Evidence-based Series 7-1-2: EDUCATION AND INFORMATION- 2013

Postoperative Adjuvant Chemotherapy, with or without Radiotherapy, in Completely Resected Non-Small Cell Lung Cancer

Members of the Lung Cancer Disease Site Group

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

An assessment conducted in November 2013 put Evidence-based Series (EBS) 7-1-2 in the Education and Information section. This means that the recommendations will no longer be maintained by may still be useful for academic or other information purposes. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol).

This EBS report, consists of:
1. Guideline Report Overview
2. Section 1: Clinical Practice Guideline
3. Section 2: Evidentiary Base
4. Section 3: EBS Development Methods and External Review Process and Results

and is available on the CCO website (http://www.cancercare.on.ca) PEBC Lung Cancer DSG page at:
https://www.cancercare.on.ca/cms/One.aspx?portalId=1377&pageId=10286

Release Date: June 11 2012

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Evidence-based Guideline 7-1-2- EDUCATION AND INFORMATION 2013

Postoperative Adjuvant Chemotherapy, with or without Radiotherapy, in Completely Resected Non-Small Cell Lung Cancer

Guideline Report History

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<td>Original version April 2005</td>
<td>1966-2005 Full Report</td>
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<td>Update Dec 2006</td>
<td>2005-2006 New data was added to original Full Report</td>
<td>Updated Web publication</td>
<td>NA</td>
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² This Evidence-based Series report, together with a companion report, Postoperative Adjuvant Radiation Therapy in Stage II or IIIA Completely Resected Non-Small Cell Lung Cancer (PG #7-1-1), replaces report #7-1, Postoperative Adjuvant Chemotherapy and/or Radiation Therapy in Stage II or IIIA Completely Resected Non-Small Cell Lung Cancer, that was completed in 1997
Evidence-based Series 7-1-2

Postoperative Adjuvant Chemotherapy, with or without Radiotherapy, in Completely Resected Non-Small Cell Lung Cancer

Guideline Review Summary

Review Date: January 2012

The 2006 guideline recommendations require UPDATE

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

OVERVIEW

Evidence-based Series History

This guidance document was originally released by Cancer Care Ontario’s Program in Evidence-based Care in 2005. In January 2012, the PEBC guideline update strategy was applied and the new updated document released in June 2012. The Clinical Practice Guideline and Evidentiary Base in this version are the same as 2006 version.

Update Strategy

Using the Document and Assessment Review Tool, the PEBC update strategy involved an updated search of the literature, review and interpretation of the new eligible evidence by clinical experts from the authoring guideline panel, and consideration of the guideline and its recommendations in response to the new available evidence.

DOCUMENT ASSESSMENT AND REVIEW RESULTS

Question Considered

Does the use of postoperative chemotherapy, with or without radiotherapy, in patients with completely resected non-small cell lung cancer improve survival? Toxicity was also an outcome of interest
Literature Search and New Evidence

The new search (June 2006 to November 2011) yielded 13 relevant new publications representing two guidelines, six meta-analyses and seven RCTs were found. Initial publications of two of the RCTs and one meta-analysis were already included in the original document. Brief results of these publications are shown in the Document and Assessment Review Tool at the end of this report.

Impact on Guidelines and Its Recommendations

The new data showed that adjuvant chemotherapy has significant improvements for IB > 4cm. In order to incorporate recommendation addressing the question of size for stage IB, Hence, the Lung Cancer DSG made a decision to UPDATE the 2006 recommendations on postoperative adjuvant chemotherapy, with or without radiotherapy, in completely resected non-small cell lung cancer.
Evidence-based Series #7-1-2: Section 1

Postoperative Adjuvant Chemotherapy, with or without Radiotherapy, in Completely Resected Non-Small Cell Lung Cancer:
A Clinical Practice Guideline

N. Alam, F.A. Shepherd, G. Darling, J.A. Mackay, Y.C. Ung, W.K. Evans
and members of the Lung Cancer Disease Site Group

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


Report Date: December 2006

Question
Does the use of postoperative chemotherapy, with or without radiotherapy, in patients with completely resected non-small cell lung cancer improve survival? Toxicity was also an outcome of interest.

Target Population
These recommendations apply to adult patients with completely resected non-small cell lung cancer. A complete resection is defined as an R0 resection.

Disease Stage-Specific Recommendations

- **Completely resected stage IA non-small cell lung cancer**
  - In the opinion of the Lung Disease Site Group (DSG), adjuvant chemotherapy should not routinely be used in this patient population due to their good overall survival and because the evidence for a survival benefit with adjuvant chemotherapy is uncertain.
  - Postoperative radiotherapy in combination with chemotherapy should not be used.

- **Completely resected stage IB non-small cell lung cancer**
  - Postoperative adjuvant platinum-based chemotherapy is not recommended for routine use in this population.
  - Postoperative radiotherapy in combination with chemotherapy should not be used.
• **Completely resected stage II non-small cell lung cancer**
  - Postoperative adjuvant cisplatin-based chemotherapy is recommended in this population.
  - Postoperative radiotherapy in combination with chemotherapy should not be used.

• **Completely resected stage IIIA non-small cell lung cancer**
  - Postoperative adjuvant cisplatin-based chemotherapy is recommended in this population.
  - The role of postoperative radiotherapy is unclear in this stage of disease.

**Treatment Dose and Schedule**

• The National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG) trial achieved a statistically and clinically significant survival benefit for adjuvant chemotherapy without postoperative radiotherapy using vinorelbine (25 mg/m² weekly for 16 weeks) combined with cisplatin (50 mg/m² given on days 1 and 8) for patients with stage IB or II (1,2). Those studies that have demonstrated benefit for adjuvant chemotherapy in stage IIIA disease used similar regimens. It is unknown whether other doses and schedules of administration of these agents will produce similar benefits. One of the drawbacks to a recommendation favouring the cisplatin-vinorelbine regimen used in both the NCIC-CTG and Adjuvant Navelbine International Trialist Association (ANITA) trials is that it involves a weekly administration of vinorelbine over 16 to 20 weeks. This is difficult for patients and providers alike. It is also not known whether more convenient treatment schedules such as the three-weekly administration of vinorelbine on days 1 and 8 and cisplatin on day 1 would have similar efficacy. The Lung DSG recommends that practitioners use the regimen and schedule that has produced the best current results in a randomized trial. If this is not possible to do, the Lung DSG recommends that medical oncologists select one cisplatin-based chemotherapy regimen to use consistently for all adjuvant lung cancer therapy, as this should optimize patient safety.

