 95% CI, 0.55 to 0.86) (24).

Few statistically significant treatment differences were reported for symptom palliation. Macbeth et al observed higher rates of symptom improvement with 17 Gy compared with 39 Gy (24), and Bezjak et al observed improvement on a number of QOL measures for patients treated with multifractionated compared with single-fractionated radiation, although there were no significant treatment differences on the primary outcome of patient-reported symptom palliation (27). In an abstract report, Gaze et al also reported higher rates of physician-assessed symptom relief with a 30 Gy multi-fraction regimen compared with a 10 Gy single-fraction radiation regimen at one month and three months (dyspnea, p=0.01; chest pain, p=0.014; cough, p=0.029) (26). Where reported, patient compliance with symptom assessments varied. Macbeth et al obtained data (≥75%) on 65% of the expected questionnaires within the first six months of treatment (24), 66-69% of patients in the trial by Bezjak et al completed a daily symptom diary up to the one-month follow-up (27), and 73% of patients surviving for more than two months were evaluable for symptom response in the trial by Senkus-Konefka et al (30). Dysphagia was a common treatment side effect and occurred at varying rates (Table 2).

**Hyperfractionated radiotherapy**

Only one phase I/II trial is available to assess the role of hyperfractionated radiotherapy in locally advanced lung cancer. That trial was designed to examine toxicity and tumour control among five different hyperfractionated radiotherapy doses, and no statistically significant survival or toxicity differences were detected (31). With acceptable acute and late toxicities in the three initial treatment arms (60-69.6 Gy), recruitment to the two lowest-dose treatment arms was closed, and two higher-dose treatment arms were added (74.4 and 79.2 Gy). Tumour response was not assessed because of the difficulty in differentiating tumour from radiation changes in the adjacent lung post-radiation therapy.

**Chemoradiation versus Radiation Alone**

**Meta-analyses**

Six meta-analyses have compared radiotherapy alone with radiotherapy combined with chemotherapy (Table 3) (4,7,32-36). One meta-analysis also compared concurrent with sequential chemoradiation (35) and is discussed in a separate section of this systematic review (Timing of radiotherapy relative to chemotherapy). In three of the meta-analyses, all published in the mid-1990’s, the chemotherapy was administered either sequentially or concurrently with radiotherapy (4,7,32,33). In three recent meta-analyses, including one published in abstract
form, only trials of concurrent chemoradiotherapy were included (34-36). There was considerable overlap in the trials included in the six meta-analyses. Three trials originally reported in one meta-analysis as unpublished or available in abstract form only were subsequently published in full (73-75).

The largest analysis, conducted by the Non-Small Cell Lung Cancer Collaborative Group (NSCLCCG), was based on individual patient data from 22 randomized trials (published and unpublished). Those trials accrued patients with locally advanced disease between January 1, 1965 and December 31, 1991 and recruited between 48 and 353 patients per trial (4,32). The overall pooled mortality HR was 0.90 (p=0.006), demonstrating an absolute survival benefit of 3% at two years in favour of chemoradiation. Among subgroup analyses conducted on the basis of the chemotherapeutic agent used, only the cisplatin-based regimens demonstrated a statistically significant survival advantage compared with radiotherapy alone, and that corresponded to a 4% absolute survival benefit at two years (32). However the test for interaction was not significant for the different chemotherapy categories, suggesting that the results of the subgroup analyses should be viewed with caution.

Three of the other four fully published meta-analyses included only published data (7,33,34), and one included unpublished data for two studies reported in abstract form (35). Results from the two meta-analyses involving both sequential and concurrent chemoradiation trials were consistent with those of the NSCLCCG meta-analysis (7,33). The two fully published meta-analyses restricted to concurrent chemoradiation trials included mainly platinum-based chemotherapy regimens with considerable overlap in the trials analyzed in each report (34,35).

In both of those meta-analyses, concurrent chemoradiation improved survival over radiotherapy alone at two years, although there was significant heterogeneity in treatment effects across the trials in one of the analyses (35) (Table 3). Both meta-analyses also reported similar results for the subgroup of trials involving weekly chemotherapy administration; however, the results were less consistent for trials involving chemotherapy administered two to four times a week.

An unplanned, exploratory subgroup analysis in one report suggested that the survival advantage of chemoradiation over radiation alone was maintained with once-daily radiation (10 trials; relative risk [RR], 0.92; 95% CI, 0.87-0.99; p=0.02) but not twice-daily radiation (four trials; RR, 0.95; 95% CI, 0.81-1.11; p=0.5) (35). The results reported in abstract form for one meta-analysis of concurrent chemoradiation versus radiation alone (36) were comparable with the results obtained in the fully published meta-analyses.

Only two meta-analyses explored the potential toxicity of treatment. Acute grade 3 or greater adverse effects were examined in the published meta-analysis by Rakovitch et al (34). Esophagitis, neutropenia, and pneumonia were more frequently associated with concurrent chemoradiation compared with radiation alone. However, the difference was statistically significant only for esophagitis (RR, 1.77; 95% CI, 1.27 to 2.48; p=0.0008) and neutropenia (RR, 9.15; 95% CI, 4.16 to 20.12; p<0.00001) and not for pneumonia (RR, 1.36; 95% CI, 0.89 to 2.07; p=0.16). That finding was consistent with the results of Rowell and O’Rourke, who reported a significantly increased rate of acute esophagitis in patients receiving chemoradiation (RR, 1.58; 95% CI, 1.19-2.09; p=0.001) but no significant treatment-related differences for acute pneumonia (RR, 1.19; 95% CI, 0.64-2.22; p=0.6) (35).

Chemotherapy as a radiosensitizer versus conventional radiotherapy alone

Chemotherapy when given concurrently with radiotherapy may enhance the local effect of the radiotherapy by sensitizing tumour cells to the radiation. Trials that primarily aim to evaluate the use of chemotherapy as a radiosensitizer, i.e., those that involve low-dose chemotherapy agents administered on a daily or weekly basis concurrently with radiotherapy, are included in this section.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Comparisons</th>
<th>Number of Studies</th>
<th>Number of Patients</th>
<th>Survival Ratio * (95% CI)</th>
<th>Absolute Survival Difference</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLCCG, 1995 (4,32)</td>
<td>RT vs. RT + any CT</td>
<td>22</td>
<td>3,033</td>
<td>HR, 0.90 p=0.006</td>
<td>3% at 2-yr 2% at 5-yr</td>
<td>Individual patient data</td>
</tr>
<tr>
<td>Subgroup analyses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Same RT schedule in both arms of each trial</td>
</tr>
<tr>
<td></td>
<td>RT vs. RT + cisplatin-based CT</td>
<td>11</td>
<td>1,780</td>
<td>HR, 0.87 (0.79-0.96) p=0.005</td>
<td>4% at 2-yr 2% at 5-yr NR</td>
<td>Test for heterogeneity in overall analysis, p=0.56</td>
</tr>
<tr>
<td></td>
<td>RT vs. RT + long-term alkylating CT</td>
<td>5</td>
<td>665</td>
<td>HR, 0.98 (0.83-1.16) p=0.81</td>
<td>NR</td>
<td>Test for interaction among CT categories, p=0.59</td>
</tr>
<tr>
<td></td>
<td>RT vs. RT + vinca alkaid CT or etoposide</td>
<td>3</td>
<td>349</td>
<td>HR, 0.87 (0.70-1.09) p=0.23</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RT vs. RT + other CT</td>
<td>3</td>
<td>239</td>
<td>HR, 0.98 (0.74-1.29) p=0.88</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Marino, 1995 (7)</td>
<td>RT vs. RT + cisplatin-based CT</td>
<td>10</td>
<td>1,410</td>
<td>2-yr OR, 0.70 (0.5-0.9) NR</td>
<td>Published data only</td>
<td>Includes 1 trial with CT as a radiosensitizer</td>
</tr>
<tr>
<td></td>
<td>RT vs. RT + non-cisplatin-based CT</td>
<td>4</td>
<td>477</td>
<td>2-yr OR, 0.82 (0.5-1.3) NR</td>
<td>Published data only</td>
<td></td>
</tr>
<tr>
<td>Pritchard, 1996 (33)</td>
<td>RT vs. RT + any CT</td>
<td>14</td>
<td>2,589</td>
<td>2-yr RR, 0.87 (0.81-0.94) 1.7 months, median</td>
<td>Published data only</td>
<td>Includes 2 trials with CT as a radiosensitizer and 2 trials using hyperfractionated or accelerated RT</td>
</tr>
<tr>
<td>Subgroup analyses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Test for heterogeneity in overall analysis, p=0.2</td>
</tr>
<tr>
<td></td>
<td>RT vs. RT + cisplatin-based CT</td>
<td>11</td>
<td>2,158</td>
<td>2-yr RR, 0.85 (0.79-0.92) 1.6 months, median</td>
<td>Test for heterogeneity in overall analysis, p=0.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RT vs. RT + sequential CT</td>
<td>8</td>
<td>1,408</td>
<td>2-yr RR, 0.85 (0.77-0.95) 1.7 months, median</td>
<td>Test for heterogeneity in overall analysis, p=0.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RT vs. RT + concurrent CT</td>
<td>6</td>
<td>1,181</td>
<td>2-yr RR, 0.89 (0.81-0.98) 1.7 months, median</td>
<td>Test for heterogeneity in overall analysis, p=0.2</td>
<td></td>
</tr>
<tr>
<td>Rakovitch, 2004 (34)</td>
<td>RT vs. RT + concurrent CT</td>
<td>10</td>
<td>1,802</td>
<td>2-yr RR, 0.92 (0.88-0.97) p=0.002</td>
<td>NR</td>
<td>Published data only</td>
</tr>
<tr>
<td>Subgroup analyses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Includes 3 trials with CT as a radiosensitizer and 4 trials using hyperfractionated or accelerated RT</td>
</tr>
<tr>
<td></td>
<td>RT vs. RT + weekly concurrent CT</td>
<td>6^b</td>
<td>1,128</td>
<td>2-yr RR, 0.93 (0.87-0.99) p=0.02</td>
<td>NR</td>
<td>9 trials used cisplatin-based CT Test for heterogeneity in overall analysis, p=0.2</td>
</tr>
<tr>
<td></td>
<td>RT vs. RT + daily concurrent CT</td>
<td>5^b</td>
<td>788</td>
<td>2-yr RR, 0.92 (0.85-1.00) p=0.05</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Rowell, 2004 (35)</td>
<td>RT vs. RT + concurrent CT</td>
<td>13</td>
<td>2,214</td>
<td>2-yr RR, 0.93 (0.88-0.98) p=0.01</td>
<td>NR</td>
<td>Published data only except for 2 abstracts (n=359)</td>
</tr>
<tr>
<td>Subgroup analyses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Includes 6 trials with CT as a radiosensitizer and 4 trials using hyperfractionated or accelerated RT</td>
</tr>
<tr>
<td></td>
<td>RT vs. RT + concurrent platinum-based CT</td>
<td>11</td>
<td>1,945</td>
<td>2-yr RR, 0.93 (0.87-0.99) p=0.02</td>
<td>NR</td>
<td>Test for heterogeneity in overall analysis, p&gt;0.2 &amp; in trials of daily chemotherapy, p=0.034</td>
</tr>
<tr>
<td></td>
<td>RT vs. RT + weekly concurrent platinum-based CT</td>
<td>5^b</td>
<td>896</td>
<td>2-yr RR, 0.91 (0.84-0.98) p=0.01</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RT vs. RT + daily concurrent platinum-based CT</td>
<td>5^b</td>
<td>716</td>
<td>2-yr RR, 0.95 (0.85-1.08)</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RT vs. RT + 2-4 weekly concurrent platinum-based CT</td>
<td>5^b</td>
<td>777</td>
<td>2-yr RR, 0.92 (0.83-1.02) p=0.12</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Auperin, 2003 (36)</td>
<td>RT vs. RT + concurrent platinum-based CT</td>
<td>9</td>
<td>1,764</td>
<td>RR, 0.89 (0.81-0.98) p=0.02</td>
<td>4% at 2-yr 2% at 5-yr</td>
<td>Individual patient data</td>
</tr>
<tr>
<td>(abstract)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3 trials, 146 patients, excluded from analysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Median follow-up, 86 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Graphical but not statistically (p=0.16) heterogeneity</td>
</tr>
</tbody>
</table>

Abbreviations: CI – confidence interval, CT – chemotherapy, HR – hazard ratio, NSCLCCG – Non-Small Cell Lung Cancer Collaborative Group, NR – not reported, OR – odds ratio, RR – risk ratio, RT – radiotherapy, vs. – versus, yr(s) – year(s).

* Ratios less than one indicate a survival benefit in favour of chemoradiation.
  b Some trials are included in more than one comparison.
Seven fully published randomized trials explored the role of low-dose platinum chemotherapy administered concurrently with radiotherapy as a radiosensitizer (37-43) (Table 4). Data from four of these trials (37-40) were included in three meta-analyses (37,39,40); however, the trials were not analyzed separately as radiosensitizing studies. Five of the trials involved multiple centres (38-40,42,43), and one trial reported using a centralized randomization process (38). Four trials described how the required sample size was determined (40-43). One trial was terminated after 46 of a planned 190 elderly (≥71 years) patients were enrolled due to a high proportion of treatment related deaths and protocol deviations (43). Five trials included at least 95% of randomized patients in survival analyses (37-39,41,42), and one trial excluded 12% of patients because of ineligibility or failure to receive treatment, although the number excluded in each treatment group was similar (40). All the trials included only patients with a good or moderate PS [0-1 (37,40), 0-2 (38,41,43), Karnofsky >50% (39)], and two also required minimal weight loss of <10% (42) or <5% in the three months preceding diagnosis (40). Two trials used linear accelerators to deliver radiotherapy to some (39) or all patients (42).

A significant overall survival advantage in favour of chemoradiation was found in two (38,41) of the seven trials. After a minimum 22-month follow-up, Schaake-Koning reported survival was significantly improved when daily cisplatin was added to radiotherapy, but no statistically significant survival benefit was detected for weekly cisplatin with radiotherapy compared with radiotherapy alone (38). In a multivariate analysis by Cakir et al, radiation alone and a radiation dose <60 Gy were each associated with poorer survival (41). No association was observed between survival and patient age, PS, or disease stage. In both trials, the survival benefit of chemoradiation may have been due to an improvement in local control (38,41). Schaake-Koning et al observed longer local recurrence-free survival with radiotherapy and daily chemotherapy (one year, 59%; two year, 31%) compared with radiotherapy alone (one year, 41%; two year, 19%; p=0.003) or radiotherapy with weekly chemotherapy (one year, 42%; two year, 30%; p=0.17) (38). Similarly, Cakir et al detected higher rates of loco-regional recurrence following radiotherapy alone (80% versus 60% of patients, p=0.0001) but lower rates of distant recurrence (7% versus 24%, p=0.07) (41). In addition, two other trials observed higher rates of local recurrence with radiation alone [46% versus 27% (37); 53% versus 43% (40)], although distant recurrence rates were higher with chemoradiation in one trial [40% versus 28% (40)] and similar across treatments in the other trial [29% to 32% (37)]. Two trials did not observe a difference in relapse patterns between chemoradiation and radiation alone (39,42). Of the trials that did not detect a significant survival difference between treatments, two involved concurrent carboplatin administration (40,42), one reported a minimum follow-up period that was shorter than the median survival time (39), one only included patients ≥71 years and was stopped early due to treatment related deaths and protocol deviations (43), and one was likely underpowered to detect a survival difference (37).

