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Evidence-based Series #7-4 Version 2 –IN REVIEW

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

Use of Preoperative Chemotherapy With or Without Postoperative Radiotherapy in Technically Resectable Stage IIIA Non-Small Cell Lung Cancer

Members of the Lung Cancer Disease Site Group

An assessment conducted in December 2016 placed Evidence-based Series (EBS) 7-4 Version 2 IN REVIEW. This means that it is undergoing review for currency and relevance. The Lung Cancer Disease Site Group has determined that it is still appropriate for this document to continue to be available while this updating process unfolds. The PEBC has a formal and standardized process to ensure the currency of each document.

(PEBC Assessment & Review Protocol)

This document is available on the CCO website and is comprised of the following 3 sections:

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

Release Date: May 16, 2013

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PEBC Report Citation (Vancouver Style): Members of the Lung Cancer Disease Site Group. Use of preoperative chemotherapy with or without postoperative radiotherapy in technically resectable stage

IIIA non-small cell lung cancer. Toronto (ON): Cancer Care Ontario; 2002 Apr [Endorsed 2012 Oct. In review 2016 Dec]. Program in Evidence-based Care Practice Guideline Report No.: 7-4 Version 2. IN REVIEW.

Journal Citation (Vancouver Style): Goss G, Paszat L, Newman T, Evans WK; Lung Cancer Disease Site Group. Use of preoperative chemotherapy with or without postoperative radiotherapy in technically resectable stage IIIa non-small cell lung cancer. Cancer Prev Control. 1998;2(1):32-9.

Guideline Report History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES AND KEY CHANGES
	Search Dates	Data		
Original version September 1997	1990-1997	Full Report	Web publication	NA
Updated version April 2002	1997-2002	New data added to original full report	Updated Web publication	NA
Current Version 2 May 2013	2002-2012	New data found in section 3: Document Review Summary and Tool	Updated Web publication	2002 recommendations is **ENDORSED**

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Evidence-based Series #7-4 Version 2: Section 1

Use of Preoperative Chemotherapy With or Without Postoperative Radiotherapy in Technically Resectable Stage IIIA Non-Small Cell Lung Cancer: Guideline Recommendations

Members of the Lung Cancer Disease Site Group

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

These guideline recommendations have been ENDORSED, which means that the recommendations are still current and relevant for decision making.
Please see Section 3: Document Review Summary and Tool for a summary of updated evidence published between 2002 and 2012, and for details on how this Clinical Practice Guideline was ENDORSED.

Report Date: May 16, 2013

Guideline Question

Should preoperative (neoadjuvant) cisplatin-based chemotherapy, with or without postoperative radiotherapy, be offered to patients with technically resectable stage IIIA non-small cell lung cancer (NSCLC), in order to improve survival? Resectability should be determined preoperatively by a thoracic surgeon.

Target Population

These recommendations apply to adult patients with technically resectable Stage IIIA NSCLC, as determined by a thoracic surgeon.

Recommendations

- Stage IIIA non-small cell lung cancer (NSCLC) has a number of different presentations including T3N0 (tumour with chest wall involvement without lymph node involvement) and N2 disease (mediastinal lymph node involvement on the same side of the mediastinum as the primary tumour). Although the surgical approach to patients with stage IIIA disease varies, it is generally accepted that T3N0 tumours should be managed by primary surgical resection. The role of surgery for patients who have histological evidence of N2 disease,

however, is controversial. Many surgeons regard the presence of N2 disease as a contraindication to surgery.

- There is evidence from four small randomized controlled trials (12 to 32 patients per treatment arm) that for patients with technically resectable stage IIIA NSCLC, the use of preoperative cisplatin-based chemotherapy and postoperative radiotherapy results in superior survival compared with surgery and postoperative radiotherapy. Whether the benefits of chemotherapy can be generalized to patients who do not receive postoperative radiotherapy cannot be determined from the existing trials.
- Although the interpretation of these trials is made difficult by their small size and presence of retrospectively identified imbalances in prognostic factors, the available evidence leads the Lung Cancer Disease Site Group (DSG) to recommend that preoperative chemotherapy and postoperative radiotherapy be offered to patients with technically resectable, histologically confirmed N2 disease for whom surgery is planned.

Methods

Entries to MEDLINE (through March 2002), CANCERLIT (through March 2002) and Cochrane Library (through Issue 1, 2002) databases and abstracts published in the proceedings of the annual meetings of the American Society of Clinical Oncology (through 2001) were systematically searched for evidence relevant to this practice guideline report. Evidence that has emerged in the most recent review of the literature is currently being reviewed by the Lung Cancer DSG. The guideline will be revised in 2002 to incorporate the relevant new evidence.

Evidence was selected and reviewed by four members of the Cancer Care Ontario Practice Guidelines Initiative's Lung Cancer DSG and methodologists. This practice guideline report has been reviewed and approved by the Lung Cancer Disease Site Group, which comprises medical and radiation oncologists, pathologists, surgeons, epidemiologists, a psychologist, and a medical sociologist. A community representative was present at one meeting during which this recommendation was discussed.

External review by Ontario practitioners was obtained through a mailed survey. Final approval of the original guideline report was obtained from the Practice Guidelines Coordinating Committee.

The Cancer Care Ontario Practice Guidelines Initiative has a formal standardized process to ensure the currency of each guideline report. This process consists of periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

Key Evidence

- Four small randomized controlled trials (RCTs) were available for review when this guideline report was originally developed. Of the four trials, two are completed and fully published, one is published in abstract form, and one is closed and reports an interim analysis. Although the RCTs used appropriate clinical trials methodology, including planned interim analyses and early stopping rules, retrospective review revealed imbalances between the treatment arms for subsets of stage IIIA disease and for prognostic factors. These factors and the small size of each study limit the interpretation of the results.
- The data from two of the four trials were not combined because the data were not mature in one case and not extractable in the other. The two fully published, completed trials reported a survival benefit for patients treated with preoperative chemotherapy ± postoperative radiotherapy compared with patients who received no preoperative chemotherapy. One trial reported a median survival of 26 months for preoperative

chemotherapy versus eight months for control ($p<0.001$). A second trial reported an estimated median survival of 64 months for preoperative chemotherapy plus surgery versus 11 months for control ($p<0.008$) and three-year survival of 56% versus 15% for the two treatment groups respectively. A pooled analysis of two-year survival data from the two completed RCTs yielded an odds ratio for death of 0.18 (95% CI, 0.06 to 0.51) in favour of preoperative chemotherapy.