**Other Recommendations**

• The use of adjuvant chemotherapy involving alkylating agents is not recommended as it has been found to be detrimental to survival.

• In the opinion of the Lung DSG, a recommendation for or against the use of the adjuvant uracil-tegafur combination (UFT) in a North American population is not appropriate at this time because the drug combination has only been tested in lung cancer patients in Japan and the results may not be generalizable to non-Japanese populations. UFT is currently not available in North America.

**Qualifying Statements**

• Although the evidence for or against the use of postoperative radiotherapy in combination with chemotherapy is unclear, in the opinion of the Lung Cancer Disease Site Group, the combination treatment should not be used in stage I or II disease. This opinion is based on the lack of a clear survival benefit for chemoradiotherapy in comparison to radiotherapy alone, a strong survival benefit associated with chemotherapy alone in stage II disease (with uncertain evidence in the case of stage IB disease), and a survival detriment associated with radiotherapy alone. In the three trials of adjuvant chemoradiotherapy reviewed in this guideline, deaths associated with the combination treatment occurred in 2% to 9% of patients, while in the trials of adjuvant chemotherapy, chemotherapy-related deaths occurred in 0.8-2% of patients. However, the appropriateness of postoperative radiotherapy is less clear for stage IIIA disease: the two trials that included stage IIIA patients, and
showed a statistically significant overall survival benefit for adjuvant chemotherapy, had methodological limitations in that they administered sequential radiotherapy according to centre choice.

- Insufficient evidence exists to identify specific subgroups of patients that may differentially benefit from the use of postoperative adjuvant platinum-based chemotherapy. Most adjuvant platinum-based chemotherapy trials have mainly involved patients with a good performance status (0-1) and included patients with a mix of disease stages (I-III); the only trial without postoperative radiotherapy that yielded an overall survival advantage only included patients with stage IB and stage II disease. In the two trials that administered postoperative radiotherapy according to centre choice and showed a statistically significant overall survival benefit for adjuvant chemotherapy, the survival benefit appeared to be greatest for stage IIIA patients from a forest plot of hazard ratios by disease stage and a comparison of survival curves by disease stage. However, no statistical analyses were reported by disease stage in either trial.

- The potential benefits, limitations, and toxicity of treatment should be fully discussed with the patient. Severe toxicities (grade 3 or 4) frequently associated with platinum-based chemotherapy include hematologic events, particularly neutropenia, nausea and vomiting, and fatigue. The Lung DSG believes that for stage II and IIIA disease, and for patients fit enough to receive chemotherapy, the survival benefits of adjuvant chemotherapy strongly outweigh the treatment toxicity.

Key Evidence

- Three large individual patient data meta-analyses and five analyses that pooled only published data, have detected a survival benefit in favour of some types of postoperative adjuvant chemotherapy.
  - In the Non-Small Cell Lung Cancer Collaborative Group (NSCLCCG) individual patient meta-analysis, an absolute survival benefit of 5% at five years was detected for adjuvant cisplatin-based chemotherapy in patients with potentially curative resections of early-stage disease (eight trials, 1,394 patients). Although not statistically significant (hazard ratio [HR], 0.87; 95% confidence interval [CI], 0.74-1.02; p=0.08), that benefit would be considered clinically significant and has been confirmed in subsequent meta-analyses. In the 1995 meta-analysis, adjuvant chemotherapy involving alkylating agents in five trials (2,145 patients) was found to be detrimental to survival, with a 5% absolute reduction in survival at five years (HR, 1.15; 95% CI, 1.04-1.27; p=0.005). No survival benefit or detriment was detected for postoperative adjuvant chemotherapy in combination with radiotherapy when compared with surgery plus postoperative radiotherapy alone (HR, 0.98; p=0.76).
  - In the Lung Adjuvant Cisplatin Evaluation (LACE) individual patient meta-analysis (five trials, 4,584 patients) an absolute survival advantage of 5.3% at five years was detected for cisplatin-based chemotherapy (HR, 0.89; 95% CI, 0.82-0.96; p=0.004). Subgroup analysis found the benefit varied by disease stage (stage IA: HR, 1.41; 95% CI, 0.96-2.09; stage IB: HR, 0.92; 95% CI, 0.78-1.10; stage II: HR, 0.83; 95% CI, 0.73-0.95; and stage III: HR, 0.83; 95% CI, 0.73-0.95).
  - In the Hamada individual patient meta-analysis (six trials, 2,003 patients with completely resected disease), a statistically significant survival benefit was associated with surgery followed by oral UFT compared with surgery alone (HR, 0.74; 95% CI, 0.61-0.88; p=0.011), corresponding to an absolute increase in survival of 4.6% at five years.

- Among the 16 randomized controlled trials of postoperative adjuvant platinum-based chemotherapy, six involving more than 100 patients per treatment arm were published after the 1995 meta-analysis.
The largest trial (n=1,867), compared cisplatin in combination with one of etoposide, vinorelbine, vinblastine, or vindesine, to a control arm of no chemotherapy, and detected a survival advantage for chemotherapy (HR, 0.86; 95% CI, 0.76-0.98; p<0.03) for patients with stage IB, II or III disease. Radiotherapy was administered according to centre choice and the survival advantage observed was not differentially associated with the use of radiation or disease stage (3).

Two recent trials detected a statistically and clinically significant survival benefit for adjuvant cisplatin with vinorelbine compared with surgery alone. One trial administered cisplatin-vinorelbine to patients with stage IB or II disease, and found a 15% absolute benefit at five years (2). The second trial also administered cisplatin-vinorelbine and found an 8.6% absolute benefit at five years. That trial included patients with stage IB and II, as well as IIIA, and used radiotherapy according to centre choice. Radiation use was associated with increased mortality in univariate analysis (HR, 1.34; 95% CI 1.10-1.63, p = 0.003) (4).