Non-hematologic toxicities were generally comparable across treatments, although patients given chemoradiation experienced more nausea and vomiting in two trials [grade 3 or 4, 25% to 28% versus 2% (38); any grade, 29% versus 10% (39)] and more bacterial pneumonitis in one trial (11% versus 4%) (37). Two trials observed increased grade 3 or 4 esophagitis when cisplatin [16% versus 8% (39)] or carboplatin [9% versus 2% (42)] was added to radiotherapy. Higher rates of grade 3 or 4 hematologic toxicity were associated with chemoradiation compared with radiotherapy alone in two trials [14% to 59% versus 2% to 44% (40); 11% versus 0% (42)]. Schaake-Koning et al reported two possibly treatment-related deaths, both in the weekly chemotherapy treatment group (38). Atagi et al reported four treatment-related deaths, three in the chemoradiation arm and one in the radiation arm (43).

In the one trial that assessed patient QOL, using the European Organization for Research and Treatment of Cancer (EORTC) scales, no statistically significant differences were detected for the 72% of patients who provided data at three months post-treatment (42).
Table 4. Randomized trials of conventional radiation with versus without chemotherapy used as a radiosensitizer.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Disease Stage</th>
<th>Treatment</th>
<th>Number Randomized (Analyzed)</th>
<th>Response, CR&amp;PR, %</th>
<th>Median, Months</th>
<th>Survival Rate, %</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soresi, 1988 (37)</td>
<td>IIIA/B</td>
<td>RT: 50.4Gy, 28fx, 5.5wks</td>
<td>50 (48)</td>
<td>45 (45)</td>
<td>64</td>
<td>p=0.2</td>
<td>p=0.18 log rank</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RT+CT: RT as above + concurrent cisplatin 15 mg/m² wkly</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schaake-Koning, 1992 (38)</td>
<td>I-III Phase II/III</td>
<td>RT: 30Gy, 10fx + 25Gy, 10fx, split-course, 5wks</td>
<td>114 (114)</td>
<td>50</td>
<td>64</td>
<td>NR</td>
<td>p=0.054 log rank</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RT+CT: RT as above + concurrent cisplatin 30 mg/m² wkly</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p=0.36 log rank RT vs. RT+CT wkly; p=0.009 log rank RT+CT daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RT+CT: RT as above + concurrent cisplatin 6 mg/m² daily</td>
<td>107 (107)</td>
<td></td>
<td>63</td>
<td>26 / 16</td>
<td></td>
</tr>
<tr>
<td>Trovó, 1992 (39)</td>
<td>IIIB</td>
<td>For 146 evaluable</td>
<td></td>
<td>NR</td>
<td>58.9</td>
<td>10.3</td>
<td>p=NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RT: 45Gy, 15fx, 3wks</td>
<td>88 (83)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>RT+CT: RT as above + concurrent cisplatin 6 mg/m² daily</td>
<td>85 (84)</td>
<td></td>
<td>50.6</td>
<td>9.97</td>
<td></td>
</tr>
<tr>
<td>Clamon, 1999 (40)</td>
<td>IIIB</td>
<td>CT-&gt;RT: Induction vinblastine 5 mg/m² wkly days 1-29 + cisplatin 100 mg/m² days 1 &amp; 29 -&gt; 60Gy, 30fx, 6wks</td>
<td>137 (120)</td>
<td>58</td>
<td>13.5</td>
<td>2-yr / 4-yr / 26 / 10</td>
<td>p=0.7426 log rank</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CT-&gt;RT+CT: Induction CT -&gt; RT as above + carboplatin 100 mg/m² wkly concurrent with RT</td>
<td>146 (130)</td>
<td>58</td>
<td>13.4</td>
<td>29 / 13</td>
<td></td>
</tr>
<tr>
<td>Cakir, 2004 (41)</td>
<td>IIIB</td>
<td>RT: 64Gy, 32fx, 6.5wks</td>
<td>93 (NR)</td>
<td>45</td>
<td>NR</td>
<td>Estimated 3-yr / 2 / 26 / 10</td>
<td>p=0.00001 log rank</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RT+CT: RT as above + concurrent cisplatin 20 mg/m² days 1-5, wks 2 and 6.</td>
<td>92 (NR)</td>
<td></td>
<td>64</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Groen, 2004 (42)</td>
<td>IIIB</td>
<td>88 eligible in each group</td>
<td>Statistically significant</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Groen, 2004 (42)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atagi 2005 (43)</td>
<td>IIIB</td>
<td>RT: 60 Gy, 30fx, 6wks</td>
<td>78 (78)</td>
<td>a</td>
<td>11.7 (95 CI, 8.1-15.5)</td>
<td>2-yr / 28</td>
<td>p=0.39 log rank</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RT+CT: RT as above + concurrent carbolaplatin, 840 mg/m², given over 6 wks</td>
<td>82 (82)</td>
<td></td>
<td>11.8 (95 CI, 9.3-14.2)</td>
<td>20</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI – confidence interval, CR – complete response, CT – chemotherapy, fx – fraction(s), Gy – Gray(s), NR – not reported, NS – not statistically significant, PR – partial response, RT – radiotherapy, vs. – versus, wk(s) – week(s), yr – year.

a Response data reported are inconsistent and range from 37% to 58%.
b Included patients ≥71 years and was terminated after 46 patients due to high proportion of treatment related deaths and protocol deviations.
Chemoradiation versus conventional radiation alone

Seven trials compared chemoradiation with radiation alone but were not included in any of the meta-analyses (Table 5) (44-48,50,76). Two trials were randomized phase II trials (44,50), three trials involved multiple centres (45-47), two used a centralized randomization process (45,46) and four described the method of sample size estimation (45,46,50,76). Two trials included at least 97% of randomized patients in their survival analyses (45,46) and one included all eligible patients but did not report if any randomized patients were considered ineligible (76). Four trials reported the type of radiotherapy equipment used [linear accelerators (44,76); cobalt-60 (48,50,76)]. Six trials included only patients with a good PS [Karnofsky ≥60 (44) or ≥70 (48), ECOG/World Health Organization (WHO) 0-2 (46,47,50,76)], and one required a weight loss of ≤10% within the previous six months (76). One trial involved 7% of patients with a WHO PS of 3 (45).

Only one of the seven trials detected a statistically significant survival difference between chemoradiation and radiation alone (76). That small, single centre trial recruited only 51 of the planned 120 patients and was likely underpowered to provide a reliable comparison of survival (76). Of the other six trials, two used older treatment regimens that are not used in Canada (44,45), including one trial that closed early because of greater toxicity with the combined treatment (45); the results of one small trial should be considered with caution because most of the 14% of patients excluded from the analyses were from the chemoradiation treatment group (47), and one was a phase II trial and was not designed to compare survival across treatments (50). In contrast to the data from most of those recent trials, three trials included in the meta-analyses (4,7,33) were subsequently updated and reported a statistically significant survival advantage for chemoradiation compared with radiation alone (77-79).

Chemoradiation was generally associated with increased toxicity compared with radiation alone, including grade 3 or 4 neutropenia [13% versus 0% (44), 57% versus 14% (48), 26.6% versus 6.6% (50)], anemia [80% versus 15% (48), 26.6% versus 13.3% (50)], thrombocytopenia [6% versus 3% (44), 36.6% versus 3.3% (50)], nausea and vomiting [100% versus 0% (44), 8% versus 3% (45), 24% versus 0% (48), 73.2% versus 16.6% (50)], esophagitis [12% versus 3% (45), 76% versus 28% (48)], and skin reactions [75% versus 30% (48)]. Ulutin et al (76) reported limited toxicity data, although chemoradiation was associated with higher rates of grade 3 or greater pulmonary toxicity (16% versus 0%) (76).

Only one trial assessed patient QOL using a validated scale (46). In a subgroup of 67 patients completing an adaptation of the EORTC questionnaire, the mean change in QOL scores over six weeks favoured chemoradiation (p=0.0002). However, these results were limited by the small number of participating patients, the assignment of most of them to chemoradiation (42 of 67 patients), and the fact that only 50 of the 67 patients completed questionnaires at both baseline and six weeks.

Chemoradiation versus hyperfractionated or accelerated radiation alone

Four randomized trials compared a hyperfractionated or accelerated radiotherapy regimen with a chemoradiation regimen involving a similar radiotherapy schedule (Table 6) (51-54). One of those trials (52) was also included in the meta-analysis by Pritchard et al (33), and all were included in the meta-analyses conducted by Rakovich et al (34) and Rowell et al (35). Only the latter meta-analysis reported separate results for hyperfractionated radiotherapy in an unplanned, exploratory, subgroup analysis.
Table 5. Randomized trials of conventional radiation with versus without chemotherapy (not included in the meta-analyses).

<table>
<thead>
<tr>
<th>Reference</th>
<th>Disease Stage</th>
<th>Treatment</th>
<th>Number Randomized (Analyzed)</th>
<th>Response, CR&amp;PR, %</th>
<th>Median, Months</th>
<th>Survival Rate, %</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minet, 1987 (44)</td>
<td>I-IV</td>
<td>RT: 24Gy, 6fx, 2wks x 2, with 2wks rest in between.</td>
<td>40 (40)</td>
<td>NR</td>
<td>6.8</td>
<td>1-yr/2-yr 31 / 6</td>
<td>X²=0.171 p=NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RT+CT: RT as above + cyclophosphamide 400 mg/m², vindesine 3 mg/m², doxorubicin 40 mg/m², + cisplatin 40 mg/m² wks 1, 5, 13, then monthly x 8, + vindesine 3 mg/m² wks 2 &amp; 6.</td>
<td>41 (41)</td>
<td>8.0</td>
<td>35 / 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ball, 1997 (45)</td>
<td>NR, advanced</td>
<td>RT: 20Gy, 5fx, 1wk</td>
<td>204 total</td>
<td>NR (101)</td>
<td>6.0</td>
<td>2-yr 26 / 4</td>
<td>p=0.36</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RT+CT: RT as above + concurrent continuous infusion fluorouracil 1 g/m² daily x 5</td>
<td>NR (99)</td>
<td>6.8</td>
<td>26 / 9</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>For 370 assessable p=0.14 chi-square</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cullen, 1999 (46)</td>
<td>NR, localized disease</td>
<td>RT: ≥40Gy, 15fx</td>
<td>461 total</td>
<td>NR (223)</td>
<td>9.7</td>
<td>2-yr/3-yr 16 / 8</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CT-&gt;RT: Induction mitomycin 6 mg/m², ifosfamide 3 g/m², + cisplatin 50 mg/m², every 3 wks x 4 then RT as above</td>
<td>NR (223)</td>
<td>11.7</td>
<td>20 / 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p=0.035</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kim, 2002 (47)</td>
<td>III/A/B</td>
<td>RT: 60-65Gy, 6-7wks</td>
<td>50 (46)</td>
<td>67</td>
<td>8.5</td>
<td>1-yr/2-yr 35 / 19</td>
<td>p=0.371 log rank</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CT-&gt;RT: Induction cisplatin 20 mg/m² days 1-5, etoposide 100 mg/m² days 2-4, + vinblastine 6 mg/m² day 1, every 3 wks x 3 then RT as above.</td>
<td>53 (43)</td>
<td>13.8</td>
<td>50 / 18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sharma, 2003 (48)</td>
<td>III/A/B</td>
<td>RT: 55-60Gy, 5.5-6wks</td>
<td>506 total</td>
<td>NR (234)</td>
<td>42.2</td>
<td>2-yr/3-yr 7.4 / 5.2</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CT-&gt;RT: Induction cisplatin 50 mg/m², ifosfamide 2 g/m², + mitomycin C 6 mg/m² every 3 wks x 3 then RT as above</td>
<td>NR (228)</td>
<td>13.1</td>
<td>20.1/11.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ulutin, 2003 (49)</td>
<td>III/A/B</td>
<td>RT: 56Gy BED (split-course), 2.5-3 Gy/day</td>
<td>NR (26)</td>
<td>70</td>
<td>12.0</td>
<td>NR</td>
<td>p=0.027 log rank</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CT+RT: RT as above + paclitaxel (3-hour infusion) 60 mg/m² day 1, 8, 15 &amp; 23.</td>
<td>NR (25)</td>
<td>15.2</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p=0.003</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beslija, 2005 (50)</td>
<td>III/A/B</td>
<td>RT: 63Gy, 34fx</td>
<td>30 (30)</td>
<td>26.6</td>
<td>10.0</td>
<td>1 yr 24 / 46</td>
<td>p=0.639 log rank</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CT-&gt; RT: Induction cisplatin 80 mg/m² day 1 + gemcitabine 1250 mg/m² days 1 &amp; 8, every 3 wks x 3, then RT as above.</td>
<td>30 (30)</td>
<td>46.6</td>
<td>12.5</td>
<td>p=0.324</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BED – biologically equivalent dose, CI – confidence interval, CR – complete response, CT – chemotherapy, fx – fraction(s), Gy – Gray(s), NR – not reported, NS – not statistically significant, PR – partial response, RT – radiotherapy, wk(s) – week(s), yr – year.

a Estimated survival rates
b The survival data is actuarial at 2-years and projected for 3-years.
c Total radiotherapy dose was 48.5 Gy (3 Gy/day x 12 given 5 days/week then 2.5 Gy/day for days 3-7 of wk 4).
Two trials involved multiple clinical sites (53,54), and all used linear accelerators to deliver radiotherapy. Two trials involved central randomization stratified by PS, histology, and clinical site (53,54). Three trials estimated the required sample size to detect a specified survival improvement (52-54), but only one enrolled the stated number of required patients (54). With the exception of one trial that closed early (53), 95% to 98% of randomized patients were included in the survival analyses. All of the trials only included patients with a moderate or good PS [Karnofsky ≥50 (51,52); ECOG 0-1 (54); ECOG 0-2 (53)], and two required that weight loss be less than or equal to 10% (53,54).

Two trials conducted by Jeremic et al detected a statistically significant survival advantage for concurrent chemoradiation with hyperfractionated radiotherapy over hyperfractionated radiotherapy alone (51,52). In one of the trials, the survival benefit was specific to a chemotherapy regimen using a lower dose of carboplatin, although both chemotherapy treatment groups received equal doses of etoposide (51). In the other trial, chemoradiation also resulted in a significant benefit on local (median, 25 versus 20 months, p=0.015) but not distant (p=0.33) recurrence-free survival (52). Of the two trials that did not detect a treatment difference in survival, one recruited only 110 of the target 375 patients and was underpowered for a survival comparison (53), and one found that accelerated radiotherapy, with or without chemotherapy, did not significantly improve survival compared with standard radiotherapy, with or without chemotherapy (p=0.76) (54).