- There was no difference in postoperative mortality in the trials reviewed. Toxicities associated with chemotherapy were limited primarily to neutropenic fever, nausea and vomiting.
- Since the release of the original guideline two randomized controlled trials published in abstract form were reviewed by the Lung Cancer DSG. Both studies reported no difference in median survival time, and one study reported no difference in the two-year survival rate. Methodologic problems existed in both these studies: in one study, patients in the immediate surgery group who were inoperable received the same chemoradiotherapy regimen as did patients in the combined modality group, and the other study was closed prematurely because of low accrual.

Related Guidelines

- #7-1: *Postoperative Adjuvant Chemotherapy and/or Radiation Therapy in Stage II and IIIA Completely Resected NSCLC*.

Funding

The PEBC is supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from its funding agencies.

Contact Information

For information about the PEBC and the most current version of all reports,
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Evidence-based Series #7-4 version 2: Section 2

Use of Preoperative Chemotherapy With or Without Postoperative Radiotherapy in Technically Resectable Stage IIIA Non-Small Cell Lung Cancer: A Systematic Review

Members of the Lung Cancer Disease Site Group

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

These guideline recommendations have been ENDORSED, which means that the recommendations are still current and relevant for decision making.
Please see Section 3: Document Review Summary and Tool for a summary of updated evidence published between 2002 and 2012, and for details on how this Clinical Practice Guideline was ENDORSED.

Section Date: April 2002

Information from the original guideline report is labeled ORIGINAL and new information that has emerged from review and updating activities is labeled UPDATE in this report.

I. QUESTION

Should preoperative (neoadjuvant) cisplatin-based chemotherapy with or without radiotherapy be offered to patients with technically resectable stage IIIA non-small cell lung cancer (NSCLC), in order to improve survival? Resectability should be determined preoperatively by a thoracic surgeon.

II. CHOICE OF TOPIC AND RATIONALE

Members of the Lung Cancer Disease Site Group (Lung DSG) were polled to ascertain their personal beliefs about what topics might be important to consider for guideline development. It was agreed that the use of preoperative treatment in patients with resectable, stage IIIA NSCLC was an important topic for a practice guideline. Although historically, patients with stage IIIA NSCLC have not been considered candidates for surgery, it is hypothesized that preoperative systemic treatment may improve resectability which, in

turn, may improve survival. There have been many phase II studies of preoperative chemotherapy (1-10), but only recently have results of randomized controlled trials (RCTs) become available examining the effectiveness of preoperative chemotherapy in patients with stage IIIA NSCLC (11-14).

The Lung DSG acknowledges that patients with resectable clinical stage IIIA NSCLC represent a heterogeneous group including such dissimilar presentations as T1N2, T3N0 and T3N1. However, there are insufficient data upon which to examine the role and value of preoperative chemotherapy in subsets smaller than the entire group of resectable clinical stage IIIA NSCLC as tested in the completed and ongoing RCTs.

III. METHODS

Guideline Development

This practice guideline report was developed by the Cancer Care Ontario Practice Guidelines Initiative (CCOPGI), using the methodology of the Practice Guidelines Development Cycle by Browman et al (1u). Evidence was selected and reviewed by four members of the CCOPGI's Lung Cancer Disease Site Group (Lung DSG) and methodologists.

The practice guideline report is a convenient and up-to-date source of the best available evidence on the use of preoperative, cisplatin-based chemotherapy with or without postoperative radiotherapy in technically resectable stage IIIA NSCLC, developed through systematic reviews, evidence synthesis and input from practitioners in Ontario. The report is intended to enable evidence-based practice. The Practice Guidelines Initiative is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

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

The CCOPGI has a formal standardized process to ensure the currency of each guideline report. This consists of periodic review and evaluation of the scientific literature, and where appropriate, integration of this literature with the original guideline information.

Guideline History

This practice guideline report was originally completed on September 15, 1997 and published in *Cancer Prevention and Control* 1998;2(1):32-39. The guideline was reviewed monthly from June 1998 through December 1999, and most recently in April 2002. New information that emerged from updating activities prior to January 2000 is included in this report. Evidence that has emerged since that time is currently being reviewed by the Lung Cancer DSG. The guideline will be revised in 2002 to incorporate the relevant new evidence. In this report, information from the original guideline report is labeled ORIGINAL and new information that has emerged from review and updating activities is labeled UPDATE.

Literature Search Strategy

Original: September 1997

MEDLINE searches of the English language literature were done for the period January 1990 to June 1997. Search terms included the following medical subject headings: non-small cell lung carcinoma, lung neoplasms, adjuvant chemotherapy, clinical trials, research design, practice guidelines; and the following text words: neoadjuvant, induction, preoperative. Recently published literature was also identified by members of the Lung DSG. Articles cited in relevant papers and recently published reviews were retrieved and reviewed. The Physician Data Query (PDQ) database was searched to find ongoing clinical trials. The Proceedings from

the meeting of the American Society of Clinical Oncology (ASCO), May 1997, were also reviewed.

Update: April 2002

The original literature search has been updated using MEDLINE (through March 2002), CANCERLIT (through March 2002), the Cochrane Library (Issue 1, 2002) and the proceedings from the annual meetings of the American Society of Clinical Oncology (1998 through 2001).

Inclusion Criteria

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

1. Randomized controlled trials (RCTs) that administered chemotherapy, with or without radiation treatment, prior to surgery, and included surgery in both treatment arms, in patients with technically resectable stage IIIA NSCLC.