One trial published in abstract form administered carboplatin-paclitaxel to 344 patients with stage IB disease and did not detect a significant difference in overall survival (HR, 0.80; 90% CI, 0.60-1.07, p=0.10), although a significant difference was found in disease-free survival (HR, 0.74; 90% CI, 0.57-0.96, p=0.027) (5,6).

The other two large trials, did not detect a statistically significant survival difference between treatments. Differences in trial characteristics (e.g., chemotherapy type, stage of disease, and use of radiotherapy) may have contributed to those conflicting results.

There is strong evidence that UFT as a postoperative adjuvant chemotherapy improves survival in patients with stage I non-small cell lung cancer, particularly adenocarcinomas. However, nine of the 13 trials of adjuvant oral chemotherapy used UFT alone or in combination with other intravenous chemotherapy agents and included between 30 and 979 patients. All nine trials were conducted in Japan and involved primarily stage I disease (68-100% of patients). Among the five trials that compared adjuvant UFT-based combination chemotherapy with surgery alone, only one small trial detected a statistically significant survival benefit for adjuvant therapy (cisplatin-vindesine-UFT, p=0.045). In addition, two trials (>100 patients per treatment arm) detected a survival benefit for adjuvant therapy only after pretreatment prognostic factors were taken into account (cisplatin-doxorubicin-UFT, p=0.044; cisplatin-vindesine-UFT, p=0.037). Among the seven trials that compared adjuvant UFT, given postoperatively for one to two years, with no UFT, four detected a statistically significant survival advantage with UFT. The largest of those four trials, involving 979 patients with stage I adenocarcinoma, detected an absolute survival benefit of 3% at five years (HR, 0.71; 95% CI, 0.52-0.98; p=0.04).

In the one study using cisplatin-vinorelbine without postoperative radiotherapy (1) patients experienced the following severe (grade 3 or 4) hematologic toxicities: neutropenia (73%), febrile neutropenia (7%), and anemia (7%).

Common and severe non-hematologic toxicity associated with cisplatin-vinorelbine without postoperative radiotherapy included malaise or fatigue, 15%; nausea and vomiting, 7-10%; and anorexia, 10%. Treatment-related mortality associated with a cisplatin-vinorelbine combination regimen has been reported as 0.8% (7) and 2% (5). In a quality-of-life analysis, only adverse effects associated with neurotoxicity persisted after treatment was completed.

Related Guidelines
Practice Guideline Report #7-1-1: Postoperative Adjuvant Radiation Therapy in Stage II or IIIA Completely Resected Non-Small Cell Lung Cancer.
REFERENCES


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Evidence-based Series #7-1-2: Section 2

Postoperative Adjuvant Chemotherapy, with or without Radiotherapy, in Completely Resected Non-Small Cell Lung Cancer: A Systematic Review

N. Alam, F.A. Shepherd, G. Darling, J.A. Mackay, Y.C. Ung, W.K. Evans and members of the Lung Cancer Disease Site Group

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


Report Date: December 2006

The systematic review that forms the evidentiary base for the clinical practice guideline is published in The Annals of Thoracic Surgery available at http://ats.ctsnetjournals.org/:


The Clinical Practice Guideline (Section 1) will be updated and posted on the Cancer Care Ontario Web site as new evidence becomes available. Updated versions of the systematic review can be obtained by contacting the PEBC office at ccopgi@mcmaster.ca

For a complete list of the Lung DSG members and the Report Approval Panel members, please visit the CCO Web site at http://www.cancercare.on.ca/

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Evidence-based Series 7-1-2: Section 3

Postoperative Adjuvant Chemotherapy, with or without Radiotherapy, in Completely Resected Non-Small Cell Lung Cancer: Guideline Development and External Review - Methods and Results

N. Alam, F.A. Shepherd, G. Darling, J.A. Mackay, Y.C. Ung, W.K. Evans
and members of the Lung Cancer Disease Site Group

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


Report Date: December 2006

This Evidence-based Series report, together with a companion report, Postoperative Adjuvant Radiation Therapy in Stage II or IIIA Completely Resected Non-Small Cell Lung Cancer (PG #7-1-1), replaces report #7-1, Postoperative Adjuvant Chemotherapy and/or Radiation Therapy in Stage II or IIIA Completely Resected Non-Small Cell Lung Cancer, that was completed in 1997.

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, 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 routine 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 use of postoperative adjuvant chemotherapy in completely resected NSCLC, developed through systematic review, evidence synthesis, and input from practitioners in Ontario.

Disease Site Group Consensus
The DSG agreed that recent meta-analyses (3-7) and clinical trials (8-12) clearly indicate a substantial survival benefit for postoperative platinum-based chemotherapy compared with surgery alone, particularly in patients with stage II or IIIA disease. In the case of stage IB disease, a clear benefit of chemotherapy has not been shown in two major published trials. Neither the NCIC-CTG (11) nor ANITA trials (12) reported a survival benefit for chemotherapy in their sub-group analyses of stage IB patients. However, the early (unpublished) results of the CALGB trial of stage IB patients showed a significant survival benefit associated with chemotherapy at four years (9,10). Based on this report and in the absence of results from the ANITA trial, the DSG initially felt that chemotherapy would be appropriate to offer in the stage IB setting. In light of the subsequent report of a lack of survival benefit in stage IB patients in the CALGB trial (13,14) and the subset analyses from the other two published trials, the DSG revised its stance on the issue in August, 2006, and issued a revised recommendation that stated it was inappropriate to recommend chemotherapy for routine use in the stage IB population.

The DSG felt that chemotherapy regimens used in the three trials with the greatest survival benefit would be appropriate postoperative treatment options. Some DSG members suggested that a variety of chemotherapy regimens could reasonably be used in stage IIIA, and that cisplatin-vinorelbine may be the preferred regimen in stage II disease. However, others felt that cisplatin-vinorelbine, the regimen used in the joint Canadian-U.S. trial (11), should be selected as the treatment option of first choice because that trial included more disease stages, provided a longer follow-up period, and showed the largest absolute survival improvement. One of the drawbacks to a recommendation favouring the cisplatin-vinorelbine regimen used in both the NCIC-CTG and ANITA trials is that it involves a weekly administration of vinorelbine over 16 to 20 weeks, which is difficult for patients and providers alike. It is not known whether more conventional regimens such as the three-weekly administration of vinorelbine on days 1 and 8 and cisplatin on day 1 would have similar efficacy. In addition, some patients are not able to
tolerate a cisplatin-based regimen. After further consideration, the DSG agreed to recommend only cisplatin-vinorelbine as an option in the adjuvant treatment of stage II and IIIA completely resected NSCLC.