Toxicity data were reported variably in the four trials. In the earlier trial by Jeremic et al, chemoradiation was associated with higher rates of grade 4 acute toxicity (high-dose carboplatin, p=0.039) and grade 3 or 4 late toxicity (low-dose carboplatin, p=0.024; high-dose carboplatin, p=0.033) (51). However, in the later trial by Jeremic et al, there were no statistically significant group differences on grade 3 or 4 acute (p=0.44) or late (p=0.75) toxicities (52). No treatment-related deaths were reported in either of the trials by Jeremic et al (51,52). Bonner et al observed higher rates of grade 3 or greater nausea and vomiting among patients receiving chemoradiation (16% to 22% versus 3% to 6%) (53), and Ball et al observed higher rates of grade 3 or 4 hematologic toxicities in patients given carboplatin (thrombocytopenia, 10% versus 0%; neutropenia, 15% versus 0%) (54). In that same trial, grade 3 or 4 esophagitis was also more common with chemoradiation (34% versus 22%) and with accelerated versus standard radiotherapy (32% to 48% versus 12% to 21%, p<0.0001) and four deaths were reported as possibly related to the administration of accelerated radiotherapy, with or without chemotherapy (54).

**Timing of Radiotherapy Relative to Chemotherapy**

One meta-analysis and three randomized trials compared concurrent chemoradiation with the sequential administration of chemotherapy and radiation (35,55,56,60,80,81), and three trials (one reported in abstract report and slide presentation) compared varying schedules of chemotherapy and radiotherapy administration (58,61,62,82) (Table 7).

All six randomized trials involved platinum-based chemotherapy. Two trials were randomized phase II trials (60,62). All trials described how the required sample size was estimated to detect a difference between treatments in the primary outcome of survival. Less than 3% of randomized patients were excluded from the survival analyses in the four reports providing that data (55,56,61,82). All trials included only patients with a good PS [ECOG 0-1 (61,82); ECOG 0-2 (55,60); Karnofsky ≥70 (56,62)], and three limited enrollment to patients with minimal weight loss [≤5% (56) or ≤10% (61,62)].
Table 6. Randomized trials of hyperfractionated or accelerated radiation with and without chemotherapy.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Disease Stage</th>
<th>Treatment</th>
<th>Number Randomized (Analyzed)</th>
<th>Response, CR&amp;PR, %</th>
<th>Median, Months</th>
<th>Survival Rate, %</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jeremic, 1995 (51)</td>
<td>IIIA/B</td>
<td>HFX RT: 64.8Gy, 1.2Gy BID</td>
<td>61 (61)</td>
<td>62</td>
<td>8</td>
<td>2-yr / 5-yr 25 / 5</td>
<td>RT vs. low-dose carboplatin p=0.0027 log rank</td>
</tr>
<tr>
<td>Jeremic, 1995 (51)</td>
<td>IIIA/B</td>
<td>HFX RT+CT: RT as above + concurrent carboplatin 100 mg days 1 and 2 and etoposide 100 mg days 1-3, given wkly during RT</td>
<td>58 (52)</td>
<td>73</td>
<td>18</td>
<td>35 / 21</td>
<td>RT vs. high-dose carboplatin, p=0.17 log rank</td>
</tr>
<tr>
<td>Jeremic, 1995 (51)</td>
<td>IIIA/B</td>
<td>HFX RT+CT: RT as above + concurrent carboplatin 200 mg days 1 and 2, and etoposide 100 mg days 1-5, wks 1, 3, and 5</td>
<td>59 (56)</td>
<td>62</td>
<td>13</td>
<td>27 / 16</td>
<td>Low-dose vs. high-dose carboplatin, p=0.14 log rank</td>
</tr>
<tr>
<td>Jeremic, 1996 (52)</td>
<td>IIIA/B</td>
<td>HFX RT: 69.6Gy, 1.2Gy BID</td>
<td>68 (66)</td>
<td>85</td>
<td>14</td>
<td>2-yr / 4-yr 26 / 9</td>
<td>p=0.021 log rank</td>
</tr>
<tr>
<td>Jeremic, 1996 (52)</td>
<td>IIIA/B</td>
<td>HFX RT+CT: RT as above + concurrent carboplatin 50 mg and etoposide 50 mg daily</td>
<td>67 (65)</td>
<td>92</td>
<td>22</td>
<td>43 / 23</td>
<td>p=0.18</td>
</tr>
<tr>
<td>Bonner, 1998 (53)</td>
<td>IIIA/B</td>
<td>RT: 60Gy, 30 daily fx, 6wks</td>
<td>110 total NR (34)</td>
<td>21</td>
<td>8.6</td>
<td>NR</td>
<td>Daily vs. BID RT comparison, p=0.10 log rank</td>
</tr>
<tr>
<td>Bonner, 1998 (53)</td>
<td>IIIA/B</td>
<td>HFX RT+CT: 30Gy, 1.5Gy BID x 2 (split-course) + concurrent cisplatin 30 mg/m^2 and etoposide 100 mg/m^2, both days 1-3 and 28-30.</td>
<td>NR (32)</td>
<td>25</td>
<td>11.6 for all BID patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bonner, 1998 (53)</td>
<td>IIIA/B</td>
<td>HFX RT: RT as above</td>
<td>NR (33)</td>
<td>45</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ball, 1999 (54)</td>
<td>I-III</td>
<td>RT: 60Gy, 30fx, 6wks</td>
<td>53 (53)</td>
<td>53</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ball, 1999 (54)</td>
<td>I-III</td>
<td>RT+CT: RT as above + concurrent carboplatin 70 mg/m^2/day x 5, wks 1 and 4</td>
<td>56 (54)</td>
<td>61</td>
<td>20.3</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>Ball, 1999 (54)</td>
<td>I-III</td>
<td>Acc RT: 60Gy, 30fx, 3 wks</td>
<td>48 (46)</td>
<td>61</td>
<td>NR</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Ball, 1999 (54)</td>
<td>I-III</td>
<td>Acc RT+CT: RT as above + concurrent carboplatin 70 mg/m^2/day x 5, wk 1</td>
<td>51 (51)</td>
<td>59</td>
<td>NR</td>
<td>24</td>
<td>p=0.82</td>
</tr>
</tbody>
</table>

Abbreviations: Acc – accelerated, BID – twice daily, CR – complete response, CT – chemotherapy, fx – fraction(s), Gy – Gray(s), HFX – hyperfractionated, NR – not reported, NS – not statistically significant, PR – partial response, RT – radiotherapy, vs. – versus, wk(s) – week(s), yr – year.

Three randomized trials comparing concurrent with sequential chemoradiation, including one reported in abstract form, detected a statistically significant survival benefit for concurrent treatment (median: 16.5 versus 13.3 months, p=0.04; 17.0 versus 14.6 months, p=0.046; 16.6 versus 12.9 months, p=0.023) after a median follow-up of five years (55), six years (56), and 39 months (60). In one of those trials, the survival advantage was specific to concurrent treatment with daily radiotherapy but not twice-daily radiotherapy (56). Radiation therapy was primarily delivered by linear accelerator in one trial (55) and Cobalt-60 machines in another (60). In the trial by Furuse et al, delivery of protocol-defined treatment was comparable for both concurrent...
and sequential schedules (82-83% of patients); however, post-protocol chemotherapy was administered to more patients following concurrent chemoradiation (59% versus 25%) (55). In the randomized phase II trial by Zatloukal et al, which was terminated early because of slow accrual and a statistically significant unplanned interim analysis, fewer patients in the sequential group received the protocol-defined treatment compared with the concurrent group (four cycles of chemotherapy, 58% versus 83%; any radiotherapy, 64% versus 94%, p=0.0002) (60). Reasons for these treatment imbalances are unclear, although they may be related to treatment effectiveness, with higher rates of chemotherapy discontinuation due to disease progression among patients receiving sequential chemoradiation (20% versus 10%). Sequential treatment was also associated with higher rates of chemotherapy discontinuation due to toxicity or other unspecified reasons (20% versus 6%), even though grade 3 or 4 toxicity was more common with concurrent treatment. The reasons for the significant differences in the amount of radiotherapy administered are unclear.

Limited toxicity data were reported in two of the three trials, although toxicities were generally more frequent with concurrent chemoradiation. Furuse et al reported more frequent myelosuppression with concurrent treatment (p=0.0001) and identical rates of esophageal toxicity for concurrent and sequential chemoradiation (55). Curran et al observed higher rates of acute grade 3 or 4 esophagitis with concurrent treatment (4% sequential, 25% concurrent with standard radiotherapy, and 47% concurrent with hyperfractionated radiotherapy), and hyperfractionated concurrent radiation was associated with less frequent grade 4 or 5 neutropenia than standard sequential or concurrent chemoradiation (48% versus 56% to 58%) (56). Late toxicities in the latter trial were similar for concurrent and sequential chemoradiation. With the exception of renal or hepatic toxicity (2% in each treatment group), all grade 3 or 4 toxicities reported by Zatloukal et al were more frequent with concurrent chemoradiation, including leukopenia (53% versus 19%, p=0.009), neutropenia (65% versus 40%, p=0.057), nausea and vomiting (39% versus 15%, p=0.044), esophagitis (18% versus 4%, p=0.076), and febrile neutropenia (8% versus 2%, not statistically significant) (60).

Three trials compared different chemoradiation schedules. Fournel et al compared sequential chemoradiation with concurrent chemoradiation followed by consolidation chemotherapy, using the same total dose of cisplatin in each treatment arm (61). In a randomized phase II trial conducted by Belani et al, patients were randomized to sequential chemoradiation followed by radiation, induction chemotherapy followed by concurrent chemoradiation, or concurrent chemoradiation followed by consolidation chemotherapy, using the same chemotherapy and radiotherapy doses in the latter two treatment arms (62). Following interim analysis, the arm receiving induction chemotherapy followed by concurrent chemoradiation was closed to patient accrual due to a low likelihood of survival benefit when compared with a historical control of sequential chemoradiotherapy. Vokes et al employed a similar regimen to that of Belani et al for induction chemotherapy followed by concurrent chemoradiation and compared that to immediate concurrent chemoradiation (58,82). None of these trials reported a statistically significant survival advantage for any treatment schedule (58,61,62,82). Concurrent chemoradiation was generally found to be more toxic than sequential treatment, and Vokes et al reported that grade 4 events were more frequent when induction chemotherapy was added to concurrent chemoradiation.

Rowell and O'Rourke pooled the two-year survival data from three trial abstracts comparing concurrent with sequential chemoradiation (35). Two of these trials have been published in full, and all three trials are included in Table 7 (56,60,61). The authors excluded the trial by Furuse et al from their analysis, because the radiotherapy administration schedule differed between the two treatment arms (55), and they included the trial by Fournel et al (61). The latter trial, which was described as a comparison of sequential versus concurrent chemoradiation, included the same total dose of cisplatin in each treatment arm; however, two cycles of chemotherapy were administered following the completion of concurrent...
chemoradiation. Given the inclusion of the trial by Fournel, it is unclear why the ACR 427 trial (62) published at that time in abstract form (83,84) was not considered for the meta-analysis. The results of the meta-analysis showed a significant survival benefit for concurrent over sequential chemoradiation at two years (RR, 0.86; 95% CI, 0.78-0.95; p=0.003); however, acute esophagitis (≥ grade 3) was also more frequent with concurrent chemoradiation (17-26% versus 0-4%, p=0.0001). The authors commented on the limitations of pooling data from abstract trial reports and suggested that, although concurrent chemoradiation was associated with a survival benefit in the meta-analysis, sequential chemoradiation should still be considered the standard of care until longer-term survival data are available and more detailed toxicity information is reported. Two of the trials in the meta-analysis has now been published in full (61,85), providing more detailed toxicity data, and another fully published trial that was excluded from the meta-analysis provides relevant and detailed outcome data (55).

Table 7. Randomized trials of radiotherapy timing relative to chemotherapy.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Disease Stage</th>
<th>Treatment Allocation</th>
<th>Number Randomized (Analyzed)</th>
<th>Response, CR&amp;PR, %</th>
<th>Median, Months</th>
<th>Survival Rate, %</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furuse, 1999 (55)</td>
<td>IIIA/B</td>
<td>CT→RT: Vindesine 3 mg/m² days 1, 8, 29, 36, cisplatin 80 mg/m² days 1, 29, and mitomycin 8 mg/m² days 1, 29, then RT, 56Gy, 28fx, 5wks CT+RT: CT as above + concurrent RT, 56Gy, 28fx, 3wks x 2 (split-course)</td>
<td>320 total NR (158)</td>
<td>66</td>
<td>13.3</td>
<td>55 / 9</td>
<td>p=0.04 log rank</td>
</tr>
<tr>
<td>Curran, 2003 (56,57) RTOG 9410 (abstract)</td>
<td>II-III</td>
<td>CT→RT: Cisplatin 100 mg/m² days 1, 29, and vinblastine 5 mg/m² wkly x 5, then RT, 63Gy total CT+RT: CT as above concurrent with daily RT as above CT+HFX RT: Cisplatin 50 mg/m² days 1, 8, 29, 36, and oral etoposide 50 mg/m² BID x 10, weeks 1, 2, 5, 6, concurrent with RT BID, 69.6Gy total</td>
<td>610 (595) total 59</td>
<td>14.6</td>
<td>31 / 12</td>
<td>CT→RT vs. CT+RT, p=0.046</td>
<td></td>
</tr>
<tr>
<td>Vokes, 2004 (58,59) CALGB 39801 (abstract)</td>
<td>III</td>
<td>RT+CT: RT 66Gy with concurrent paclitaxel 50 mg/m² and carboplatin AUC 2 given wkly CT→CT+RT: Paclitaxel 200 mg/m² and carboplatin AUC 6 q3wks x 2 followed by concurrent CT and RT as above</td>
<td>182 (161) 66</td>
<td>11.4</td>
<td>2-yr / 3-yr</td>
<td>HR, 0.85</td>
<td></td>
</tr>
<tr>
<td>Zatloukal, 2004 (60) Randomized Phase II</td>
<td>IIIA/B</td>
<td>CT→RT: Cisplatin 80 mg/m² day 1 and vinorelbine, 12.5 mg/m² (cycles 2 &amp; 3), 25 mg/m² (cycles 1 &amp; 4), days 1, 8, 15, 4wks, then RT, 60Gy, 30fx, 6wks CT+RT: CT as above + concurrent RT as above, starting day 4 of CT cycle 2</td>
<td>50 (50) evaluable</td>
<td>98</td>
<td>47</td>
<td>1-yr/2-yr/3-yr</td>
<td>HR, 0.61, 95% CI, 0.39-0.93</td>
</tr>
</tbody>
</table>

p=0.023 log rank
Trials comparing different chemotherapies within chemoradiation regimens

Eight randomized trials have compared different chemotherapy regimens within a combined-modality treatment approach, including two reported in abstract form (Table 8) (63-70). Three older trials involved treatment approaches that are no longer used in Canada [split-course radiotherapy in combination with chemotherapy regimens involving lonidamine (64), DTIC (63), or cyclophosphamide with doxorubicin (63,65)] are summarized in Table 8 but are not discussed in further detail. Similarly, data from two abstract reports of small trials are presented in Table 8 but are not discussed in the text. Although both reports provide an indication of activity for the chemotherapy regimens used, the trials were not designed (70) or powered (67) to compare survival across treatments.