Synthesizing the Evidence

Original: September 1997

Survival data from two of the four RCTs were pooled to obtain a more precise estimate of the effect of preoperative chemotherapy + surgery ± radiotherapy versus surgery ± radiotherapy. The third trial did not report survival data in a manner that allowed extraction of the data for this analysis. The results of the fourth trial were neither mature nor fully published and were therefore excluded from the pooled analysis. Odds ratios and 95% confidence intervals were calculated using a random effects model (15). Results are expressed such that an odds ratio greater than 1.0 favours the surgery alone arm and an odds ratio less than 1.0 favours the preoperative chemotherapy ± radiotherapy arm. The Meta-Analyst[0.988] program provided by Dr. J. Lau, Tufts New England Medical Centre, was used to perform this analysis.

Update: April 2002

A meta-analysis was not repeated with the two abstracts that emerged from updating activities since the available data was limited and there were indications of methodological problems with both (2u, 3u). New evidence that is currently under review by the Lung DSG will be considered for data synthesis.

IV. RESULTS

Literature Search Results

Original: September 1997

Four relevant trials were identified for review and are discussed in this report. Two of the four trials are fully published and report final results (11-12), the third trial reports an interim analysis (13), and the fourth trial reports preliminary results in an abstract published in the 1997 proceedings of the American Society of Clinical Oncology (ASCO) (14). All four trials were designed to compare preoperative cisplatin-based chemotherapy followed by surgery against surgery alone in patients with technically resectable stage IIIA NSCLC. However, in three of the four trials, some patients received postoperative radiotherapy. The features of the trials and results are presented in Table 1.

Update: April 2002

The new evidence includes two randomized controlled trials reported in abstract form (2u, 3u). The new evidence is inconsistent with the data used to inform the original practice guideline report. However, the strength of the new evidence *does not alter* the conclusions of the original document. The features of the trials and results have been added to Table 1. Additional evidence is currently under review by the Lung DSG (4u-8u).

Table 1. Randomized controlled trials of preoperative chemotherapy plus surgery versus surgery alone.

Trial	Disease Stage	n	Treatment Allocation	Median Follow-up (mo)	Median Disease-free Survival (mo)	p-value	Median Survival (mo)	Overall Survival (%)	p-value
Rosell (11)	IIIA	30 30	CT+S* S alone	24 19	20 (95% CI, 12 to 30) 5 (95% CI, 4 to 7)	p<0.001 (Kaplan-Meier)	26 (95% CI, 16 to 34) 8 (95% CI, 7 to 10	23% (2yr) 0%	p<0.001 (Kaplan-Meier)
Roth (12)	IIIA	28 2	CT+S† S alone	37 overall	Not yet reached 9	p=0.015	64‡§ 11	56‡ (3yr) 15	NR
Pass (13)	IIIA (N2)	13 14	CT+S+CT S+RT	30 35	NR	NR	29 16	NR	NR
Elias (14)	IIIA (N2)	23 24	CT+S+CT+RT RT+S+RT	NR	9 12	0.98	19 23	NR	0.64
Yoneda (2u)	IIIA IIIB	42 41	CT + RT + S S alone	NR	NR	NR	14 15	40% (2yr) 37%	NR
Payne (3u)	IIIA	35 T	CT + S + CT RT alone	≥ 24	NR	NR	19 16	NR	NR

Notes: CI – confidence interval, CT – chemotherapy, mo – month(s), n – number, NR – not reported, RT – radiotherapy, S – surgery, T – total, yr – year.

* Both groups received mediastinal RT to 50 Gy 4 weeks post-surgery.
† 53% versus 59% of patients in the CT+S versus S alone arms respectively received RT post-surgery.
‡ Estimated figures
§ p<0.008

Outcomes

Summary of Randomized Trials

Original: September 1997

Both completed RCTs randomly allocated patients to receive either preoperative chemotherapy plus surgery or surgery alone (11,12). However, in both treatment arms in both trials, some patients also received postoperative radiotherapy. The two RCTs showed highly significant survival differences in favour of preoperative cisplatin-based chemotherapy with or without radiotherapy (11,12).

Rosell et al randomized 30 patients to preoperative chemotherapy and 30 patients to surgery without preoperative chemotherapy (11). Both groups received post-operative radiotherapy (50 Gy in four weeks). Median survival for the preoperative chemotherapy group was 26 months (95% CI, 16 to 34) versus 8 months (95% CI, 7 to 10) in the group that did not receive preoperative chemotherapy (p<0.001). Overall survival rates at 2 years were 23% and 0% for treatment with preoperative chemotherapy and without.

Roth et al randomized 28 patients to preoperative chemotherapy plus surgery and 32 patients to surgery alone (12). Just over half of the patients in each group received post-operative radiotherapy. Estimated median survival time was 64 months in the surgery plus preoperative chemotherapy group and 18 months for control (p=0.008). Overall survival rates at three years were estimated at 56% and 15% in the two groups respectively. The trials by Rosell and Roth trials stopped accrual in advance of achieving enrolment targets because interim analyses demonstrated statistically significant survival differences between the

treatment groups. The interim analysis by Roth et al was conducted according to a preplanned stopping rule.

The third RCT is an ongoing U.S. National Cancer Institute (NCI) trial which reported preliminary results in 1992 (13). Patients are assigned to either preoperative chemotherapy plus surgery plus postoperative chemotherapy (n=13 at time of reporting) or surgery plus postoperative irradiation (n=14 at time of reporting). An interim analysis demonstrated a trend in favour of the preoperative chemotherapy group for median survival (28.7 months versus 15.6 months for postoperative chemotherapy, p=0.095).

The fourth RCT by the Cancer and Leukemia Group B (CALGB) was designed to compare best local regional therapy with or without chemotherapy (14). Patients were randomized to receive two cycles of etoposide/cisplatin (PE), followed by surgery, two more cycles of PE, then radiotherapy of 60 to 64 Gy (n=23) or radiotherapy of 40 Gy, followed by surgery and radiotherapy of 16 to 20 Gy (n=24).