The DSG noted the survival improvement obtained with postoperative UFT in early-stage NSCLC but also noted that, to date, the drug combination has only been tested in lung cancer patients in Japan and is not currently available in North America. Considering the potential differences in patient characteristics (including genetics) and tumour biology (different distributions of histology) between the two populations, the DSG feels that these results are not generalizable to a North American population. Therefore, a recommendation for or against the use of UFT was not made at this time.

Based largely on the results of one individual patient data meta-analysis (15,16) and one large RCT (17), which both detected a significant survival detriment for postoperative radiotherapy compared with surgery alone, DSG practice guideline #7-1-1 recommended against the use of postoperative radiotherapy for patients with completely resected stage II NSCLC. No definitive recommendation was made for or against the use of postoperative radiotherapy in patients with completely resected stage IIIA disease. Although the evidence for or against the use of postoperative radiotherapy in combination with chemotherapy is unclear, in the opinion of the Lung DSG, combination chemoradiotherapy treatment should not be used in stage II disease. This opinion is based on the survival detriment associated with postoperative radiotherapy alone in stage II disease and the lack of a clear survival benefit for postoperative radiotherapy combined with chemotherapy when compared with postoperative radiotherapy alone (18-22). The evidence is insufficient to recommend for or against the use of postoperative radiotherapy combined with chemotherapy in stage IIIA disease.

External Review by Ontario Clinicians

An earlier version of this practice guideline and systematic review, dated October 7, 2004, was circulated to 138 Ontario clinicians for feedback. Box 1 summarizes the draft clinical recommendations and supporting evidence that was circulated to clinicians from the earlier version. Since that time, newly available data from two key trials of platinum-based agents have resulted in changes to these recommendations (presented in Section 1). Data from the ANITA trial, which evaluated adjuvant cisplatin-vinorelbine in patients with stage IB, II and IIIA NSCLC, was subsequently incorporated into the guideline, and the recommendation for stage IIIA revised accordingly. As well, abstract data from the CALGB trial of paclitaxel and carboplatin reported at ASCO 2006 (13,14) led to a change in the recommendation for stage IB.

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<th>BOX 1:</th>
<th>DRAFT RECOMMENDATIONS (approved for external review October 7, 2004)</th>
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<tbody>
<tr>
<td><strong>Target Population</strong></td>
<td>These recommendations apply to adult patients with completely resected NSCLC</td>
</tr>
<tr>
<td><strong>Recommendation</strong></td>
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<tr>
<td><strong>Completely resected stage IA NSCLC:</strong></td>
<td></td>
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<tr>
<td>➢ In the opinion of the Lung DSG, adjuvant chemotherapy should not routinely be used in this patient population because of their good overall survival and because the evidence for a survival benefit with adjuvant chemotherapy is uncertain.</td>
<td></td>
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<tr>
<td><strong>Completely resected stage IB and II NSCLC:</strong></td>
<td></td>
</tr>
<tr>
<td>➢ Postoperative adjuvant platinum-based chemotherapy improves survival compared with surgery alone and is recommended.</td>
<td></td>
</tr>
<tr>
<td>➢ Based on the available evidence from randomized trials, both cisplatin-vinorelbine and carboplatin-paclitaxel appear to be acceptable alternatives as postoperative adjuvant</td>
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therapy.

- The large randomized trials that showed a statistically and clinically significant survival benefit for adjuvant chemotherapy used either vinorelbine (25 mg/m² weekly for 16 weeks) combined with cisplatin (50 mg/m² given on days 1 and 8 every four weeks for four cycles) or four cycles of paclitaxel (200 mg/m² over three hours) combined with carboplatin (area under curve [AUC] 6) administered every three weeks. It is unknown whether other doses and schedules of administration of these agents will produce similar benefit.
- Postoperative radiotherapy in combination with chemotherapy should not be used.
- The potential benefits, limitations, and toxicity of treatment should be fully discussed with the patient.

- **Completely resected stage IIIA NSCLC:**
  - Adjuvant cisplatin-based chemotherapy may also be considered. The magnitude of the observed benefit may be less and the role of adjuvant radiotherapy is unclear in this stage of the disease.

- **Qualifying Statements**
  - Although the evidence for or against the use of postoperative radiotherapy in combination with chemotherapy is unclear, in the opinion of the Lung DSG the combination treatment should not be used in stage IB or II disease. This opinion is based on the strong survival benefit associated with postoperative chemotherapy alone in these disease stages, the survival detriment associated with postoperative radiotherapy alone in stage II disease, and the lack of a clear survival benefit for postoperative radiotherapy combined with chemotherapy when compared with postoperative radiotherapy alone.
  - Insufficient evidence exists to identify specific subgroups of patients that may differentially benefit from the use of postoperative adjuvant cisplatin-based chemotherapy. Most adjuvant cisplatin-based chemotherapy trials have included patients with a mix of disease stages (I-III); however, the two trials that yielded the greatest survival advantages included only patients with stage IB disease (both trials) or stage II disease (one trial).
  - Grade 3 or 4 toxicities frequently associated with cisplatin-based chemotherapy include hematologic events, particularly neutropenia, and nausea and vomiting. In most trials reviewed in this guideline, chemotherapy-related deaths occurred in less than 1% of patients, although, in three trials of adjuvant chemoradiotherapy, deaths associated with the combination treatment occurred in between 2% and 9% of patients. Adjuvant UFT is associated with limited grade 3 or 4 toxicity (2% or less).
Methods
Feedback was obtained through a mailed survey of 138 practitioners in Ontario, including 37 medical oncologists, 24 radiation oncologists, 26 surgeons, 32 respirologists, and 19 other practitioners. The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. The survey was mailed out on October 7, 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-seven responses were received out of the 138 surveys sent (41% response rate). Responses include returned completed surveys as well as phone, fax, and email responses. One respondent was excluded from the data analysis because their comments on the feedback questionnaire appeared to relate to a different guideline. Of the remaining practitioners who responded, 35 indicated that the report was relevant to their clinical practice, including medical oncologists (40%), surgeons (26%), radiation oncologists (11%), and respirologists (6%), and they completed the survey. Key results of the survey are summarized in Table 5.