Of the remaining three trials, two trials were randomized phase II trials (66,69). Two trials reported using linear accelerators to deliver radiotherapy (68,69), although Vokes et al also used Cobalt-60 machines (69). One of the randomized trials reported using a centralized randomization process (69), and two trials met projected sample size requirements (68,69). Between 93% (66) and 98% (68) of randomized patients were included in the trial survival analyses, with exclusion primarily due to patient ineligibility or failure to receive trial treatment. Two of the trials limited enrollment to patients with a good PS (0-1) and limited weight loss (<5% in three to six months pre-diagnosis) (66,69).

The trial by Vokes et al detected no statistically significant differences in objective response, overall survival, or local progression-free survival (two year, 44% versus 37%; five year, 27% versus 28%; p=0.66) for concurrent chemoradiation involving hyperfractionated radiotherapy, with or without chemotherapy administered on the weekend, respectively (68). That trial was imbalanced in the proportion of patients with stage IIIA disease receiving each chemotherapy regimen (gemcitabine-cisplatin, 63%; paclitaxel-cisplatin, 52%; vinorelbine-cisplatin, 40%), which could have had an impact on trial outcomes (69).
Toxicity varied in each trial according to the chemotherapy regimen used. Clamon et al observed generally comparable or more frequent grade 3 or 4 toxicity with sequential cisplatin-vinblastine compared with concurrent carboplatin (granulocytopenia, 53% versus 17%, p<0.003; leukopenia, 43% versus 19%; peripheral neuropathy, 17% versus 0%, p=0.007; nausea/vomiting, 20% versus 7%, p=0.175) (66). However, thrombocytopenia was more common in the carboplatin treatment arm (12% versus 0% patients, p=0.058). (66). Jeremic et al reported comparable toxicity data for regimens with or without weekend chemotherapy, with the exception of grade 3 or 4 hematologic toxicity (29% versus 12%, p=0.0046) and treatment interruptions (21% versus 6%, p=0.0018), which were more common with weekend treatment (68). During the induction chemotherapy phase of the trial by Vokes et al, grade 3 or 4 granulocytopenia was common in all treatment arms (48% to 55%), grade 3 or 4 thrombocytopenia occurred more frequently with gemcitabine-cisplatin (25% versus 0% to 2%), grade 3 or 4 leukopenia was more common with vinorelbine-cisplatin (27% versus 12% to 15%), and two treatment-related deaths occurred in the paclitaxel-cisplatin treatment arm (69). During concurrent chemoradiation, grade 3 or 4 toxicity was generally more frequent with gemcitabine-cisplatin compared with paclitaxel-cisplatin or vinorelbine-cisplatin, respectively: thrombocytopenia (56% versus 6% versus 2%), anemia (32% versus 4% versus 19%), granulocytopenia (51% versus 53% versus 27%), and esophagitis (52% versus 39% versus 25%). Radiotherapy interruptions were also more common with gemcitabine-cisplatin (35% versus 13% to 16%). However, one death due to treatment-related respiratory failure was associated with vinorelbine-cisplatin chemoradiation.

Table 8. Randomized trials of chemoradiation comparing different chemotherapy regimens.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Disease Stage</th>
<th>Treatment</th>
<th>Number Randomized (Analyzed)</th>
<th>Response, CR&amp;PR, %</th>
<th>Median, Months</th>
<th>Survival Rate, %</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eagan, 1979 (63)</td>
<td>NR Locally advanced</td>
<td>Both treatment arms: Cyclophosphamide 400 mg/m² and doxorubicin 40 mg/m² q4wks x 10 plus concurrent split-course RT, 20Gy, 5fx over 5-7 days, wks 1 and 5. Arm 1: Cisplatin 40 mg/m² q4wks x 10</td>
<td>37 (34)</td>
<td>59</td>
<td>16.6</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Gallo-Curcio, 1988 (64)</td>
<td>I–III</td>
<td>Arm 1: CT, cisplatin 100 mg/m² day 1 + etoposide 120 mg/m² days 4, 6, 8, q4wks x 2, followed by 3wk split-course RT, 30Gy + 20Gy, and 2 additional cycles of CT Arm 2: As arm 1 + lonidamine 150 mg p.o. TID/day until tumour progression</td>
<td>56 (47)</td>
<td>17</td>
<td>Actuarial 10.3</td>
<td>Actuarial 2-yr 11</td>
<td>NR</td>
</tr>
<tr>
<td>Robinow, 1989 (65)</td>
<td>II–III</td>
<td>All treatment arms: Cyclophosphamide 400 mg/m² day 3, doxorubicin 40 mg/m² day 1, and cisplatin 20 mg/m² days 1-3 (reduced to 8 mg/m² days 1-5 during RT) x 5 cycles plus concurrent split-course RT, 20 Gy, 4Gy/fx, cycles 3 &amp; 4 Arm 1: No additional CT</td>
<td>48 (38)</td>
<td>14.8</td>
<td>61 / 13 / 3</td>
<td>1-yr/3-yr/5-yr Arm 1 vs. Arm 2, p=0.08</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Arm 2: Etoposide 60 mg/m² days 1-3</td>
<td>47 (39)</td>
<td>16.2</td>
<td>67 / 26 / 18</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Arm 3: Triazinate 150 mg/m² (reduced to 125 mg/m² during RT) days 1-3</td>
<td>31 (25)</td>
<td>14.6</td>
<td>56 / 20 / 16</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### DISCUSSION

To date, the evidence is insufficient to determine the most appropriate dose, schedule, or timing of radiotherapy in the palliation of locally advanced NSCLC. There is only one fully published trial comparing immediate with delayed administration of radiotherapy and it did not detect any difference in symptom control or survival, although the trial was likely underpowered to detect a survival difference (18). There are no consistent data to suggest the superiority of one radiotherapy schedule over another, but amongst the trials comparing different doses and

<table>
<thead>
<tr>
<th>Reference</th>
<th>IIIA/B</th>
<th>Treatment arms</th>
<th>Patients</th>
<th>1-yr</th>
<th>3-yr</th>
<th>5-yr</th>
<th>Statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clamon, 1994 (66)</td>
<td>IIIA/B</td>
<td>Both treatment arms: Cisplatin 100 mg/m² days 1, 29 and vinblastine 5 mg/m² days 1, 8, 15, 22, 29 followed on day 50 by RT, 60Gy, 30fx, 6wks</td>
<td>91 total</td>
<td>NR</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Arm 1: Cisplatin 100 mg/m² q4wks x 4, and vinblastine 5 mg/m² q2wks x 8, starting 3wks post-RT</td>
<td>NR (41)</td>
<td>53 (95% CI, 34-75)</td>
<td>11.9</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Arm 2: Carboplatin 100 mg/m² wkly x 6, given concurrently with RT</td>
<td>NR (44)</td>
<td>59 (95% CI, 43-74)</td>
<td>12.44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morales, 2000 (67) (abstract)</td>
<td>IIIA/B</td>
<td>Both treatment arms: Cisplatin-based CT q3wks x 3, followed after 4wks by RT, 60Gy over 6wks</td>
<td>35 total</td>
<td>NR</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Arm 1: No additional CT</td>
<td>NR (11)</td>
<td>54</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Arm 2: Paclitaxel 60 mg/m² wkly x 6, given concurrently with RT</td>
<td>NR (11)</td>
<td>73</td>
<td>13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jeremic, 2001 (68)</td>
<td>IIIA/B</td>
<td>Arm 1: HFX RT, 69.6Gy, 1.2Gy BID weekdays + concurrent carboplatin and etoposide, both 50 mg daily on weekdays</td>
<td>101 (98)</td>
<td>85</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Arm 2: HFX RT as above + concurrent carboplatin and etoposide, both 30 mg daily on weekdays and 100 mg daily on weekends</td>
<td>99 (97)</td>
<td>88</td>
<td>22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vokes, 2002 (69) (abstract)</td>
<td>IIIA/B</td>
<td>All treatment arms: CT given q3wks x 4 + concurrent RT 66Gy, 2Gy/fx, cycles 3 &amp; 4</td>
<td>187 total</td>
<td>1-yr</td>
<td>3-yr</td>
<td>NR</td>
<td>p=0.68</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Arm 1: CT, cisplatin 80 mg/m² day 1 + gemcitabine 1250 mg/m² cycles 1 &amp; 2, 600 mg/m² cycles 3 &amp; 4, days 1,8</td>
<td>NR (62)</td>
<td>74 (95% CI, 60-86)</td>
<td>18.3</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Arm 2: CT, cisplatin 80 mg/m² day 1 + paclitaxel 225 mg/m² cycles 1 &amp; 2, 135 mg/m² cycles 3 &amp; 4, day 1</td>
<td>NR (58)</td>
<td>67 (95% CI, 52-80)</td>
<td>14.8</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Arm 3: CT, cisplatin 80 mg/m² day 1 + vinorelbine 25 mg/m² cycle 1 q1wk, cycle 2 days 1,8; 15 mg/m² cycles 3 &amp; 4, days 1,8</td>
<td>NR (55)</td>
<td>73 (95% CI, 57-85)</td>
<td>17.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antonadou, 2003 (70) (abstract)</td>
<td>IIIA/B</td>
<td>Both treatment arms: RT 55-60Gy, 2 Gy/fx, 5-6wks</td>
<td>85 total</td>
<td>6-months</td>
<td>NR</td>
<td>p=0.267</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Arm 1: Concurrent weekly paclitaxel 60 mg/m²</td>
<td>NR (36)</td>
<td>89</td>
<td>83</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Arm 2: Concurrent weekly carboplatin AUC 2</td>
<td>NR (35)</td>
<td>80 (p=0.043)</td>
<td>71</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AUC – area under curve, BID – twice daily, CI – confidence interval, CR – complete response, CT – chemotherapy, DTIC – dacarbazine, fx – fraction(s), Gy – Gray(s), HFX – hyperfractionated, NR – not reported, NS – not statistically significant, p.o. – orally, PR – partial response, q – every, RT – radiotherapy, TID – three times daily, vs. – versus, wk(s) – week(s), yr – year.
schedules of radiotherapy for the palliation of symptoms, the most commonly reported schedule was 17 Gy given in two fractions over one week. That radiation dose and fractionation schedule is used primarily in the United Kingdom. A Medical Research Council (MRC) trial involving more than 500 patients detected a statistically significant survival advantage for a schedule of 39 Gy given in 13 fractions over three weeks compared with the 17 Gy schedule; however that study was limited to patients with good PS. The survival advantage was offset, in part, by lower levels of symptom palliation for the 39 Gy schedule (24). Bezjak et al randomized 230 patients to the commonly used Canadian schedule of 20 Gy in five fractions and compared this to a hypofractionated schedule of 10 Gy given in a single fraction (27). Although that trial detected no significant difference in the primary outcome of symptom control, a statistically significant advantage for the multi-fractionated schedule was observed on the secondary outcomes of survival and QOL. Another trial reported in abstract form observed significantly better symptom palliation with a multi-fractionated schedule compared with a single-fraction of 10 Gy (26). Based on this evidence, reasonable schedules of radiotherapy for symptom palliation for symptomatic patients with poor PS and significant weight loss include 20 Gy in five fractions and 17 Gy in two fractions given one week apart. Shorter regimens, including single fractions of less than 10 Gy, should not be considered a standard approach, but may be appropriate in some clinical circumstances.

With regard to curative treatment, one large individual patient data meta-analysis and five smaller overlapping meta-analyses, all demonstrate a statistically significant survival advantage for chemoradiation therapy, particularly platinum-based, over radiotherapy alone (4,7,32-36). The absolute improvement in survival is small and in the order of 4% at two years and 2% at five years (4,32). This magnitude of survival benefit, however, is generally considered to be clinically significant. This small difference in absolute survival benefit may explain why individual clinical trials have frequently failed to detect a significant survival advantage for this treatment approach.

One meta-analysis and all three trials that compared sequential with concurrent chemoradiation detected a statistically significant survival benefit for concurrent administration (35,55,56,60). Only limited toxicity data has been reported, and hematologic (55,60) and non-hematologic (35,56,60) toxicities were more frequently associated with concurrent chemoradiation. Based on this evidence concurrent chemoradiation is recommended for patients with good PS and minimal weight loss. A reasonable treatment schedule includes cisplatin-based chemotherapy and thoracic radiation of at least 60 Gy in 30 fractions given over a six-week period. When concurrent chemoradiation is used, the two treatment modalities should be started at the same time and as early as possible after diagnosis. The patient and physician should have a full discussion of the benefits, limitations, and toxicities of therapy, and if the toxicities are felt to be unacceptable by the patient, sequential chemoradiation may be an alternative treatment option recognizing that survival benefits are inferior to concurrent therapy. The role of induction or consolidation chemotherapy in combination with concurrent chemoradiation is unclear. One noncomparative trial observed a trend towards a survival benefit for immediate concurrent chemoradiation followed by consolidation chemotherapy compared with induction chemotherapy followed by concurrent chemoradiation (62). The other trial detected no statistical difference in survival for chemoradiation with or without induction chemotherapy (58,82). A recent phase II trial using consolidation docetaxel following concurrent chemoradiation in patients with stage IIIIB disease has shown promising results (86); however that will need to be confirmed by randomized trials. If clinicians choose to administer consolidation chemotherapy, in line with recent randomized trials, two or three cycles could be administered (61,62,86).

Evidence in favour of using chemotherapy as a radiosensitizer is limited and inconsistent. Local control may be improved when cisplatin is administered in divided doses either daily or less frequently but concurrent with radiotherapy. Two of the seven trials using
cisplatin as a radiosensitizer with concurrent radiotherapy demonstrated a statistically significant survival advantage at three years (38,41). That observation lends some further support to the results of the studies evaluating concurrent versus sequential chemoradiation. The evidence for using altered fractionation radiotherapy within a chemoradiation regimen is limited and suggests the use of hyperfractionated radiotherapy should be confined to clinical trials.

The impact of chemoradiation on QOL or symptom control is uncertain because none of the meta-analyses evaluated these outcomes and, of the two chemoradiation trials that formally assessed QOL, one only enrolled 67 of 461 patients in the QOL assessment (46), and the other did not detect any statistically significant differences on the EORTC QOL scales (42). Patients receiving chemoradiation generally experience higher rates of toxicity than those given radiotherapy alone. In individual clinical trials, serious hematologic adverse effects occurred more frequently when carboplatin was given concurrently with radiotherapy (40,42), severe nausea and vomiting occurred more often when cisplatin-based chemotherapy was given concurrently (38,44,53) or sequentially (48) with radiation, and esophagitis was worse with both carboplatin-based (42,54) and cisplatin-based (39,48) chemoradiation. The results of two meta-analyses also indicated that neutropenia (34) and esophagitis (grade 3 or greater) (34,35) are more common with chemoradiation.