The trial closed early due to slow and poor accrual. The median follow-up time was not reported. The failure-free median survival time was 12 months for surgery plus pre- and post-operative radiotherapy versus nine months for preoperative chemotherapy plus surgery plus chemo-radiotherapy (p=0.98). Median survival was 23 months for surgery plus pre- and post-operative radiotherapy versus 19 months for preoperative chemotherapy plus surgery plus chemo-radiotherapy (p=0.64). The preliminary results did not confirm the findings of the two fully published trials which detected a survival benefit for preoperative chemotherapy in stage IIIA NSCLC; the results from further follow-up are awaited.

Update: April 2002

Yoneda et al reported in abstract form the results of a prospective randomized trial using induction chemoradiotherapy (vindesine/cisplatin for $\geq$2 courses; radiotherapy 50-60 Gy) followed by surgery versus immediate surgery in 83 patients with stage IIIA and IIIB disease (IIIA 39 patients; IIIB 44 patients) (2u). Only 23 of the 42 (55%) combined-modality-treated patients underwent thoracotomy and 15 had a complete resection. Of those assigned to immediate surgery, 20 of 41 (49%) underwent thoracotomy and 16 had a complete resection. There were more pathological confirmed negative lymph nodes in those treated by induction chemoradiotherapy (11/42 vs. 3/41, intent-to-treat analysis) but there was no major difference in the median survival time (14 vs. 15 months) or in the two year survival rate (40% vs. 37%)(significance not reported). The design of the study makes it difficult to assess the impact of the combined modality therapy under investigation, because patients in the immediate surgery group who were inoperable received the same chemoradiotherapy regimen as did patients in the combined modality group.

Although the second RCT does not directly address the specific topic of this guideline, it does inform the issue of management of patients with stage IIIA NSCLC. For many oncologists, the treatment of choice has been radiotherapy alone. In this study, 35 patients with technically resectable, early stage IIIA NSCLC were randomized to induction chemotherapy (C), surgery (S), and postoperative C (C: cisplatin 120 mg/m^2 IV d1, 29 and vinblastine 6 mg/m^2 d 1, 15, 22, 29, 43) or radiotherapy (RT) alone to the primary and mediastinum (RT: 60 Gy/30 X 2 Gy/6 weeks) (3u). Thirty one eligible patients (C+S arm, n=15; RT arm, n=16) were balanced for gender, performance status, cell type, node size, but not median age (C+S arm, 61 years; RT arm, 52 years). With minimum follow-up of 24 months, median survivals in the C+S arms and RT arms were 19 vs. 16 months respectively (not significantly different, no statistical data provided). The study was closed prematurely because of low accrual. There is, therefore, insufficient evidence to conclude that radiotherapy alone is equivalent to preoperative chemotherapy followed by surgery.

Pooled Analysis

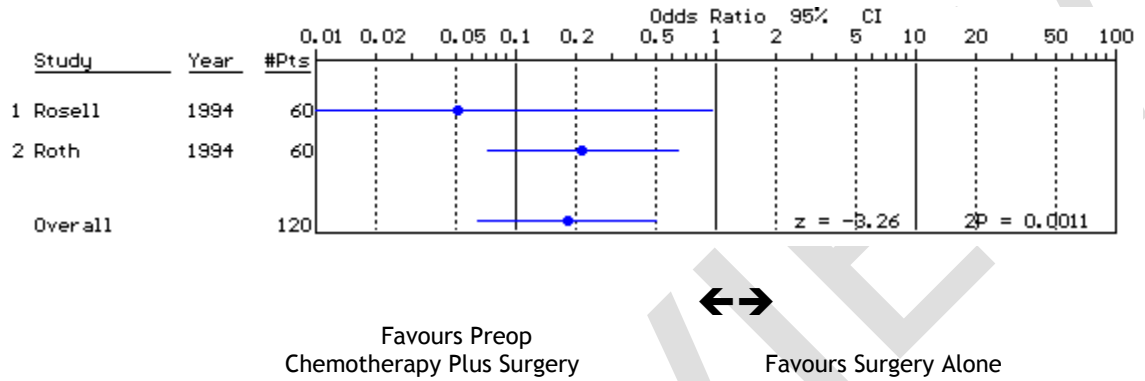
Original: September 1997

The pooled analysis of two-year survival data from the Roth and Rosell randomized trials (11,12) yielded an odds ratio of 0.18 (95% CI, 0.06 to 0.51) (Figure 1). This result favours the use of preoperative chemotherapy ± radiotherapy.

Update: April 2002

There is no additional evidence on this topic at this time.

Figure 1. Meta-analysis of two trials of preoperative chemotherapy + surgery vs surgery alone.



Toxicity

Original: September 1997

Acute toxicity from chemotherapy was mild in the Rosell trial with no episodes of serious myelosuppression, renal or gastrointestinal toxicity noted (11). Chemotherapy in the Roth trial produced more serious myelotoxicity; 80% of patients developed grade 3 or 4 neutropenia after their first course of chemotherapy and four patients (15%) required hospitalization for the treatment of neutropenic fever. (12) Of the patients who received more than one cycle of chemotherapy, 70% required dosage reduction due to grade 4 neutropenia. Other toxicities included nausea and vomiting, diarrhea, hypomagnesemia and alopecia. There were no differences in post-operative morbidity or mortality between treatment groups.

Update: April 2002

There is no additional evidence on this topic at this time.

V. INTERPRETIVE SUMMARY

Original: September 1997

During the development of the original practice guideline, the interpretative summary was not a unique component of the practice guideline report

Update: April 2002

The new evidence reported in abstract form is inconsistent with the data used to inform the original practice guideline report. However, the strength of the new evidence does not alter the conclusions of the original document. The recommendations in the original report remain unchanged.

VI. ONGOING TRIALS

Protocol ID(s)	Title and details of trial
CTSU, E-S9900, NCCTG-S9900, RTOG-L0015, SWOG-S9900	Phase III randomized study of surgery with or without preoperative paclitaxel and carboplatin in patients with stage IB, II, or selected IIIA non-small cell lung cancer. Projected accrual: 600 patients over 4 years. Status: active. Summary last modified: 08/2001.