Table 5. Practitioner responses to eight items on the practitioner feedback survey.

<table>
<thead>
<tr>
<th>Item</th>
<th>Number (%)</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>33 (94%)</td>
<td>1 (3%)</td>
<td>1 (3%)</td>
<td></td>
</tr>
<tr>
<td>There is a need for a clinical practice guideline on this topic.</td>
<td>33 (94%)</td>
<td>2 (6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The literature search is relevant and complete.</td>
<td>31 (89%)</td>
<td>4 (11%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The results of the trials described in the report are interpreted according to my understanding of the data.</td>
<td>33 (94%)</td>
<td>1 (3%)</td>
<td>1 (3%)</td>
<td></td>
</tr>
<tr>
<td>The draft recommendations in this report are clear.</td>
<td>34 (97%)</td>
<td>1 (3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I agree with the draft recommendations as stated.</td>
<td>32 (91%)</td>
<td>2 (6%)</td>
<td>1 (3%)</td>
<td></td>
</tr>
<tr>
<td>This report should be approved as a practice guideline.</td>
<td>33 (94%)</td>
<td>1 (3%)</td>
<td>1 (3%)</td>
<td></td>
</tr>
<tr>
<td>If this report were to become a practice guideline, how likely would you be to make use of it in your own practice?</td>
<td>Very likely or likely</td>
<td>28 (82%)</td>
<td>2 (6%)</td>
<td>3 (9%)</td>
</tr>
<tr>
<td></td>
<td>Unsure</td>
<td>2 (6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not at all likely or unlikely</td>
<td>2 (6%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a Due to rounding, percentages may not total 100%.
b One respondent indicated this question was ‘not applicable’ and another respondent did not answer the question.

Summary of Written Comments
Of the eight respondents (23%) who provided written comments, most indicated their support for the summary of the evidence and the final recommendations. Two raised issues that required a response by the DSG:
1. One family physician commented that the indications regarding treatment toxicity or side effects were unclear and that these were the issues of interest to his or her patients.
2. One physician indicated that some questions on the feedback questionnaire were not appropriate for all practitioners. The same physician suggested that the presentation of data within the guideline could be simplified.
Modifications/Actions
1. In response to the request for clarification regarding side effects of chemotherapy, the Lung DSG decided to include details of the toxicities associated with the recommended regimens in Section 1: Practice Guideline. A related document focusing on nursing issues, including treatment toxicity, is under development and, when complete, will be incorporated into the guideline. However, given the magnitude of the survival benefit associated with postoperative adjuvant chemotherapy in recent trials and meta-analyses, the Lung DSG believes the benefits of this treatment outweigh its side effects.
2. The Lung DSG acknowledged that the current guideline format and feedback questionnaire are primarily intended for physicians that treat lung cancer. The PEBC is exploring new formats and methods of dissemination for the guidelines, which may address the concerns expressed by the respondent.

Practice Guidelines Coordinating Committee Approval Process
The practice guideline report was circulated to members of the Practice Guidelines Coordinating Committee for review and approval. Seven of 13 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 Committee members approved the practice guideline report as written. One member required a number of primarily editorial revisions, as well as clarification on why the results from the Japanese UFT trials may not be generalizable to North American populations. In the opinion of the DSG, the main reasons for the lack of generalizability include potential differences between the populations in patient characteristics (including genetics) and tumour biology (different distributions of histology). A statement to this effect was added to Disease Site Group Consensus in Section 2.

The DSG provided notice to the PEBC Report Approval Panel of its decision to change its recommendations for stage IB and IIIA disease. A letter of information was circulated to practitioners involved in the earlier external review of the report to inform them of the change to the recommendation.

Policy Review
Vinorelbine and paclitaxel are currently funded in the province of Ontario through the New Drug Funding Program for the indication of advanced NSCLC. In September 2004 the Lung DSG requested a revision to the funding policy for adjuvant chemotherapy after complete resection of stage IB and II NSCLC. Vinorelbine and paclitaxel were funded in the province of Ontario through the New Drug Funding Program for this indication. The recent evidence of a very substantial survival improvement in patients receiving adjuvant chemotherapy after complete resection of stage IIIA NSCLC will require that the funding policy also be revised to include stage IIIA. A request for a revision to the funding policy, along with a copy of this evidence-based series report, will be submitted for consideration to the Oncology Subcommittee of the Drug Quality and Therapeutics Committee of Ontario.

RELATED PRINT AND ELECTRONIC PUBLICATIONS

Subsequent publications include:
• Alam N, Darling G, Shepherd FA, Mackay JA, Evans WK, the Lung Cancer Disease Site
  Group of Cancer Care Ontario’s Program in Evidence-Based Care. Postoperative

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For information about the PEBC and the most current version of all reports,
please visit the CCO Web site at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-525-9140, ext. 22055     Fax: 905-522-7681
REFERENCES


**EBS7-1-2 Document Assessment and Review Tool.**

| Number and title of document under review | 7-1-2 Postoperative Adjuvant Chemotherapy, with or without Radiotherapy in Completely Resected Non-Small Cell Lung Cancer |
| Date of current version | Dec 2006 |
| Clinical reviewer | Dr. Peter Ellis |
| Research coordinator | Chika Agbassi |
| Date initiated | 3 August 2011 |
| Date and final results / outcomes | 12 March 2012 [ UPDATE] |

**Instructions.** Beginning at question 1, below, answer the questions in sequential order, following the instructions in the highlighted boxes as you go.