Although the evidence supports combining cisplatin-based chemotherapy with radiotherapy to improve survival, particularly where the two are administered concurrently, there are insufficient data to determine which chemotherapy regimen or radiotherapy schedule is most effective. Cisplatin combined with one of etoposide (86-88), vinorelbine (60,69), or vinblastine (56,80) have achieved reasonable survival in clinical trials. Full dose vinorelbine (25-30 mg/m² weekly) should not be used in combination with cisplatin and concurrent radiotherapy because of toxicity concerns. In a phase I dose-escalation trial, higher rates of severe myelosuppression and esophagitis were observed with standard doses of vinorelbine (20-25 mg/m² weekly) and cisplatin (100 mg/m² every three weeks) compared with lower doses of each agent (vinorelbine, 15 mg/m² days 1 and 8; and cisplatin, 80 mg/m² day 1, every three weeks) combined with concurrent radiotherapy (89). The two trials of concurrent cisplatin–vinorelbine and radiotherapy in this review used a lower dose of vinorelbine (12.5-15 mg/m² generally administered weekly) (60,69).

Adequate assessment of performance status is important when evaluating treatment options for unresected NSCLC patients. For patients with a good PS and minimal weight loss, there is a definite survival benefit for chemoradiation with cisplatin-based regimens compared to radiotherapy alone. As most of the chemoradiation trials reviewed in this systematic review involved patients with a good PS (generally ECOG/WHO ≤2 or Karnofsky ≥70), and some required patients to have limited weight loss (<5-10%); recommendations for a curative treatment approach should be limited to that patient group. Concurrent chemoradiation with cisplatin-based chemotherapy and thoracic radiation of at least 60 Gy in 30 fractions given over a six-week period is a reasonable regimen. Cisplatin combined with one of etoposide, vinorelbine, or vinblastine have achieved reasonable survival and are acceptable treatment combinations. There is limited evidence for patients with good PS who refuse combined modality treatment. One randomized trial found a survival benefit for a radiation regimen using 39 Gy in 13 fractions compared to 17 Gy in 2 fractions for patients with good PS (24). Radiation alone with 39 Gy in 13 fractions may be an alternative, although this fractionation scheme is not generally used in Canada. There is no consensus amongst radiation oncologists on a standard radiotherapy regimen for this population in Canada. Depending on the goals of therapy, clinicians may offer these patients radical or palliative radiotherapy alone. For less fit patients in whom potential toxicity may be a concern, sequential therapy is a treatment option, depending upon other patient factors and following a full discussion with the patient of the treatment options, goals of therapy, and potential adverse effects. For symptomatic patients with poor PS and significant weight loss, palliative radiotherapy offers the potential for symptomatic relief.
Reasonable treatment options include 20 Gy in five fractions and 17 Gy in two fractions given one week apart. Hyperfractionated radiation is not recommended outside the context of a clinical trial.

This review is limited by the lack of high quality evidence to recommend for or against the use of induction or consolidation chemotherapy, and to recommend specific chemotherapy doses and schedules. Randomized controlled trials addressing these questions should be the focus of future clinical research.

**ONGOING TRIALS**

The National Cancer Institute (NCI) clinical trials database on the Internet ([http://www.cancer.gov/search/clinical_trials/](http://www.cancer.gov/search/clinical_trials/)) was searched for ongoing trials. Those trials are summarized in Appendix B, along with relevant ongoing trials reported in abstract form.

**CONFLICT OF INTEREST**

The primary authors of this guideline report declared no potential conflicts of interest.

**JOURNAL REFERENCES**


**ACKNOWLEDGEMENTS**

The Lung DSG would like to thank Drs Gordon Okawara, William K. Evans, and Yee C. Ung and Ms. Jean A. Mackay and Jessica A. Vanderveen for taking the lead in drafting and revising this practice guideline report.

For a complete list of the Lung DSG members, please visit the CCO Web site at [http://www.cancercare.on.ca/](http://www.cancercare.on.ca/)

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Phone: 905-527-4322 ext. 42822  Fax: 905-526-6775  E-mail: ccopgi@mcmaster.ca
REFERENCES


SYSTEMATIC REVIEW – page 38


Appendix A. Recommendations/guidance of recent practice guidelines and systematic reviews.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Recommendations/Guidance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RT</strong></td>
<td></td>
</tr>
</tbody>
</table>
| Macbeth, 2001 (8) Systematic Review | - The majority of patients with locally advanced NSCLC and thoracic symptoms, especially those with poor PS, should be treated with short courses of palliative RT (such as 10 Gy/1 fraction or 16-17 Gy/2 fractions). Care should be taken to reduce the dose to the spinal cord if the regimen of 17 Gy/2 fractions is used.  
- Selected patients with good PS should be considered for treatment with higher dose palliative regimens (such as 36 Gy/12 fractions), if the chance of a modest increase in survival is, after informed discussion with the patient, considered to be worth the extra visits to hospital and the increased risk of toxicity (especially esophagitis). |
| Sirzén, 2003 (9) Systematic Review | - There is strong evidence that RT can palliate symptoms associated with the intrathoracic tumour burden.  
- There is some evidence that two large fractions may be as effective as conventional schedules consisting of 10-13 smaller fractions in terms of palliation of symptoms. |
| Robinson, 2003 (10) Practice Guideline | - In patients with good PS, RT should not be administered alone in treating unresectable stage IIIA lung cancer. |
| Pfister, 2004 (12) ASCO Practice Guideline | - RT should be included as part of treatment for selected patients with unresectable locally advanced NSCLC.  
- Candidates for definitive thoracic RT with curative intent should have PS 0, 1, or possibly 2, adequate pulmonary function, and disease confined to the thorax. Patients with malignant pleural effusions and those with distant metastatic disease are not appropriate candidates for definitive thoracic RT.  
- Definitive dose thoracic RT should be no less than the biologic equivalent of 60 Gy in 1.8-2.0 Gy fractions.  
- Local symptoms from primary or metastatic NSCLC can be relieved by a variety of doses and fractionations of external beam RT. In appropriately selected patients, hypofractionated palliative RT (of one to five fractions instead of 10) may provide symptomatic relief with acceptable toxicity in a more time-efficient and less costly manner. |
| **RT combined with CT** |                           |
| Sirzén, 2003 (9) Systematic Review | - There is strong evidence that combined modality treatment with platinum-based CT and RT, either neoadjuvant or concomitant, is superior to RT alone in terms of survival in locally advanced unresectable NSCLC and should be the standard of care in patients with good PS.  
- There is some evidence that concomitant CT-RT is associated with increased survival compared with sequential CT-RT, albeit at the price of increased toxicity. Comment: combined CT-RT of primary non-resectable stage III NSCLC followed by surgery in responders lacks evidence from prospective randomized trials and cannot be recommended for routine use. |
| Robinson, 2003 (10) Practice Guideline | - In patients with unresectable locally advanced lung cancer, platinum-based CT plus RT provides improved survival rates over RT alone and should be used for primary treatment.  
- Because in patients with stage IIIA lung cancer the optimal technique of combining CT and RT has not been determined, then factors such as patient PS and age should be used to guide treatment planning. |
| Jett, 2003 (11) Practice Guideline | - For patients with stage IIIB disease without malignant effusions, PS 0 or 1, and minimal weight loss (less than or equal to 5%), combined CT-RT should be the standard of care.  
- In patients with stage IIIB NSCLC and PS 2 or those with substantial weight loss (greater than or equal to 10%), combined modality treatment could be used after careful consideration.  
- For stage IIIB NSCLC patients with PS 0 or 1 and minimal weight loss, concurrent therapy would be recommended. Concurrent CT-RT is associated with an increased rate of acute esophagitis compared to sequential therapy. Concurrent therapy appears to be associated with improved survival over that of sequential therapy. |
| Pfister, 2004 (12) ASCO Practice Guideline | - CT in association with definitive thoracic RT is appropriate for selected patients with unresectable, locally advanced NSCLC.  
- In unresectable stage III disease, CT plus RT prolongs survival compared with RT alone and is most appropriate for individuals with good PS (ECOG/Zubrod PS 0 or 1, and possibly 2).  
- CT given to NSCLC patients [with unresectable stage III disease] should be a platinum-based combination regimen.  
- In patients with unresectable stage III NSCLC, who are candidates for combined CT and RT, the duration of chemotherapy should be 2 to 4 cycles of initial, platinum-based CT [and] in the absence of compelling data, the Panel consensus is that...the duration of initial platinum-based CT should be no more than 4 cycles.  
- In patients with unresectable stage III disease, CT may best be started soon after the diagnosis of unresectable NSCLC has been made. Delaying CT until PS worsens or weight loss develops may negate the survival benefits of treatment. |

Appendix B: Ongoing and recently closed trials

<table>
<thead>
<tr>
<th>Protocol ID</th>
<th>Title and details of trial</th>
<th>Projected accrual:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berghmans, 2004 (91) (abstract)</td>
<td>Randomized trial comparing concomitant chemoradiation (cisplatin, gemcitabine, and vinorelbine) as induction versus consolidation treatment in locally advanced unresectable non-metastatic NSCLC.</td>
<td>140 patients.</td>
</tr>
<tr>
<td>CALGB-30407</td>
<td>Phase II randomized study of pemetrexed disodium, carboplatin, and thoracic radiotherapy with or without cetuximab in patients with unresectable stage III non-small cell lung cancer</td>
<td>102 patients.</td>
</tr>
<tr>
<td>CASE-CWRU-LILY-2503</td>
<td>Phase II randomized study of induction therapy comprising cisplatin, etoposide, and radiotherapy followed by consolidation therapy comprising gemcitabine with or without docetaxel in patients with unresectable stage IIIB non-small cell lung cancer</td>
<td>102 patients.</td>
</tr>
<tr>
<td>CRUK-SOCCAR</td>
<td>Randomized phase III trial of sequential cisplatin and vinorelbine ditartrate followed by radical radiotherapy versus concurrent chemo-radiotherapy followed by chemotherapy in patients with inoperable stage III NSCLC and good performance status.</td>
<td>508 patients.</td>
</tr>
<tr>
<td>Douillard, 2000 (92) (abstract)</td>
<td>Multicentre, randomized phase III trial of vinorelbine-cisplatin as induction chemotherapy followed by radiation with or without daily carboplatin in locally advanced unresectable NSCLC. Projected accrual: 585 patients.</td>
<td>585 patients.</td>
</tr>
<tr>
<td>ECOG-3598</td>
<td>Phase III randomized study of carboplatin, paclitaxel and chemoradiotherapy with or without thalidomide in patients with stage III non-small cell lung cancer. Projected accrual: 588 patients</td>
<td>588 patients.</td>
</tr>
<tr>
<td>GERCOR-B03-1</td>
<td>Phase II randomized study of celecoxib versus observation after radiotherapy and docetaxel in patients with previously treated stage II-IIIB non-small cell lung cancer Projected accrual: 80 patients</td>
<td>80 patients.</td>
</tr>
<tr>
<td>HOG LUN01-24</td>
<td>Phase III trial of cisplatin/etoposide/radiotherapy +/- consolidation docetaxel in advanced stage III non-small cell lung cancer</td>
<td>288 patients.</td>
</tr>
<tr>
<td>INRC-PITCAP</td>
<td>Phase III randomized study of paclitaxel and carboplatin or cisplatin followed by radiotherapy with or without concurrent paclitaxel in patients with unresectable stage III NSCLC. Projected accrual: 300 patients</td>
<td>300 patients.</td>
</tr>
<tr>
<td>JCOG0301</td>
<td>Phase III trial to evaluate radiotherapy with or without carboplatin in elderly patients with non-small cell lung cancer</td>
<td>508 patients.</td>
</tr>
<tr>
<td>Morere, 2003 (93) (abstract)</td>
<td>Randomized phase II study of concurrent chemoradiotherapy with either paclitaxel and carboplatin or etoposide and cisplatin in patients with locally advanced NSCLC.</td>
<td>288 patients.</td>
</tr>
<tr>
<td>SLCG 0008</td>
<td>Phase II randomized trial of induction or consolidation chemotherapy with docetaxel and gemcitabine plus concomitant chemoradiotherapy with docetaxel and carboplatin for unresectable stage III non-small cell lung cancer patients</td>
<td>80 patients</td>
</tr>
<tr>
<td>Garrido 2005 (abstract) (90)</td>
<td>Phase II randomized study of paclitaxel, carboplatin, and radiotherapy with or without paclitaxel and carboplatin in patients with stage II or III unresectable NSCLC. Projected accrual: 390 patients</td>
<td>390 patients.</td>
</tr>
<tr>
<td>TROG 03.07</td>
<td>Randomised phase II trial of chemoradiotherapy in patients with localised lung cancer</td>
<td>288 patients.</td>
</tr>
</tbody>
</table>

Closed trials (not yet reported)

<table>
<thead>
<tr>
<th>Title and details of trial</th>
<th>Projected accrual:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fairlamb, 2003 (95) (abstract) The Big Lung Trial (BLT). Radical radiotherapy with or without chemotherapy in patients with NSCLC. Chemotherapy could be given before or after radiotherapy. Acceptable chemotherapy regimens included: cisplatin-vindesine, mitomycin-ifosfamide-cisplatin, mitomycin-vinblastine-cisplatin, or vinorelbine-cisplatin</td>
<td>288 radical radiotherapy patients.</td>
</tr>
<tr>
<td>FRE-GERCOR-B00-1 Phase III randomized study of paclitaxel, carboplatin, and radiotherapy with or without adjuvant paclitaxel and carboplatin in patients with stage II or III unresectable NSCLC. Projected accrual: 390 patients</td>
<td>390 patients.</td>
</tr>
<tr>
<td>HOG-LUN91-1 Phase III randomized study of definitive radiotherapy with versus without hydroxyurea following cisplatin/vinblastine induction therapy for previously untreated stage I/II/III/IIIB unresectable NSCLC. Projected accrual: 140 patients</td>
<td>140 patients.</td>
</tr>
<tr>
<td>MDA 99303 NCI-T99-0046 RTOG 02-70 Lu, 2005 (94) (abstract) Phase III Randomized Study of Induction Platinum-Based Chemotherapy and Radiotherapy With or Without AE-941 (Neovastat) in Patients With Unresectable Stage IIIA or IIIB Non-Small Cell Lung Cancer Projected accrual: 756 patients.</td>
<td>756 patients.</td>
</tr>
<tr>
<td>RTOG-9701 Phase III randomized study of radiation therapy alone versus concurrent chemotherapy (carboplatin-etoposide) plus radiation therapy for poor-risk stage III NSCLC. Projected accrual: 316 patients.</td>
<td>316 patients.</td>
</tr>
</tbody>
</table>

NCI – National Cancer Institute, NSCLC – non-small cell lung cancer.
Evidence-based Series #7-3 Version 2.2005: Section 3

Management of Unresected Stage III Non-Small Cell Lung Cancer: Guideline Development and External Review - Methods and Results

G. Okawara, J.A. Mackay, W.K. Evans, Y.C. Ung, and the Lung Cancer Disease Site Group

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

The 2005 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.


THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, called Disease Site Groups (DSGs) and Guideline Development Groups (GDGs), mandated to develop the PEBC products. These panels are comprised of clinicians, other health care providers, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based practice guideline reports, using the methods of the Practice Guidelines Development Cycle (1,2). The PEBC reports consist of a comprehensive systematic review of the clinical evidence on a specific cancer care topic, an interpretation of and consensus agreement on that evidence by our DSGs and GDGs, the resulting clinical recommendations, and an external review by Ontario clinicians in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each clinical practice guideline report, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original clinical practice guideline information.

The Evidence-based Series: A New Look to the PEBC Practice Guidelines
Each Evidence-based Series is comprised of three sections.
Section 1: Clinical Practice Guideline. This section contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the DSG or GDG involved and a formalized external review by Ontario practitioners.

Section 2: Systematic Review. This section presents the comprehensive systematic review of the clinical and scientific research on the topic and the conclusions reached by the DSG or GDG.

Section 3: Guideline Development and External Review: Methods and Results. This section summarizes the guideline development process and the results of the formal external review by Ontario practitioners of the draft version of the clinical practice guideline and systematic review.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES

Development and Internal Review

This evidence-based series was developed by the Lung DSG of CCO’s PEBC. The series is a convenient and up-to-date source of the best available evidence on the management of unresected stage III NSCLC developed through systematic review, evidence synthesis, and input from practitioners in Ontario.

This practice guideline was discussed at Lung DSG meetings in 2003 and 2004. Much of the discussion centred on those patients suitable for aggressive chemoradiotherapy. Although a full publication of the Radiation Therapy Oncology Group (RTOG) 9410 phase III study is not yet available, the most recent update of that trial was reported in abstract form at the 2003 ASCO meeting (3,4). The results showed a statistically significant survival advantage for concurrent over sequential chemoradiotherapy and were consistent with the data from two other trials, one published phase III trial (5) and one published randomized phase II trial (6). The DSG members agreed that a recommendation for concurrent treatment should be made.

The role of induction or consolidation chemotherapy, in combination with concurrent chemoradiation, was discussed by the DSG, and the contrasting results of two trials were noted. One trial observed a trend towards a survival benefit for immediate concurrent chemoradiation followed by consolidation chemotherapy compared with induction chemotherapy followed by concurrent chemoradiation (7), and the other trial detected no statistical difference in survival for chemoradiation with or without induction chemotherapy (8,9). An informal poll of DSG members in 2003 indicated that most Ontario cancer centres have already adopted a treatment scheme of early concurrent chemoradiation without induction chemotherapy; however, the group felt that the conflicting evidence did not allow a firm recommendation to be made regarding the use of induction or consolidation chemotherapy.

While most of the studies provided aggressive treatment to a patient population with good PS (ECOG 0-1) and limited weight loss (typically defined as <5% in the preceding three months), it was pointed out that some trials included patients with a weight loss of up to 10%. For those less fit patients, the DSG felt that it was reasonable to consider concurrent or sequential therapy, depending upon other patient factors and following, as always, a full discussion with the patient of the treatment options, goals of therapy, and potential adverse effects. For symptomatic patients with poor PS or significant weight loss, standard radiation alone offers the potential for symptomatic relief. However, the DSG agreed that single-fraction radiation of 10 Gy should not be considered a standard approach given the decreased survival and QOL observed in comparison with a multifractionated regimen in one trial (10). The DSG emphasized the importance of adequate PS assessment when evaluating treatment options.

External Review by Ontario Clinicians

Following review and discussion of sections 1 and 2 of this evidence-based series, the Lung DSG circulated the clinical practice guideline and systematic review to clinicians in Ontario for review and feedback. Box 1 summarizes the draft clinical recommendations and supporting evidence developed by the panel.

BOX 1:
DRAFT RECOMMENDATIONS (approved for external review July 14, 2004)

Target Population

These recommendations apply to adult patients with unresected, clinical or pathological, stage III NSCLC. Unresected disease is defined as tumours that, for either technical or medical reasons, cannot be completely resected or removed.

Recommendation

DEVELOPMENT & METHODS – page 43
For patients with good PS (ECOG 0-1) and minimal weight loss (usually defined as <5% in the preceding three months):
- Chemoradiation improves survival compared with radiotherapy alone and concurrent chemoradiation is recommended, with cisplatin-based chemotherapy and thoracic radiation of at least 60 Gy in 30 fractions given over a six-week period.
- Insufficient evidence exists to recommend a specific cisplatin-based regimen for use in a concurrent chemoradiation schedule. However, in the opinion of the Lung DSG, the regimens frequently used in Ontario, cisplatin-etoposide or cisplatin-vinorelbine, are reasonable options.

For symptomatic patients with poor PS (ECOG >1) and significant weight loss (usually defined as >10% in the preceding three months):
- Radiotherapy for symptom palliation is recommended.
- Insufficient evidence exists to determine the optimal dose or timing of radiotherapy when the goal of therapy is symptom palliation. Reasonable treatment options include 20 Gy in five fractions and 17 Gy in two fractions given one week apart. Radiotherapy administered in a single fraction of 10 Gy is not recommended based on the decreased survival and QOL observed when compared with multifractionated radiotherapy in one Canadian trial. However, single fractions of radiotherapy less than 10 Gy may be appropriate in some circumstances.
- Palliative chemotherapy for patients with stage III disease is not reviewed in this guideline. For guidelines on palliative chemotherapy for locally advanced (stage IIIb) or metastatic (stage IV) disease, please visit the Cancer Care Ontario Web site.

For patients with borderline PS or moderate weight loss (5-10%):  
- Concurrent or sequential chemoradiation is an option though the quality and quantity of evidence is not as compelling as that for patients with good PS and minimal weight loss.

Hyperfractionated radiation is not recommended outside the context of a clinical trial (see Related Guidelines section below).

**Qualifying Statements**
- Where single fraction radiation is used for symptom palliation, treatment volume and critical structures in the radiation field, such as the spinal cord, need to be given careful consideration in order to minimize potential toxicities.
- Insufficient evidence exists to recommend for or against the use of chemotherapy as an induction treatment before chemoradiation or consolidation treatment after chemoradiation.
- Increased toxicity, particularly esophagitis and hematologic events, is associated with the addition of chemotherapy to radiotherapy. The results of one randomized phase II trial comparing three different cisplatin-based doublets combined with concurrent radiotherapy suggest that these toxicities occur more frequently with gemcitabine-cisplatin compared with paclitaxel-cisplatin or vinorelbine-cisplatin.
- The patient and physician should have a full discussion of the benefits, limitations, and toxicities of therapy.

**Methods**
Practitioner feedback was obtained through a mailed survey of 121 practitioners in Ontario, including 22 radiation oncologists, 36 medical oncologists, 27 surgeons, 33 respirologists, one hematologist, one pathologist, and one practitioner from nuclear medicine. In addition, the guideline and practitioner survey was mailed out to 150 family physicians, randomly selected from a database of approximately 1000 members, to gauge their interest in the current guideline documents and to determine if they would like to participate in the practitioner feedback process in the future. The survey consisted of items evaluating the method, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations above should be approved as a practice guideline. Written comments were invited. The practitioner feedback survey was mailed out on July 14, 2004. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Lung DSG reviewed the results of the survey.
Results

Fifty-three responses were received out of the 121 surveys sent (44% response rate). Responses include returned completed surveys as well as phone, fax, and email responses. Of the practitioners who responded, 42 indicated that the report was relevant to their clinical practice, and they completed the survey. Key results of the practitioner feedback survey are summarized in Table 9.

Table 9. Practitioner responses to eight items on the practitioner feedback survey.

<table>
<thead>
<tr>
<th>Item</th>
<th>Strongly agree or agree</th>
<th>Neither agree nor disagree</th>
<th>Strongly disagree or disagree</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>40 (95%)</td>
<td>2 (5%)</td>
<td>0</td>
</tr>
<tr>
<td>There is a need for a clinical practice guideline on this topic.</td>
<td>38 (90%)</td>
<td>4 (10%)</td>
<td>0</td>
</tr>
<tr>
<td>The literature search is relevant and complete.</td>
<td>34 (81%)</td>
<td>7 (17%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>The results of the trials described in the report are interpreted according to my understanding of the data.</td>
<td>36 (86%)</td>
<td>6 (14%)</td>
<td>0</td>
</tr>
<tr>
<td>The draft recommendations in this report are clear.</td>
<td>38 (90%)</td>
<td>3 (7%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>I agree with the draft recommendations as stated.</td>
<td>37 (88%)</td>
<td>3 (7%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>This report should be approved as a practice guideline.</td>
<td>38 (90%)</td>
<td>2 (5%)</td>
<td>2 (5%)</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>40 (95%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>

a Due to rounding, percentages may not total 100%.
b One respondent did not answer this question.

Summary of Written Comments

Seven respondents (17%) provided written comments, the main points of which are summarized below.

Radiotherapy

Two practitioners questioned why the 17 Gy / two-fraction schedule was considered a reasonable treatment option for symptom palliation but the 39 Gy / 13-fraction schedule was not, given that a survival advantage was observed with the latter schedule in the MRC study involving patients with a good PS (11). In addition, one respondent suggested that Bezjak et al detected no difference in any outcome between a 10 Gy / single fraction radiation schedule and a 20 Gy / five-fraction schedule in a subgroup of patients with PS >1 (10). As a result, the respondent questioned the recommendation against the use of 10 Gy / single-fraction radiation for symptom palliation in patients with a poor PS.

Chemoradiation

One practitioner questioned the appropriate dose of vinorelbine-cisplatin for a concurrent chemoradiation treatment approach and suggested that concurrent chemoradiation should be started on day one of treatment because the evidence supports a recommendation against the use of induction chemotherapy. The same practitioner suggested that it is standard practice to use cisplatin-etoposide as consolidation after chemoradiation and requested clarification on the role of docetaxel in this setting. Another practitioner suggested that the modest survival advantage observed with concurrent chemoradiation may be offset by the increased toxicity associated with that treatment, resulting in lower quality-adjusted survival.

General

Two practitioners described the recommendations as well researched and clearly explained, and one indicated that the recommendations represented their current practice. However, one respondent felt that the report was difficult to read for non-oncologists and suggested that more graphics would be useful (e.g., meta-analysis plot), alternative analyses could be employed (e.g., cluster analysis), and a more objective measure of PS than the ECOG classification is required given the importance of PS to the recommendations.

Modifications/Actions

The Lung DSG discussed the issues described above and responded as follows:
Radiotherapy

Following further discussion on the use of radiotherapy for symptom palliation, the Lung DSG decided not to revise the recommendations. Although the 1996 MRC trial reported a small, statistically significant survival advantage for 39 Gy in 13 fractions over 17 Gy in two fractions, the study was limited to patients with a good PS (11). The currently recommended treatment for patients with a good PS is combined modality therapy with radical radiation and chemotherapy; therefore, the results of that study of radiotherapy alone are less relevant today. If a patient refuses combined modality treatment, treatment with radiation alone using 39 Gy in 13 fractions may be an alternative, although this is not a fractionation scheme in general use in Canada.

Subgroup analyses in the trial by Bezjak et al were reported only for survival and did suggest that the benefit for multifractionated (20 Gy) compared with single fraction (10 Gy) radiation was confined to patients with a good PS (10). However, the study did not intentionally seek to answer this question (the subgroup analyses were not pre-planned) and was likely underpowered to do so. In addition, overall, the five-fraction regimen was associated with greater improvements in several QOL measures. Therefore, the recommendation against the use of a single 10 Gy fraction for symptom palliation in patients with poor PS was retained. However, the Lung DSG agreed that, although evidence is lacking, the use of single fractions of less than 10 Gy may be appropriate for patients with limited treatment options.

Chemoradiation

The DSG acknowledged that guidance on appropriate chemotherapy doses and schedules for a concurrent regimen would be helpful. They agreed that cisplatin combined with one of etoposide (12-14), vinorelbine (6,15), or vinblastine (3,4) have achieved reasonable survival in clinical trials and would be acceptable treatment combinations. There is insufficient evidence to recommend specific chemotherapy doses and schedules at this time; however, the DSG recognize that toxicity is a concern when full-dose vinorelbine combined with cisplatin is administered with concurrent radiation and recommend that, in this setting, a lower dose of vinorelbine should be used. In a phase I dose-escalation trial, higher rates of severe myelosuppression and esophagitis were observed with standard doses of vinorelbine (20-25mg/m² weekly) and cisplatin (100mg/m² every three weeks) compared with lower doses of each agent (vinorelbine, 15mg/m² days 1 and 8; and cisplatin, 80mg/m² day 1, every three weeks) combined with concurrent radiotherapy (16). In addition, trials involving this treatment combination have used a lower dose of vinorelbine (12.5mg/m² three out of four weeks or 15 mg/m² two out of three weeks) during the radiation phase of the trial (6,15). The Lung DSG also acknowledged that it is common practice in Ontario to administer radiotherapy concurrently with chemotherapy as early as possible in the treatment cycle and, although the evidence is currently limited, they agreed to acknowledge this in the guideline Qualifying Statements. The promising results of a recent phase II trial using consolidation docetaxel following concurrent chemoradiation in patients with stage IIIIB disease were noted (17); however, the Lung DSG felt that insufficient evidence exists to make a recommendation for or against the use of consolidation chemotherapy at this time. If clinicians choose to administer consolidation chemotherapy, the Lung DSG felt that, in line with recent randomized trials, two or three cycles of consolidation chemotherapy could be administered (7,12,18).

Although concurrent chemoradiation is generally more toxic than sequential treatment; the available QOL data are limited and the DSG felt that the primary outcome of interest in radically treated patients is survival. The DSG emphasized in the guideline Qualifying Statements that, during initial patient/physician consultations, toxicity should always be discussed and, if felt to be unacceptable by the patient, sequential chemoradiation may be an alternative treatment option recognizing that survival benefits are inferior to concurrent therapy.

General

The Lung DSG acknowledged that the guideline report is primarily intended for physicians likely to use chemotherapy or radiotherapy in the treatment of patients with unresected stage III NSCLC and, as such, may not meet the needs of non-oncologists. The PEBC is exploring alternative formats for guidelines to address this issue. Although the comments regarding statistical analysis and associated graphics were of interest, the Lung DSG felt that these were not appropriate for this guideline, particularly given the diversity of the treatment regimens used in the trials reviewed. The Lung DSG acknowledged that PS measurement is subject to some limitations; however, the ECOG scale is currently one of the most widely used PS measures in North America and the DSG is limited to the data reported in the published research.
Family Physicians

From the sample of 150 family physicians invited to provide feedback on the guideline, 11 responded (7%), and three indicated that the guideline was relevant to their clinical practice. With the exception of one missing response, two physicians agreed or strongly agreed with all statements in Table 9, indicating that they would be very likely to make use of the guideline in their practice. The other physician agreed or neither agreed nor disagreed with the statements in Table 9 and was unsure if they would make use of the guideline in their practice. None of the three responding family physicians provided additional comments on the guideline.