VII. DISEASE SITE GROUP CONSENSUS PROCESS

Original: September 1997

The Lung Cancer DSG deliberated extensively over the evidence on this topic. Although there is evidence from randomized controlled trials suggesting a benefit for patients treated with preoperative chemotherapy, there are concerns about the data reported in the two completed trials. The concerns include:

a) The small number of patients in the treatment arms of the trials. In one study, accrual was terminated early because of a statistically significant difference at the interim analysis; the alternative (ie. not stopping the study) would have raised an ethical issue of continuing a trial despite an unanticipated huge difference that was highly significant, both statistically and clinically.
b) The inclusion of a heterogeneous group of stage III patients, including clinical stage IIIA patients in one study, 40% of whom proved to be stage IIIB upon pathological staging. An imbalance of stage III subsets between the arms of trials may contribute to, or be responsible for some of the observed differences in survival.
c) The prevalence of a known prognostic factor (mutated K-ras oncogenes) was different between the preoperative chemotherapy arm and the control arm of the Rosell study ($p=0.05$). This may account for some of the observed difference in survival between the two arms of this study.
d) The chemotherapy regimens administered in the trials are not comparable; there is a two-fold difference in the dose of cisplatin used in the two trials. However, given that the data are from RCTs and that both trials demonstrate a benefit for preoperative chemotherapy, the findings suggest that the intervention is effective at either dose of chemotherapy. The dose and schedule of the chemotherapy regimens would be problematic if the trial results were not consistent.
e) All subjects in the Rosell et al study (11) received post-operative radiation treatment, as did a majority of subjects in the Roth et al study (12). It is impossible to assess the independent or interdependent contributions of the post-operative radiation to the main outcome of interest, which is survival. The improved result with preoperative chemotherapy may be due to the chemotherapy or to the combination of chemotherapy and radiation treatment. However, patients in both of the completed trials received radiation and thus, in the context of an RCT, this criticism is weak. The trials show that for patients who received postoperative radiation, preoperative chemotherapy works. The question then is whether this result can be generalized to patients who do not receive postoperative radiation.
f) Both trials were conducted in single institutions which may increase the risk of nongeneralizable results. While the potential for bias exists, this is the best available evidence at this time. The fact that there are two very positive completed RCTs with a third trial that appears to be positive lends credence to the findings; there is consistency in randomized trials for the benefit of preoperative chemotherapy. The design and completion of a multicentre trial would enhance the generalizability of these findings.
g) The extremely large differences in survival were felt to be much greater than could reasonably be expected to occur. Although the magnitude of difference is large, the two

trials described in this report independently found survival differences that were similar in magnitude. If, in fact, the findings are "too good to be true", it is more likely that the difference is smaller than observed rather than that there is no difference at all.

h) The inclusion of only a small number of T3N0 patients in these trials makes it impossible to comment on how this subset of stage IIIA NSCLC should be managed. The issue is how generalizable the findings are to the entire population of stage IIIA patients. Based on the data available, it is impossible to answer this question.

The preliminary results of the CALGB trial do not confirm the survival benefit reported in the two completed trials. Further follow-up and analysis of the data is anticipated.

Members of the Lung Cancer DSG strongly support ongoing trials investigating management strategies for patients with stage IIIA disease. Such trials may investigate not only the role of preoperative chemotherapy, but also the role of preoperative radiotherapy or the role of combined preoperative chemotherapy plus preoperative radiotherapy in the treatment of patients with stage IIIA NSCLC.

Update: April 2002

The Lung DSG members agreed that although the new evidence was inconsistent with the data used to inform the original practice guideline report, its strength did not alter the conclusions or recommendations of the original document. The Lung DSG members are currently reviewing additional evidence that has emerged during updating activities. The guideline will be revised in 2002 to incorporate the new evidence.

VIII. EXTERNAL REVIEW OF THE PRACTICE GUIDELINE REPORT

Original: September 1997

This section describes the external review activities undertaken for the original guideline report. For a description of external review activities of the new information presented in the updated sections of this report, please refer to Update below.

Draft Recommendations

Based on the evidence contained under the Original subtitles throughout this report, the Lung Cancer DSG drafted the following recommendations:

Target Population

These recommendations apply to adult patients with technically resectable Stage IIIA NSCLC, as determined by a thoracic surgeon.

Draft Recommendations

- Stage IIIA non-small cell lung cancer has a number of different presentations including T3N0 (tumour with chest wall involvement without lymph node involvement) and N2 disease (mediastinal lymph node involvement on the same side of the mediastinum as the primary tumour). Although the surgical approach to patients with stage IIIA disease varies, it is generally accepted that T3N0 tumours should be managed by primary surgical resection. The role of surgery for patients who have histological evidence of N2 disease, however, is controversial. Many surgeons regard the presence of N2 disease as a contraindication to surgery.
- There is evidence from four small randomized controlled trials that for patients with technically resectable stage IIIA NSCLC, the use of preoperative cisplatin-based chemotherapy and postoperative radiotherapy results in superior survival compared with surgery and postoperative radiotherapy. Whether the benefits of chemotherapy can be

generalized to patients who do not receive postoperative radiotherapy cannot be determined from the existing trials.
- Therefore, it is recommended that for patients presenting with histological evidence of N2 disease which is considered by the surgeon to be technically resectable and for which surgery is planned, preoperative chemotherapy +/- postoperative radiotherapy be offered.

Related Guidelines

Cancer Care Ontario Practice Guidelines Initiative's Practice Guideline Report#7-1: *Postoperative Adjuvant Chemotherapy and/or Radiation Therapy in Stage II and IIIA Completely Resected NSCLC*.

Practitioner Feedback

Based on the evidence contained under the Original subtitles in this report and the draft recommendations presented above, feedback was sought from Ontario clinicians.