1. Is there still a need for a guideline covering one or more of the topics in this document as is? Answer Yes or No, and explain if necessary:
   - 1. Yes. This remains a relevant clinical question
   - If No, then the document should be **ARCHIVED** with no further action; **go to 11.** If Yes, then **go to 2.**

2. Are all the current recommendations based on the current questions definitive or sufficient, and have less than 5 years elapsed since the latest search? Answer Yes or No, and explain if necessary:
   - 2. No. The current document is close to 5 years old. There are updated publications on several of the trials and the recommendations are no longer accurate.
   - If Yes, the document can be **ENDORSED** with no further action; **go to 11.** If No, **go to 3.**

3. Is there expected or known evidence that contradicts the current recommendations, such that they may cause harm or lead to unnecessary or improper treatment if followed? Answer Yes or No, and explain if necessary, providing references of known evidence:
   - 3. No
   - If Yes, the document should be taken off the website as soon as possible. A **WARNING** should be put in its place informing a user that the document is only available by email, with a brief explanation of the reasons. If No, **go to 4.**

4. Do current resources allow for an updated literature search to be conducted at this time? Answer Yes or No, and explain as necessary. Provide an expected date of completion of the updated search, if applicable:
   - 4. **YES**
   - • there is a designated research co-ordinator at the PEBC to carry out the literature search
   - If No, a **DEFERRAL** should be placed on the document indicating it cannot be updated at this time, but will be reviewed again on a yearly basis. If Yes, **go to 5.**

5a. **Guideline Research Questions.** Please review the original guideline research questions below and if applicable, list any MINOR changes to the questions that now must be considered. If a question is no longer relevant, it can be deleted. The DART process evaluates the guideline as is and CANNOT accommodate significant changes to the questions or the addition of new questions introducing new patient populations or new agents/interventions because if this is required in order to make this guideline relevant, then a brand new document should be produced and this guideline as is should be **ARCHIVED** (i.e., go back to Q1 of this DART form and answer NO).

   **Original Question(s):**
   Does the use of postoperative chemotherapy, with or without radiotherapy, in patients with completely resected non-small cell lung cancer improve survival? Toxicity was also an outcome of interest.

   **Target Population:**
   These recommendations apply to adult patients with completely resected non-small cell lung cancer. A complete resection is defined as an R0 resection.
5b. Inclusion and Exclusion criteria. List below any changes to the selection criteria in the original version made necessary by new questions, changes to existing questions, or changes in available evidence (e.g., limit a search to randomized trials that originally included non-randomized evidence).

Inclusion criteria:
1. Evidence-based practice guidelines addressing the role of postoperative adjuvant chemotherapy following complete resection of NSCLC and published since 2000; or
2. Randomized controlled trials (RCTs) or meta-analyses that:
   a) compare postoperative chemotherapy to the same treatment without chemotherapy in patients with completely resected NSCLC; and
   b) report overall survival or disease-free survival as one of the main outcomes; and
   c) are fully published or reported in abstract form.

Exclusion Criteria
1. Articles published in a language other than English were not considered unless an English abstract was available.
2. Studies involving alkylating chemotherapy agents, alone or in combination with non-platinum agents, were not considered since these have previously been shown to have no benefit for patients.

Studies involving immunotherapy were not considered.

5c. Conduct an updated literature search based on that done for the current version and modified by 5a and 5b above. Report the results below.

Search Period
- June 2006 to Nov 2011 (Medline + Embase)
- 2006 to 2011 (ASCO Annual Meeting)

Brief Summary/Discussion of New Evidence
Of 394 total hits from Medline + Embase and 2 hits from ASCO abstract searches, 15 references representing 7 pooled/meta-analyses and 8 RCTs were found. 5 of the references are full reports of 2 RCTs and one meta analysis that were already included in the existing guideline (rows highlighted in grey in the Table). The other 6 RCTs are potentially new studies.