Practice Guidelines Coordinating Committee Approval Process

Following completion of the practitioner feedback process, the literature search was updated and the new evidence was consistent with the guideline recommendations. The revised guideline was circulated to 13 members of the PGCC for review and approval. Nine members of the Committee returned ballots. One member is a co-chair of the Lung DSG and was therefore not eligible to comment on the document. Six PGCC members approved the practice guideline report as written. One member requested clarification on whether a "wait and see" strategy for palliative radiation alone, as described in the Choice of Topic and Rationale section of the guideline, is a policy for any organization. In addition, one member commented that radiotherapy may be delayed at centres where radiation services are limited and concurrent chemoradiation may then be difficult to implement, and one member expected that fatigue, which is frequently associated with chemotherapy administration, would also be a common toxicity with chemoradiation.

Modifications/Actions

A "wait and see" strategy for palliative radiation, which is equivalent to delaying administration of radiotherapy until a patient becomes symptomatic, was described as a policy option in two trials of palliative radiation (19,20). However, as indicated in Appendix A of Section 2, few organizations provide treatment recommendations for patients with asymptomatic stage III NSCLC that is not suitable for chemoradiation or radical radiotherapy; therefore, the Topic and Rationale section of the guideline was revised accordingly. With regard to the impact of radiation delays on the implementation of a concurrent chemoradiation treatment approach, the DSG did consider the practical implications of this treatment approach but believe that the evidence to date supports the concurrent treatment option. Finally, although fatigue is a common adverse effect of chemotherapy, it is rarely reported in clinical trials of chemoradiation. In the few trials reporting that data, the incidence of fatigue was similar for radiation alone and chemoradiation (21,22).

Policy Review

Alone or in combination with cisplatin, palliative vinorelbine is currently available for the treatment of advanced NSCLC and funded for this indication through Cancer Care Ontario’s New Drug Funding Program. Vinorelbine-cisplatin has been shown to improve survival when administered as adjuvant therapy for patients with completely resected stage IB or II NSCLC and Cancer Care Ontario has recommended that this new indication for vinorelbine be funded by the provincial government. The current guideline recommends the use of cisplatin combined with one of etoposide, vinorelbine, or vinblastine, and concurrent radiotherapy in selected patients with unresected NSCLC treated with curative intent. Reimbursement for vinorelbine should be extended to encompass this new indication.

RELATED PRINT AND ELECTRONIC PUBLICATIONS


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Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca
REFERENCES


Evidence-based Series #7-3 Version 2.2005: Section 4

Management of Unresected Stage III Non-Small Cell Lung Cancer: Guideline Development and External Review - Methods and Results

Members of the Lung Cancer Disease Site Group

Review Date: May 6, 2012

OVERVIEW

The original version of this guidance document was released by Cancer Care Ontario’s Program in Evidence-based Care in 1997, and rewritten in 2005.

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 reviewed and interpreted the new eligible evidence and proposed the existing recommendations could be endorsed. The Lung Cancer Disease Site Group (DSG) decided to update the recommendations found in Section 1 (Clinical Practice Guideline) in April 2012.

DOCUMENT ASSESSMENT AND REVIEW RESULTS

Question Considered

1. What is the role of different schedules or doses of radiotherapy as a treatment in patients with unresected stage III non-small cell lung cancer?
2. Does chemotherapy combined with radiotherapy improve survival compared with radiotherapy alone in patients with unresected stage III non-small cell lung cancer?
3. Which sequence of radiotherapy combined with chemotherapy is most effective in improving survival for patients with unresected stage III non-small cell lung cancer?
4. Which chemotherapy regimen(s), combined with radiotherapy, is most effective in improving survival for patients with unresected stage III non-small cell lung cancer?

Literature Search and New Evidence

The new search December 2005 to September 2012) yielded 21 references representing 1 meta-analysis, and 15 RCTs (5 RCTs had 2 publications each), evaluating the management of unresected stage III non-small cell lung cancer. Ten of these references had full text publications and 11 were in abstract form. There was one ongoing studies identified from clinicaltrials.gov. Brief results of these searches are shown in the Document Review Tool.

Impact on Guidelines and Its Recommendations

The new data supports existing recommendations. However, the Lung Cancer DSG felt the guideline was outdated. Thus, they agreed to UPDATE the 2005 recommendations on the management of unresected stage III non-small cell lung cancer in April 2013.
Original Question(s):

5. What is the role of different schedules or doses of radiotherapy as a treatment in patients with unresected stage III non-small cell lung cancer?

6. Does chemotherapy combined with radiotherapy improve survival compared with radiotherapy alone in patients with unresected stage III non-small cell lung cancer?

7. Which sequence of radiotherapy combined with chemotherapy is most effective in improving survival for patients with unresected stage III non-small cell lung cancer?

8. Which chemotherapy regimen(s), combined with radiotherapy, is most effective in improving survival for patients with unresected stage III non-small cell lung cancer?

Target Population:
Adult patients with unresected, clinical or pathological, stage III non-small cell lung cancer. Unresected disease is defined as a tumour that, for either technical or medical reasons, cannot be completely resected or removed.

Study Section Criteria:

Inclusion Criteria
fully published reports or abstract of meta-analyses or randomized trials (phase II or III) comparing the following in patients with unresectable stage III NSCLC:

1. Different schedules or doses of radiotherapy as a single modality treatment; or
2. Radiotherapy alone versus the same radiotherapy regimen combined with chemotherapy; or
3. Different chemoradiation regimens that differ only in the radiation regimen used; or
4. Different chemoradiation regimens that differ only in the chemotherapy regimen used; or
5. Timing of radiotherapy and chemotherapy administration within a chemoradiation treatment approach.

Exclusion Criteria
The following were not considered:

1. Trials evaluating any of the following treatment options or comparisons: older radiotherapy equipment (e.g., equipment that antedated Cobalt-60), 3D conformal radiotherapy, bronchial artery
infusion chemotherapy, split-course radiotherapy when compared with another radiotherapy schedule or conventional compared with altered fractionation radiotherapy.

2. Trials randomizing only patients that had responded to, or did not progress on, induction chemotherapy.

3. Trials that did not report the required outcomes by treatment group. For trials with palliative intent, required outcomes included symptom control or QOL; for other trials, survival data were required.

4. Letters and editorials reporting trial data.

5. Papers published in a language other than English.

Search Details:
- December 2005 to September 2012 (Medline September wk 3 and Embase wk 39)
- January 2009 to September 2012 (ASCO Annual Meeting)
- December 2005 to September 2012 (clinicaltrials.gov)

Brief Summary/Discussion of New Evidence:
Of 315 total hits from Medline, Embase + 10 total hits from ASCO + 48 total hits from clinicaltrials.gov, 21 references representing 1 meta-analysis, and 15 RCTs (5 RCTs had 2 publications each), were found evaluating the management of unresected stage III non-small cell lung cancer. Ten of these references had full text publications and 11 were in abstract form. There was one ongoing studies identified from clinicaltrials.gov.

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Population</th>
<th>N of studies</th>
<th>Outcomes</th>
<th>Brief results</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-conventional Radiotherapy Vs.</td>
<td>Patients with locally advanced, inoperable NSCLC</td>
<td>13 RCTs</td>
<td>OS</td>
<td>• The non-conventional radiotherapy group significantly improved the objective response rate (OR 1.68, 95% confidence intervals (CI) 1.19-2.37) and overall survival of up to 1-year (OR 1.30, 95% CI 1.09-1.54), 2-year (OR 1.41, 95% CI 1.17-1.70), 3-year (OR 1.55, 95% CI 1.24-1.94), 4-year (OR 1.60, 95% CI 1.20-2.15), 5-year (OR 1.63, 95% CI 1.11-2.38); and local control rate in 1-year (OR 1.35, 95% CI 1.09-1.68), 2-year (OR 1.57, 95% CI 1.23-1.99), 3-year (OR 1.45, 95% CI 1.10-1.91) compared with the conventional radiotherapy group. • With regard to the side effects, non-conventional radiotherapy was more likely to result in level III and IV radioactive esophagitis (OR 1.64, 95% CI 1.09-2.46), but there was no significant difference in the incidence of radioactive pneumonitis (OR 0.96, 95% CI 0.67-1.39). • In the subgroup analysis, late course accelerated hyperfractionated radiotherapy (LCHRT) improved 1-year OS (OR 2.29, 95% CI 1.29-4.06), 2-year OS (OR 4.22, 95% CI 2.03-8.77), 3-year OS (OR 2.49, 95% CI 1.24-5.02) and Objective response rate (OR 2.38, 95% CI 1.17-4.83). • However, hyperfractionated radiotherapy (HRT)</td>
<td>Zhang et al, 2011</td>
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</table>
and accelerated hyperfractionated radiotherapy (AHRT) could not improve 1-, 2-, 3-year OS or OR compared with conventional fractionation radiotherapy.

## Randomized control trials

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Population</th>
<th>Follow up</th>
<th>Outcomes</th>
<th>Brief results</th>
<th>References</th>
</tr>
</thead>
</table>
| Chemoradiotherapy (60 Gy + concurrent low-dose carboplatin) vs. Radiotherapy alone | Patients older than 70 years with unresectable stage III NSCLC, Median age, 77yrs (n=200) | Median, 19.4 months | P: OS | • Median OS for the chemoradiotherapy and radiotherapy alone groups were 22.4 months (95% CI 16.5-33.6) and 16.9 months (13.4-20.3), respectively (hazard ratio 0.68, 95.4% CI 0.47-0.98, stratified log-rank test one-sided p value=0.0179).  
• More patients had grade 3-4 haematological toxic effects in the chemoradiotherapy group than in the radiotherapy alone group, including leucopenia (61 [63.5%] vs none), neutropenia (55 [57.3%] vs none), and thrombocytopenia (28 [29.2%] vs two [2.0%]).  
• Grade 3 infection was more common with chemoradiotherapy (12 patients [12.5%]) than with radiotherapy (four patients [4.1%]).  
• Incidences of grade 3-4 pneumonitis and late lung toxicity were similar between groups.  
• There were 7 treatment-related deaths: three of 100 patients (3.0%) in the chemoradiotherapy group and four of 100 (4.0%) in the radiotherapy group. | Atagi et al, 2012 & Atagi et al, 2011 (Abstract) |
| Radiation therapy (RT) alone vs. Radiochemotherapy (RT-CHT) | Patients with locally advanced, inoperable NSCLC having favourable prognosis (Stage IIIA, KPS 70-100, no weight loss > 5%) | NR | OS, LPFS, DMFS, Toxicity | • The median times and 5-year OS, LPFS and the DMFS rates for all 222 patients were 33 months, 31 months and not attained yet, respectively and 36%, 43% and 57%, respectively.  
• RT-CHT was superior to RT alone in terms of both OS (MST, 38 vs 21 months, respectively; 5-yr, 41% vs 16%, respectively; p<0.001) and LPFS (MTLP, 38 vs 22 months, respectively, 5yr LPFS, 48% vs 23%, respectively; p<0.001), but not the DMFS.  
• The most frequent acute high-grade (>3) toxicity was esophageal and bronchopulmonary (8% each) and the most frequent late high-grade toxicity was esophageal (6%).  
• RT-CHT caused only significantly more haematological high-grade toxicity. | Jeremic et al, 2012 (Abstract) |
| Chemotherapy + | Patients with NR | Survival | The median of control time was 16 months | Dzhugashvili |
Radiotherapy alone vs. Chemoradiotherapy

### Radiotherapy alone vs. Chemoradiotherapy

<table>
<thead>
<tr>
<th>Inoperable Locoregionally Advanced NSCLC (Stage IIIb 80%, IIIa 20%)</th>
<th>Median age, 62yrs (n=60)</th>
<th>Probabilities at 5 years (range: 1.2 - 64).</th>
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<tbody>
<tr>
<td>- The overall survival rate in the palliative treatment regime group was 3.6% and in the curative treatment regime group 28.6%.</td>
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<td>- The maximum control time in the palliative treatment group was 6 months.</td>
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</table>

### Radiotherapy alone vs. Palliative Radiotherapy alone

<table>
<thead>
<tr>
<th>Patients with Unresectable Stage III &amp; B NSCLC</th>
<th>Median, 13.6 months P: OS S: TTP, response, Toxicity</th>
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<tbody>
<tr>
<td>- Toxicities during the induction phase were mild.</td>
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<tr>
<td>- During radiotherapy, overall toxicity rates were not significantly different between the two arms.</td>
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<tr>
<td>- Median survival times in the radiotherapy group and chemoradiotherapy group were 14.1 months (95% CI, 11.8 to 16.3 months) and 18.7 months (95% CI, 14.1 to 23.3 months; difference not statistically significant, P = .091).</td>
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<tr>
<td>- Median TTP significantly favored simultaneous chemoradiotherapy (11.5 months; 95% CI, 8.3 to 14.7 months) versus radiotherapy alone (6.3 months; 95% CI, 5.0 to 7.6 months; P &lt; .001, log-rank test).</td>
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</table>

### Chemoradiation regimens involving different chemotherapies

<table>
<thead>
<tr>
<th>Paclitaxel/carboplatin (PC) + 60 Gy of TRT vs. Cisplatin/etoposide (PE) + 60 Gy of TRT</th>
<th>Patients with unresectable stage III NSCLC, ECOG performance status ≤1; ≤10% weight loss in the 3 months before inclusion</th>
<th>Median, 46 months P: OS S: response and treatment-related toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>- The 3-year OS was significantly better in the PE arm than in the PC arm (33.1% vs. 13%, P = .04).</td>
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<tr>
<td>- The incidence of Grade 3/4 neutropenia was 78.1% in the PE arm and 51.5% in the PC arm (P = .05).</td>
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<tr>
<td>- The rate of Grade 2 or greater radiation pneumonitis was 25% in the PE arm and 48.5% in the PC arm (P = .09).</td>
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<table>
<thead>
<tr>
<th>Cisplatin+ Cetuximab + IMRT (CRT+Cet) vs. Cisplatin + IMRT (CRT)</th>
<th>Patients with inoperable locally advanced NSCLC</th>
<th>NR P: OS S: response and treatment-related toxicities</th>
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<tbody>
<tr>
<td>- Although generally well tolerated, 12% of patients were unable to complete protocol treatment.</td>
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<tr>
<td>- Grade ≥3 acute toxicities for the most common side effects of standard (CRT) versus experimental arm (CRT+Cet): Anorexia (6% vs 22%) and Dysphagia (15% vs 22%) and Fatigue (17% vs 18%).</td>
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<tr>
<td>- Acneiform rash (8%) and Pneumonia (10%) were encountered in the experimental arm only.</td>
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<tr>
<td>- Overall there were more patients experiencing grade ≥ 3 toxicities in the experimental arm.</td>
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</table>
### Development & Methods