Methods

Practitioner feedback was obtained through a mailed survey of 148 practitioners in Ontario. The survey consisted of items evaluating the methods, results and interpretive summary used to inform the draft recommendations and whether the draft recommendations above should be approved as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). A third reminder was sent at six weeks. The Lung DSG reviewed the results of the survey.

Results

Key results of the practitioner feedback survey of the original draft guideline report are summarized. Eighty-six (58%) surveys were returned. Eighty-six percent of the respondents agreed or strongly agreed that the methodology and data synthesis used in the development of the report was acceptable. Eighty-one percent of the respondents endorsed the recommendations and 67% agreed or strongly agreed the report should be approved as a practice guideline.

Summary of Main Findings

The main points were:

1. Concern about the small sample size of studies.
2. Statements that N2 patients were not candidates for surgery in practitioners' institutions.
3. Disbelief of results reported in the literature and, consequently, an unwillingness to adopt the recommendation in clinical practice.

Modifications/Actions

The points raised for discussion from the practitioner feedback had previously been discussed and debated by the Lung DSG during the development of the evidence-based recommendations. Specifically, the Lung DSG was also uncomfortable with the small size of the trials, the heterogeneity of stage IIIA disease and the distribution of the IIIA subsets between the treatment arms of the RCTs and other potential confounding factors. The DSG recognized that N2 disease is not considered to be operable cancer by many Canadian surgeons even if it is technically resectable. Despite practitioner feedback on these issues, the DSG felt that the available evidence was important and could not be ignored. After

extensive review of the feedback, the DSG decided not to alter the evidence-based recommendation but to closely monitor the literature for any further studies that would inform this recommendation.

Approved Practice Guideline Recommendations

These practice guideline recommendations reflect the integration of the draft recommendations with feedback obtained from the external review process. They have been approved by the Lung DSG and the Practice Guideline Coordinating Committee.

- Stage IIIA non-small cell lung cancer (NSCLC) has a number of different presentations including T3N0 (tumour with chest wall involvement without lymph node involvement) and N2 disease (mediastinal lymph node involvement on the same side of the mediastinum as the primary tumour). Although the surgical approach to patients with stage IIIA disease varies, it is generally accepted that T3N0 tumours should be managed by primary surgical resection. The role of surgery for patients who have histological evidence of N2 disease, however, is controversial. Many surgeons regard the presence of N2 disease as a contraindication to surgery.
- There is evidence from four small randomized controlled trials (12 to 32 patients per treatment arm) that for patients with technically resectable stage IIIA NSCLC, the use of preoperative cisplatin-based chemotherapy and postoperative radiotherapy results in superior survival compared with surgery and postoperative radiotherapy. Whether the benefits of chemotherapy can be generalized to patients who do not receive postoperative radiotherapy cannot be determined from the existing trials.
- Although the interpretation of these trials is made difficult by their small size and presence of retrospectively identified imbalances in prognostic factors, the available evidence lead the Lung Cancer Disease Site Group (DSG) to recommend that preoperative chemotherapy and postoperative radiotherapy be offered to patients with technically resectable, histologically confirmed N2 disease for whom surgery is planned.

Update: April 2002

Because there was very little new evidence that emerged from updating activities and no modifications were made to the guideline recommendations, this updated document was not subject to an additional external review.

IX. PRACTICE GUIDELINE

This practice guideline reflects the most current information and integrates the new evidence with evidence from the original guideline report.

Target Population

These recommendations apply to adult patients with technically resectable Stage IIIA NSCLC, as determined by a thoracic surgeon.

Recommendations

- Stage IIIA non-small cell lung cancer (NSCLC) has a number of different presentations including T3N0 (tumour with chest wall involvement without lymph node involvement) and N2 disease (mediastinal lymph node involvement on the same side of the mediastinum as the primary tumour). Although the surgical approach to patients with stage IIIA disease varies, it is generally accepted that T3N0 tumours should be managed by primary surgical resection. The role of surgery for patients who have histological evidence of N2 disease, however, is controversial. Many surgeons regard the presence of N2 disease as a contraindication to surgery.

- There is evidence from four small randomized controlled trials (12 to 32 patients per treatment arm) that for patients with technically resectable stage IIIA NSCLC, the use of preoperative cisplatin-based chemotherapy and postoperative radiotherapy results in superior survival compared with surgery and postoperative radiotherapy. Whether the benefits of chemotherapy can be generalized to patients who do not receive postoperative radiotherapy cannot be determined from the existing trials.
- Although the interpretation of these trials is made difficult by their small size and presence of retrospectively identified imbalances in prognostic factors, the available evidence leads the Lung Cancer Disease Site Group (DSG) to recommend that preoperative chemotherapy and postoperative radiotherapy be offered to patients with technically resectable, histologically confirmed N2 disease for whom surgery is planned.

Related Guidelines

Cancer Care Ontario Practice Guidelines Initiative's Practice Guideline Report #7-1: *Postoperative Adjuvant Chemotherapy and/or Radiation Therapy in Stage II and IIIA Completely Resected NSCLC*.

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Original: September 1997

This section includes all references from the original guideline report.

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Update: April 2002

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

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Appendix 1: Regimens and Schedules used in the Randomized Controlled Trials

Rosell (11)

Chemotherapy

Mitomycin (6 mg/m^2 IV)
Ifosfamide (3 g/m^2 IV) + mesna (1 g/m^2)
Cisplatin (50 mg/m^2 IV)
(plus an antiemetic, metoclopramide, 3 mg/kg IV administered 30 minutes pre-CT and 90 minutes post-CT)
3 courses of CT were offered, then patients underwent surgery

Surgery

Thoracotomy within 4-5 weeks post course 3 chemotherapy for the combination arm and within 2 weeks of enrollment for the surgery alone arm.

Radiotherapy

Both groups of patients received mediastinal radiotherapy (to 50 Gy) 4 weeks post-surgery.