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Name of RCT (median F/U)</th>
<th>Population</th>
<th>Outcomes</th>
<th>Brief results</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adj CT vs. Surgery alone</td>
<td>Meta-analysis of 31 RCTs (EL-1 = 11 RCTs EL-2 = 20 RCTs)</td>
<td>EL-1 (n=1,530) EL-2 (n=8,985)</td>
<td>OS</td>
<td>Using the 11 high evidence level trials, CT was significantly better that surgery alone with an HR= 0.87 (95%CI: 0.83-0.93) and the significance was maintained when level 2 evidence trials was added.</td>
<td>Schmutz E. et al 2011 [ABSTRACT]</td>
</tr>
<tr>
<td>Adj CT vs. Surgery alone</td>
<td>Meta-analysis of 34 RCTs</td>
<td>Operable NSCLC (n= 8447)</td>
<td>*OS</td>
<td>With a 4% (95% CI; 3-6) increase in the absolute survival, the addition of CT after surgery was shown to be significantly better than surgery alone. HR = 0.86 (95%CI 0.81-0.92) P&lt;0.0001.</td>
<td>NSCLC Meta-analysis Collaborative group April 2010</td>
</tr>
<tr>
<td>Adj CT plus RT vs. Adj CT</td>
<td>Meta-analysis of 13 RCTs</td>
<td>(n=2660)</td>
<td>OS</td>
<td>The advantage of CT plus RT over CT alone was shown to be statistically significant with an HR = 0.88 (95%CI 0.81-0.97) P&lt;0.0009.</td>
<td></td>
</tr>
<tr>
<td>Adj platin based CT vs. Surgery alone</td>
<td>Meta-analysis of 13 RCTs Heterogeneity N/S</td>
<td>(n=7334)</td>
<td>OS PFS/DFS</td>
<td>OS: There is a significant difference in favour of CT with a relative benefit of 7-12% and an absolute benefit ranging from 2.5% to 4.1%.</td>
<td>Bria E. et al 2009</td>
</tr>
<tr>
<td>Adj UFT vs. Surgery alone</td>
<td>Re-analysis of the 2005 meta-analysis (5yrs)</td>
<td>Stage I TA =TD ≤2cm T1a =TD ≤2 - ≤ 3 cm (n=1269)</td>
<td>*OS, DFS</td>
<td>For patients with T1b tumour, survival rate was significantly better in the UFT arm than the surgery alone arm (HR = 0.62, 95%CI: 0.42-0.90) p= 0.011. T1a did not show a significant difference between arms.</td>
<td>Hamada</td>
</tr>
<tr>
<td>cisplatin plus Vinorelbin vs. Surgery alone</td>
<td>LACE-Vinorelbin subgroup analysis of 4 trials Heterogeneity N/S (5.2yrs)</td>
<td>(n=1888)</td>
<td>*OS, DFS</td>
<td>Compared to observation, the combination of cisplatin and VIN showed a significant survival benefit of 8.9% (HR=0.80, 95%CI: 0.70-0.91, p&lt;0.001) but stage was shown to be a significant predictor for survival (p=0.02). DFS: showed similar result with Stage I HR = 0.95 (95% CI; 0.76 to 1.19) Stage II HR = 0.69 (95% CI; 0.57 to 0.83) Stage III HR = 0.62 (95% CI; 0.50 to 0.76)</td>
<td>Douillard J. et al 2010</td>
</tr>
<tr>
<td>Adj cisplatin based CT vs. Surgery alone.</td>
<td>Pooled analysis of 5 trials N/S (5.2yrs)</td>
<td>DFS : HR = 0.84 (95% CI; 0.78 to 0.91) P&lt;0.001. Cisplatin + VIN combination was also shown to be superior to cisplatin + other CT (p=0.04)</td>
<td>The hazard ratio of death in young 0.86 (95% CI; 0.78 -0.94), micdiagnosis 0.90 (95% CI; 0.76 -1.06), elderly 0.87 (95% CI; 0.68-1.11). With a 5yr absolute benefit of 5.4%, adjuvant cisplatin based CT was shown to be significantly better than no CT. but the significance varies with stage of disease. Overall HR = 0.89 (95% CI; 0.82 to 0.96) P&lt;0.005. Stage III HR = 0.89 (95% CI; 0.78 to 1.10). Stage II HR = 0.83 (95% CI; 0.73 to 0.95). Stage III HR = 0.89 (95% CI; 0.72 to 0.94). DFS : HR = 0.84 (95% CI; 0.78 to 0.91) P=0.001</td>
<td>Fruh M. et al 2008</td>
<td></td>
</tr>
<tr>
<td>Cisplatin based CT vs. Observation</td>
<td>IALT (7.5yrs)</td>
<td>Stage I-III Med Age =59 WHO-PS = 0-2 (n=1,867)</td>
<td>OS, DFS</td>
<td>Compared to observation, DFS was significantly better in the CT arm with a HR of 0.88 (95%CI 0.76 to 0.97) P= 0.01. OS favoured the CT arm but was not significantly different. HR=0.91 (95%CI, 0.81 to 1.02) P= 0.10</td>
<td>Arriagada R. et al 2010</td>
</tr>
<tr>
<td>Vinorelbine plus cisplatin vs. Surgery alone</td>
<td>JBR.10 Trial (9.3yrs)</td>
<td>Stage IB or II (n=458)</td>
<td>OS, DSS</td>
<td>DSS remained significantly prolonged in the ACT arm with a HR of 0.73 (95%CI; 0.55 to 0.97) P=0.03. The observation arm had higher risk of death. P=0.02</td>
<td>Butts C. et al 2010</td>
</tr>
<tr>
<td>Adj Vinorelbine or Paclitaxel + Cisplatin vs. Surgery alone</td>
<td>Terminated early (29mos)</td>
<td>Stage IIIA-N2 Med Age=57 (n=150)</td>
<td>OS, DFS</td>
<td>CT arm was significantly better than the observation arm. OS=33mos vs. 24mos; P= 0.037 DFS = 32mos vs. 20mos. P = 0.020</td>
<td>Ou W. et al 2010</td>
</tr>
<tr>
<td>Adj Paclitaxel + Cisplatin vs. observation</td>
<td>CALGB 9633 (74mos)</td>
<td>T2N0 AGE &gt;18yrs ECOG-PS 0-1 (n=344)</td>
<td>*OS DFS</td>
<td>Survival was not significantly different between the groups: HR= 0.83 (95%CI; 0.64 to 1.08) P=0.12. An exploratory analysis showed a significant survival advantage in tumours ≥4cm</td>
<td>Strauss G. et al 2008</td>
</tr>
<tr>
<td>Surgery plus 6 cycle of Cisplatin (100mg/m² d1) + Etoposide (120mg/m² d1-3) vs. Surgery alone</td>
<td>Mean F/U (40.31 + 30.86)</td>
<td>Stage IB (n=140)</td>
<td>*OS DFS</td>
<td>When compared to observation, CT was not associated with any clinically significant morbidity. The OS and DFS were significantly better with median survival time of 84.8 vs. 41.6mos (p=0.02) and 99.2 vs. 30.4 (p=0.003) respectively. The 5 and 10 yrs OS rates were 62% and 44% in the CT arm versus 42% and 20% in the observation arm respectively.</td>
<td>Roselli M. et al 2006</td>
</tr>
<tr>
<td>Vinorelbine plus Cisplatin (30/100mg/m²) vs. Surgery alone</td>
<td>ANITA (76mos)</td>
<td>Stage IB-IIIa (n=840)</td>
<td>*OS</td>
<td>The median survival was better in the CT arm: 65.7mos (95%CI; 47.9-88.5) against 43.7mos (95%CI; 35.7-52.3) in the observation arm. The risk of death was significantly reduced in the CT arm with a HR of 0.80 (95%CI; 0.66-0.96) P= 0.017.</td>
<td>Douillard J. et al 2006</td>
</tr>
<tr>
<td>Stage I (n=172) Surgery plus UFT (400mg/d x1yr) vs. Surgery alone.</td>
<td>Stage I-IIIA Age &lt;75 ECOG PS = 0-2 (n=267)</td>
<td>OS</td>
<td>In the stage 1 population, the OS rate was significantly better in the CT arm; 74.2% (95%CI; 64.4-84.0%) against 57.6(46.4-68.8%) in the observation arm. P=0.045. In stage II-IIIA population there was no difference between the two arms.</td>
<td>Nakagawa K. et al 2006</td>
<td></td>
</tr>
<tr>
<td>Adj UFT vs. Surgery alone.</td>
<td>Stage 1 ECOG PS 0-2 (n=999)</td>
<td>OS</td>
<td>OS was significantly better in the UFT arm (P= 0.035). The 5yr survival rates were 88% in the UFT arm against 85% in the observation arm.</td>
<td>Ichinohe Y. et al 2006</td>
<td></td>
</tr>
</tbody>
</table>