#### Carboplatin + pemetrexed with TRT (70 Gy)(Arm A) Vs. Carboplatin, pemetrexed + cetuximab with TRT (70 Gy)(Arm B)

<table>
<thead>
<tr>
<th>Patients with unresectable stage IIIA &amp; B NSCLC, ECOG performance status ≤1</th>
<th>Median age, 66yrs (n=101)</th>
<th>Median, 32 months</th>
<th>P: OS S: Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>The 18-month OS rate was 58% (95% CI, 46% to 74%) in arm A and 54% (95% CI, 42% to 70%) in arm B.</td>
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<tr>
<td>No significant difference in OS between patients with squamous and nonsquamous NSCLC was observed (P= .667).</td>
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<td>The toxicities observed were consistent with toxicities associated with concurrent chemoradiotherapy.</td>
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<tr>
<td>The rates of observed grade 3 and 4 hematologic AEs were 42% and 28%, respectively, in arm A and 38% and 32%, respectively, in arm B.</td>
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<tr>
<td>No grade 5 hematologic AEs were observed in either arm.</td>
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#### MVP + TRT (Arm A) Vs. CBDDCA + Irinotecan + TRT (Arm B) Vs. CBDDCA + Paclitaxel + TRT (Arm C)

<table>
<thead>
<tr>
<th>Patients with unresectable stage III NSCLC, ECOG performance status ≤1</th>
<th>Median age, 62yrs (n=456)</th>
<th>Median, 3 years</th>
<th>P: OS S: PFS, Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>The median survival time and 5-year survival rates were 20.5, 19.8, and 22.0 months and 17.5%, 17.8%, and 19.8% in arms A, B, and C, respectively.</td>
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<tr>
<td>Although no significant differences in overall survival were apparent among the treatment arms, noninferiority of the experimental arms was not achieved.</td>
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<tr>
<td>The incidences of grade 3 to 4 neutropenia, febrile neutropenia, and gastrointestinal disorder were significantly higher in arm A than in arm B or C (P &lt;.001).</td>
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<tr>
<td>Chemotherapy interruptions were more common in arm B than in arm A or C.</td>
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</table>

#### Tegafur-uracil/cisplatin (UP) + 60 Gy of TRT Vs. Vinorelbine / Cisplatin (VC) + 60 Gy of TRT

<table>
<thead>
<tr>
<th>Patients with locally advanced unresectable stage III NSCLC</th>
<th>Median age, 62yrs (n=66)</th>
<th>Median, 11.8 months</th>
<th>P: ORR S: PFS, OS, and toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORRs were 80% (95%CI: 67-93) and 71% (95%CI: 55-87) for the UP arm and the VC arm, respectively.</td>
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<tr>
<td>Median PFS in the UP arm was 7.9 months and in the VC arm was 5.9 months.</td>
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<tr>
<td>Grade 3/4 neutropenia occurred in 20% and 58% of pts in the arms UP and VC, respectively.</td>
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<tr>
<td>There was no remarkable difference in other toxicities between both arms.</td>
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</table>

Authors: Govindan et al, 2011 & Govindan et al, 2010 (abstract)
Two pts in the VC arm died of radiation pneumonitis.

<table>
<thead>
<tr>
<th>Treatment 1</th>
<th>Treatment 2</th>
<th>Patients with inoperable stage IIIA/B NSCLC Median age, NR (n=71)</th>
<th>NR</th>
<th>P: 2-yr OS S: RR, TTP, Median survival and Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pemetrexed/ carboplatin (PCb) + CRT</td>
<td>Vs.</td>
<td>Pemetrexed/ Cisplatin (PC) + CRT</td>
<td>NR</td>
<td>This is an interim update of the study</td>
</tr>
<tr>
<td></td>
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<td>Average dose compliance was PCb: 92.2% P, 90.2% Cb; PC: 90.4% P, 89.2% C.</td>
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<tr>
<td></td>
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<td>Average dose compliance for CRT was PCb: 91.2%, PC: 85.5%.</td>
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<td>Dose interruptions occurred with 23 pts.</td>
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<td>The PCb arm had 15 pts evaluable for response: CR, 1 (6.7%); PR, 6 (40.0%); SD, 7 (46.7%) and PD, 1 (6.7%).</td>
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<tr>
<td></td>
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<td></td>
<td>The PC arm had 20 evaluable pts: CR, 1 (5.0%); PR, 11 (55.0%), SD, 5 (25.0%) and PD, 3 (15.0%).</td>
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<td></td>
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<td>Choy et al, 2010 (Abstract)</td>
</tr>
</tbody>
</table>

**Chemoradiation sequencing**

<table>
<thead>
<tr>
<th>Accelerated radical radiotherapy + Concurrent (con) Cisplatinum and Vinorelbine</th>
<th>Patients with unresectable stage III NSCLC Median age, 62yrs (n=130)</th>
<th>Median, 31 months</th>
<th>OS, Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td>This is a feasibility study</td>
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<td>Compliance: median chemo cycles three (con) vs four (seq).</td>
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<td>Dose delays 53% con vs 60% seq.</td>
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<td></td>
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<td>Toxicity: treatment related deaths - two con vs one seq; deaths within 6 months of starting treatment - three con vs two seq.</td>
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<td></td>
<td>SAEs - 46% con vs 47% seq. CTC grade 3 oesophagitis - six con vs one seq, Grade 4 oesophagitis did not occur.</td>
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<tr>
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<td></td>
<td>Survival: deaths 52.2% con vs 68.3% seq; median survival (months) - 27.4 con vs 18.6 seq; 2 year survival 54% con vs 42% seq. 3 year survival 38% con vs 27% seq</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Maguire et al, 2011 (Abstract)</td>
</tr>
</tbody>
</table>

**Chemoradiotherapy alone (Arm A)**

<table>
<thead>
<tr>
<th>Induction Chemotherapy + Chemoradiotherapy (Arm B)</th>
<th>Patients with unresectable stage III NSCLC Median age, 63yrs (n=366)</th>
<th>Median, 38 months</th>
<th>P: effect of induction chemotherap y on overall survival as well as toxicity and pattern of failure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td>Grade 3 or 4 toxicities during induction chemotherapy on arm B consisted mainly of neutropenia (18% and 20%, respectively).</td>
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<td>During concurrent chemoradiotherapy, there was no difference in severity of in-field toxicities of esophagitis (grade 3 and 4 were, respectively, 30% and 2% for arm A v 28% and 8% for arm B) and dyspnea (grade 3 and 4 were, respectively, 11% and 3% for arm A v 15% and 4% for arm B).</td>
</tr>
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<td>Survival differences were not statistically significant (P = .3), with a median survival on arm A of 12 months (95% CI, 10 to 16 months) versus 14 months (95% CI, 11 to 16 months) on</td>
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<tr>
<td></td>
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<td>Vokes et al, 2007</td>
</tr>
</tbody>
</table>
arm B and a 2-year survival of 29% (95% CI, 22% to 35%) and 31% (95% CI, 25% to 38%).

- Age, weight loss before therapy, and performance status were statistically significant predictive factors.

<table>
<thead>
<tr>
<th>Radiotherapy alone (grp A)</th>
<th>Patients with unresectable stage III NSCLC</th>
<th>Mean, 2 years</th>
<th>Initial treatment responses, Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vs. Sequential chemoradiotherapy (grp B)</td>
<td>Median age, 58yrs (n=103)</td>
<td></td>
<td></td>
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<tr>
<td>Vs. Concurrent chemoradiotherapy (grp C)</td>
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</tbody>
</table>

- Initial treatment responses were significantly higher in group ‘B’ (P<0.05) and ‘C’ (P<0.03), compared to group ‘A’.
- Follow-up observations showed that addition of chemotherapy brought down distant metastases from 62.5% (group ‘A’) to 48.6% (group ‘B’) and 44.4% (group ‘C’).
- The median time to tumour progression also improved from 16 months (Group ‘A’) to 21 months (Group ‘B’ and ‘C’).
- 2 year follow up did not show any survival benefit.
- Acute toxicities were more frequent in group ‘B’ and ‘C’, but were manageable.

<table>
<thead>
<tr>
<th>Elective nodal irradiation (ENI)</th>
<th>Patients with unresectable stage IIIA &amp; B NSCLC</th>
<th>Median, 27 months</th>
<th>P: local control rates S: Toxicity, Response rate, OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vs. Involved-field irradiation (IFI)</td>
<td>Median age, 63yrs (n=200)</td>
<td></td>
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</tr>
</tbody>
</table>

- Patients in the IFI arm achieved better overall response rate (90% vs. 79%, P=0.032) and better 5-years local control rate (51% vs. 36%, P = 0.032) than those in the ENI arm.
- The radiation pneumonitis rate in patients with IFI was lower than in patients with ENI (17% vs. 29%, P = 0.044), and similar trends appeared in the radiation esophagitis, myelosuppression, and radiation pericarditis between 2 study arms, although not significantly.
- The 1-, 2-, and 5-year survival rates were 60.4%, 25.6%, and 18.3% for the ENI arm and 69.9%, 39.4%, and 25.1% for the IFI arm, respectively.
- Only the 2-year survival rates were statistically significant (P = 0.048)

<table>
<thead>
<tr>
<th>Once-daily radiation therapy (qdRT)</th>
<th>Patients with unresectable stage IIIA &amp; B NSCLC</th>
<th>Min, 36 months</th>
<th>P: OS S: TTP, response, Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vs. HART</td>
<td>Age range, 40-77yrs (n=119)</td>
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</tbody>
</table>

- Median survival was 20.3 and 14.9 months for HART and qdRT, respectively (P=.28).
- Overall response was 25% and 22% for HART and qdRT, respectively (P=.69).
- Two- and 3-year survival was 44% and 34% for HART, and 24% and 14% for qdRT, respectively.
Grade ≥3 toxicities included esophagitis in 14 v 9 patients and pneumonitis in 0 v 6 patients for HART and qdRT, respectively.

Study was terminated early due to slow accrual

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Official title</th>
<th>Status</th>
<th>Protocol ID</th>
<th>Completion Date</th>
<th>Last updated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concomitant Radiochemotherapy - Radiotherapy 66 Gy, Cisplatin, and Docetaxel Vs. Concomitant Chemoradiotherapy - Radiotherapy 66 Gy, Cisplatin, and Docetaxel</td>
<td>A Phase III Randomised Study Comparing Concomitant Radiochemotherapy With Cisplatin and Docetaxel as Induction Versus Consolidation Treatment in Patients With Locally Advanced Unresectable Non-small Cell Lung Cancer.</td>
<td>Recruiting (N=246)</td>
<td>NCT00633568</td>
<td>December 2012</td>
<td>June 22, 2011</td>
</tr>
</tbody>
</table>

Abbreviations: OS=Overall survival; TRT=Thoracic radiotherapy; ECOG= Eastern Cooperative Oncology Group; MVP=Vindesine, Cisplatin, Mitomycin; CBDCA=Carboplatin AUC 2; TTP=Time to progression; LPFS= Local Progression-Free Survival; DMFS= Distant Metastasis-Free Survival; ORR= Overall Response Rate; PFS=Progression-Free Survival; CRT= Concurrent Radiation Therapy

Clinical Expert Interest Declaration:
No potential conflict of interest was declared by the clinical expert

Instructions. For each document, please respond YES or NO to all the questions below. Provide an explanation of each answer as necessary.

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? NO. Standard would be concurrent thoracic RT + cisplatinum based chemo.

2. On initial review,
   a. Does the newly identified evidence support the existing recommendations? a. YES
   b. Do the current recommendations cover all relevant subjects addressed by the evidence, such that no new recommendations are necessary? b. YES...except should acknowledge that standard is to offer RT to involved lymph nodes only (no prophylactic nodal radiation)

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 updating the guideline? Answer Yes or No, and explain if NO...the addition of cetuximab is still under evaluation, and should not be recommended at this point
necessary:

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?  

YES

Review Outcome | UPDATE
---|---

DSG/GDG Approval Date | 12 April, 2013

DSG/GDG Commentary | - Many of the comments addressed the original guideline and not the update.
- Comments were made about splitting the document since it is very large.
- Discussion about including altered fractionation in this guideline, although this would be problematic because this addressed in another guideline.
- The consensus was that this document would need to be updated next.

New References Identified (alphabetic order):


**Search strategy:**

Medline

1. meta-Analysis as topic.mp. [mp=ti, ab, ot, nm, hw, ps, rs, ui, sh, tn, dm, mf, dv, kw]
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 synthesis$ 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 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 search$).ab.
10. (selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
11. (study adj selection).ab.
12. 10 or 11
13. review.pt.
14. 12 and 13
15. exp randomized controlled trials as topic/ or exp clinical trials, phase III as topic/ or exp clinical trials, phase IV as topic/
16. (randomized controlled trial or clinical trial, phase III or clinical trial, phase IV).pt.
17. random allocation/ or double blind method/ or single blind method/
18. (randomi$ 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$.tw.
23. (clinic$ adj trial$1).tw.
24. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
25. placebos/
26. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
27. (allocated adj2 random).tw.
28. or/23-27
29. practice guidelines/
30. practice guideline?.tw.
31. practice guideline.pt.
32. or/29-31
33. 7 or 8 or 9 or 14 or 19 or 22 or 28 or 32
34. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.
35. 33 not 34
36. limit 35 to english
37. Animal/
38. Human/
39. 37 not 38
40. 36 not 39
41. exp lung neoplasms/
42. (cancer? or carcinoma? or neoplasms? or tumor?).tw.
43. non small cell lung.tw.
44. 42 and 43
45. 41 or 44
46. (radiotherapy or radiation or irradiation).tw.
47. (chemotherapy or chemoradiation).tw.
48. 46 or 47
49. 45 and 48
50. (inoperable$ or unresect$).tw.
51. 49 and 50
52. 40 and 51
54. 52 and 53

Embase
1. exp meta analysis/ or exp systematic review/
2. (meta analy$ or metanaaly$).tw.
3. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes? or quantitative overview).tw.
4. (systematic adj (review$ or overview$)).tw.
5. exp review/ or review.pt.
6. (systematic or selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
7. (study adj selection).ab.
8. 5 and (6 or 7)
9. or/1-4,8
10. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
11. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
12. exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/
13. randomization/ or single blind procedure/ or double blind procedure/
14. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
15. or/12-14
16. (phase II or phase 2).tw. or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/
17. 16 and random$.tw.
18. (clinic$ adj trial$1).tw.
19. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
20. placebo/
21. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
22. (allocated adj2 random).tw.
23. or/18-22
24. practice guidelines/
25. practice guideline?.tw.
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28. 9 or 10 or 11 or 15 or 17 or 23 or 27
29. (editorial or note or letter or erratum or short survey).pt. or letter/ or case study/
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42. (chemotherapy or chemoradiation).tw.
43. 41 or 42
44. 40 and 43
45. (inoperable$ or unresect$).tw.
46. 44 and 45
47. 35 and 46
48. (200547$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$).ew.
49. 47 and 48

ASCO Annual Meeting - searched http://www.ascopubs.org/search with keywords: Chemoradiotherapy and unresectable NSCLC

Clinicaltrials.gov - searched http://clinicaltrials.gov/ct2/home with keywords: Chemoradiotherapy and unresectable NSCLC
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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.