Roth (12)

Chemotherapy

Cyclophosphamide (500 mg/m^2 IV day 1)
Etoposide (100 mg/m^2 IV, days 1,2 & 3)
Cisplatin (100 mg/m^2 IV day 1)
CT administered q 28 days for 3 courses, then patients underwent surgery

Surgery

Thoracotomy; all resected patients underwent mediastinal lymph node dissection.

Pass (13)

Chemotherapy

Preoperatively, two 21 day cycles of:
Etoposide (120 mg/m^2 bolus IV on 3 consecutive days)
Cisplatin (80mg/m^2)
Postoperatively, four cycles of the same regimen.

Surgery

Resection of the primary tumour with concomitant interlobar and mediastinal lymph node dissection.

Radiotherapy

Postoperatively, 54 to 60 Gy mediastinal radiation in 6.5 weeks.

Elias (14)

Chemotherapy

Preoperatively and postoperatively, two cycles of:
Cisplatin (35 mg/m^2 days 1-3)
Etoposide (200 mg/m^2 days 1-3)
G-CSF support

Surgery

Type of surgery not reported.

Radiotherapy
Preoperatively, 40 Gy
Total dose of RT on both arms: 54 Gy if completely resected, 60 Gy if incompletely resected.

Yoneda (2u)

Chemotherapy
Vindesine/cisplatin for ≥ 2 courses

Radiotherapy
50-60 Gy

Surgery
23 of 42 combined-modality-treated patients had thoracotomy, and 15 had a complete resection.
20 of 41 surgery-alone-treated patients had thoracotomy, and 16 had a complete resection.

Payne (3u)

Chemotherapy
Cisplatin 120 mg/m^2 IV d 1, 29 and vinblastine 6 mg/m^2 d 1, 15, 22, 29, 43

Radiotherapy
60 Gy/30 x 2 Gy/6 weeks.

Ontario
Cancer Care Ontario
Action Cancer Ontario

Evidence-based Series #7-4 Version 2: Section 3

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

Use of Preoperative Chemotherapy With or Without Postoperative Radiotherapy in Technically Resectable Stage IIIA Non-Small Cell Lung Cancer:

Document Review Summary

N. Leighl, N. Ismaila, and the Lung Cancer Disease Site Group

Review Date: October 1, 2012

The 2002 guideline recommendations are

ENDORSED

This means that the recommendations are still current and relevant for decision making.

OVERVIEW

The original version of this guidance document was released by Cancer Care Ontario's Program in Evidence-based Care in 1997, and updated in 2002.

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

DOCUMENT ASSESSMENT AND REVIEW RESULTS

Question Considered
Should preoperative (neoadjuvant) cisplatin-based chemotherapy, with or without postoperative radiotherapy, be offered to patients with technically resectable stage IIIA non-small cell lung cancer (NSCLC), in order to improve survival? Resectability should be determined preoperatively by a thoracic surgeon.

Literature Search and New Evidence
The new search (April 2002 to February 2012) yielded 11 (3 meta-analysis, 5 RCTs and 2 ongoing studies) references representing 17 RCTs comparing neoadjuvant chemotherapy + surgery versus surgery alone with or without postoperative radiotherapy, of which 4 RCTs were already included inthe existing guideline (these 4 RCTs were also included in the 3 meta-analysis identified). Seven RCTs are potentially new studies, of which 4 have full text publications, 2 are on-going studies and 1 is in abstract form. Brief results of these searches are shown in the Document Review Tool.

Impact on Guidelines and Its Recommendations
The new data supports existing recommendations. Hence, the Lung Cancer DSG ENDORSED the 2002 recommendations on the use of preoperative chemotherapy with or without postoperative radiotherapy in technically resectable stage IIIa non-small cell lung cancer.

Document Review Summary and Tool

Number and title of document under review	7-4 Use of Preoperative Chemotherapy With or Without Postoperative Radiotherapy in Technically Resectable Stage IIIA Non-Small Cell Lung Cancer
Current Report Date	April 2002
Clinical Expert	Dr. Natasha Leighl
Research Coordinator	Nofisat Ismaila
Date Assessed	September 2011
Approval Date and Review Outcome (once completed)	1 October 2012, ENDORSED

Original Question(s):
Should preoperative (neoadjuvant) cisplatin-based chemotherapy, with or without postoperative radiotherapy, be offered to patients with technically resectable stage IIIA non-small cell lung cancer (NSCLC), in order to improve survival? Resectability should be determined preoperatively by a thoracic surgeon.

Target Population:
These recommendations apply to adult patients with technically resectable Stage IIIA NSCLC, as determined by a thoracic surgeon.

Study Section Criteria:
Inclusion criteria:
Articles were eligible if they met the following inclusion criteria:

1. They were published/unpublished reports, or abstracts
2. Meta-analysis or randomized controlled trials (RCTs) that administered chemotherapy, with or without radiation treatment, prior to surgery, and included surgery in both treatment arms, in patients with technically resectable stage IIIA NSCLC.

Exclusion criteria:

- Non-randomized trials were excluded

Search Details:

- April 2002 to February 2012 (Medline wk 2 and Embase wk 7)
- 2006 to February 2012 (ASCO Annual Meeting)
- April 2002 to February 2012 (clinicaltrials.gov)

Brief Summary/Discussion of New Evidence:

Of 317 total hits from Medline + Embase, 12 total hits from ASCO conference abstracts, and 105 hits from clinicaltrials.gov searches, 11 (3 meta-analysis, 5 RCTs and 2 ongoing studies) references representing 17 RCTs were found comparing neoadjuvant chemotherapy + surgery versus surgery alone with or without postoperative radiotherapy, of which 4 RCTs were already included in the existing guideline (these 4 RCTs were included in the 3 meta-analysis identified). 7 RCTs are potentially new studies, of which 4 have full text publications, 2 are on-going studies and 1 is in abstract form.