**New References Identified (alphabetical order)**


Literature Search Strategy

MEDLINE
1. meta-Analysis as topic.mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
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 synthe$ or quantitative overview?).tw.
5. (systematic adj (review$ or overview$)).tw.
6. (exp Literature as topic/ or review.pt. or exp review/) and systematic.tw.
7. or/1-6
8. (cochrane or embase or psychnet or psycinfo or mdpinfo or cinahl or cinhal or science citation index or scisearch or bids or sige or cancerlit).ab.
9. (reference list$ or bibliography$ or hand-search$ or relevant journals or manual search$).ab.
10. (selection criteria or data extraction or quality assessment or Jadad scale or methodological quality).ab.
11. (study adj selection).ab.
12. 10 or 11
13. review.pt.
14. 12 and 13
15. exp randomized controlled trials as topic/ or exp clinical trials, phase III as topic/ or exp clinical trials, phase IV as topic/
16. (randomized controlled trial or clinical trial, phase III or clinical trial, phase IV).pt.
17. random allocation/ or double blind method/ or single blind method/
18. (random$ 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. limit 36 to human
38. exp Carcinoma, Non-Small-Cell Lung/
40. 38 and 39
41. 37 and 40
42. (200606$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$).ed.
43. 41 and 42

EMBASE
1. exp meta analysis/ or exp systematic review/
2. (meta analy$ or metaanaly$).tw.
3. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthesis$ or quantitative overview).tw.
4. (systematic adj (review$ or overview$)).tw.
5. exp review/ or review.pt.
6. (systematic or selection criteria or data extraction or quality assessment or Jadad scale or methodological quality).ab.
7. (study adj selection).ab.
8. 5 and (6 or 7)
9. or/1-8
10. (cochrane or embase or psychlit or psycit or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sgle or cancerlit).ab.
11. (reference list$ or bibliography$ or hand-search$ or relevant journals or manual search$).ab.
12. exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/
13. randomization/ or single blind procedure/ or double blind procedure/
14. (random$ 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.
27. or/24-26
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 abstract report/ or letter/ or case study/
30. 28 not 29
31. limit 30 to english
32. limit 31 to human
33. exp lung non small cell cancer/
34. (adjuvant? or postoperative).tw.
35. 33 and 34
36. 32 and 35
37. (200625$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$).ew.
38. 36 and 37

ASCO Annual Meeting - searched http://www.ascopubs.org/search with keywords: (non-small cell lung cancer) AND (adjuvant
<table>
<thead>
<tr>
<th>Step</th>
<th>Question</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.</td>
<td>Is the volume and content of the new evidence so extensive such that a simple update will be difficult?</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>The findings are still consistent.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>If Yes, then the document should be <strong>ARCHIVED</strong> with no further action; <strong>go to 11</strong>. If No, <strong>go to 7</strong>.</td>
<td></td>
</tr>
<tr>
<td>7.</td>
<td>On initial review, does the newly identified evidence support the <strong>existing recommendations</strong>? Do the current recommendations <strong>cover all relevant subjects</strong> addressed by the evidence, such that no new recommendations are necessary? Answer Yes or No, and explain if necessary:</td>
<td>NO</td>
</tr>
<tr>
<td></td>
<td>The subgroup analyses from CALGB 9633 (Strauss) and BR10 (Butts) examined the effect of adjuvant chemotherapy in stage IB according to tumor size. These are the only two trials that have data for such an analysis and both show significant improvements for IB &gt; 4cm. This recommendation should be incorporated into guideline recommendations to bring them in line with clinical practice. Supporting indirect evidence comes from the IASLC staging project in which node negative tumors &gt; 5cm (previously IB) were reclassified as stage II based on worse prognosis.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>If Yes, the document can be <strong>ENDORSED</strong>. If No, <strong>go to 8</strong>.</td>
<td></td>
</tr>
<tr>
<td>8.</td>
<td>Does any of the newly identified evidence, on initial review, contradict the current recommendations, such that the current recommendations may cause harm or lead to unnecessary or improper treatment if followed? Answer Yes or No, and explain if necessary, citing newly identified references:</td>
<td>NO</td>
</tr>
<tr>
<td></td>
<td>No contradictions, but as above support a recommendation for adjuvant chemo in stage IB &gt; 4cm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>If Yes, a <strong>WARNING</strong> note will be placed on the web site. If No, <strong>go to 9</strong>.</td>
<td></td>
</tr>
<tr>
<td>9.</td>
<td>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 necessary:</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>If Yes, the document update will be <strong>DEFERRED</strong>, indicating that the document can be used for decision making and the update will be deferred until the expected evidence becomes available. If No, <strong>go to 10</strong>.</td>
<td></td>
</tr>
<tr>
<td>10.</td>
<td>An update should be initiated as soon as possible. List the expected date of completion of the update:</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>An <strong>UPDATE</strong> will be posted on the website, indicating an update is in progress.</td>
<td></td>
</tr>
<tr>
<td>11.</td>
<td>Circulate this form to the appropriate Disease Site Group for their approval. Once approved, a copy of this form should be placed behind the cover page of the current document on the website. Notify the original authors of the document about this review.</td>
<td></td>
</tr>
</tbody>
</table>

**DSG Approval Date:** 20 April, 2012

**Comments from DSG members:** None
DART DEFINITIONS

DART Terms

*DEFINITIVE RECOMMENDATIONS – Definitive means that the current recommendations address the relevant subject area so fully that it would be very surprising to identify any contradictory or clarifying evidence.

§SUFFICIENT RECOMMENDATIONS – Sufficient means that the current recommendations are based on consensus, opinion and/or limited evidence, and the likelihood of finding any further evidence of any variety is very small (e.g., in rare or poorly studied disease).

¶WARNING – A warning indicates that, although the topic is still relevant, there may be, or is, new evidence that may contradict the guideline recommendations or otherwise make the document suspect as a guide to clinical decision making. The document is removed from the website, and a warning is put in its place. A new literature search may be needed, depending on the clinical priority and resources.

DART Outcomes

1. ARCHIVE - An archived document is a document that will no longer be tracked or updated but may still be useful for academic or other informational purposes. The document is moved to a separate section of our website, and each page is watermarked “ARCHIVED”.

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

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

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