Meta-analysis

Intervention	Type of study	Disease stage	n	Outcome	Brief results	References
CT + surgery vs. surgery alone	Meta-analysis of 4 RCTs	Stage IIIA	209	Survival	The fixed effects HR on survival was 0.72 (95% CI 0.56-0.93) in favour of addition of induction chemotherapy to a standard surgical procedure	Berghmans et al 2005
	Meta-analysis of 5 RCTs	Stage IIIA	331		The combined HRs at 1, 3, and 5 years after surgery were 0.65 (95% CI, 0.43—1.00), 0.87 (95%CI, 0.74—1.03), and 0.88 (95% CI, 0.72—1.07), respectively. However, none of the HRs was significant (p= 0.052, 0.108, and 0.212)	Nakamura et al 2006
	Meta-analysis of 8 RCTs	Stage III & IIIA	1586		HR on survival was 0.84 (95% CI, 0.75–0.95; p=0.005) in favour of neoadjuvant chemotherapy.	Song et al 2010

Randomized control trials not included in the meta-analysis above

Intervention	Population	Median follow up (mo)	Outcomes	Brief results	References
CT + Surgery or RT Vs. Surgery or RT alone	Patients with stage IIIA or locally treatable IIIB NSCLC Median age, 62 yrs (n=274)	12 overall	**P**:Median survival **S**:Median time to disease progression , CR, PR and toxicity	• Median survival was 14.8 months in the docetaxel group and 12.6 months in the control group (difference not statistically significant). • Median times to disease progression were 9.0 months (docetaxel arm) and 7.6 months (control arm) (difference not statistically significant). • There were three complete responses and 25 partial responses in patients treated with docetaxel who were evaluable for response	Mattson et al 2003

				(n = 101). • Docetaxel was well-tolerated: 103 patients (77%) received all three planned cycles. The major toxicity was grade 4 neutropenia (69 patients, 55%) and neutropenic fever (eight patients, 6%). • Radiotherapy was well-tolerated after docetaxel administration.	
CT + Surgery Vs. Surgery alone	Patients who had histologically proved NSCLC and potentially resectable stage IIIA disease Median age, 62 yrs (n=56)	38	**P**: OS **S:** DFS, RR, and toxicity	• The overall response rate to neoadjuvant chemotherapy was 53.6%, with a complete response of 7.1%. • The complete resection rates were 78.6% in the neoadjuvant chemotherapy arm and 60.7% in the primary surgery arm. • The median OS and median DFS was 30 months and 24 months, respectively, in the neoadjuvant chemotherapy arm as compared to 16 months and 11 months in the primary surgery arm (P = 0.04 and P = 0.048). • The 3-year and 5-year survival rate was 49.7% and 31.9%, respectively, for the neoadjuvant chemotherapy arm and 29.2% and 3.6% for the primary surgery arm.	Li et al 2009
RT + Surgery + RT Vs. CT + Surgery + CT + RT	Patients with surgically staged IIIA NSCLC and pathologically documented ipsilateral mediastinal nodal involvement (N2) Median age, 60 yrs (n=50)	41	**P**: OS and failure free survival	• The median failure-free and OS rates were 12 months (95% confidence interval [CI], 9-23 months) and 23 months (95% CI, 19 months-∞) for the RSR arm and 11 months (95% CI, 5-20 months) and 18 months (95% CI, 12-32 months) for the CSCR arm. • The rates of overall and complete surgical resection, downstaging of nodal involvement, and failure-free (P = 0.92) and overall survival (P = 0.41) did not differ between the two treatment arms. • Moreover, in this trial, the chemotherapy regimen was sufficiently toxic to have had a lower completion rate of prescribed therapy in the CSCR arm than in the RSR arm.	†Elias et al 2002
CT + RT + Surgery	Patients with stage	70	**P:** PFS	• In patients with complete resection, the proportion of those	Thomas et al 2008

Vs. CT + Surgery + RT	IIIA–IIIB NSCLC and invasive mediastinal assessment Median age, 59 yrs (n=558)		**S:** OS and the proportion of patients undergoing surgery	with mediastinal downstaging (45 of 98 [46%] and 24 of 84 [29%], p=0·02) and pathological response (59 of 98 [60%] and 17 of 84 [20%], p<0·0001) favoured the interventional group. • However, there was no difference in PFS between treatment groups—either in eligible patients (median PFS 9·5 months, range 1·0–117·0 [95% CI 8·3–11·2] vs 10·0 months, range 1·0–111·0 [8·9–11·5], 5-year PFS 16% [11–21] vs 14% [10–19], hazard ratio (HR) 0·99 [0·81–1·19], p=0·87), in those undergoing tumour resection, or in patients with complete resection. • In patients receiving a pneumonectomy, treatment-related mortality increased in the interventional group compared with the control group (7/50 [14%] vs 3/54 [6%])	
CT + RT + Surgery Vs. CT + Surgery	Patients with stage IIIA NSCLC with mediastinal lymph node metastases Median age, 57 yrs (n=60)	NR	**P**: OS	• Objective response rate was 25% for the both groups. • Surgical resection was performed in 86% and 89%of the patients in CS and CRS groups, respectively. • Event free survival at 3 year was 18% and 32% for patients in CS and CRS group, respectively (HR=0.64; 95% CI: 0.36–1.17, P=0.15). • OS at 3 year was 44.4 %. and 52.7% (HR=0.84; 95% CI: 0.44–1.62, P=0.62), respectively. • Grade 3 and 4 neutropenia occurred in 74 and 89%, respectively • There have been 37 deaths to date.	†Tada et al 2009 (Abstract)

Ongoing trials
Retrieved from www.clinicaltrials.gov

Interventions	Official title	Status	Protocol ID	Last updated
Chemotherapy + surgery vs. Chemoradiotherapy + surgery	Pre-operative Chemotherapy Versus Concurrent Chemoradiotherapy in N2 Positive IIIA Non Small Cell Lung Cancer (NSCLC)	Recruiting	NCT00452803	July 9, 2010
Erlotinib + Surgery vs.	Erlotinib Versus Gemcitabine/Cisplatin as	Recruiting	NCT014078	August

Gemcitabine/cisplatin + surgery	(Neo)Adjuvant Treatment in Non-small Cell Lung Cancer		22	1, 2011

NSCLC, Non-Small Cell Lung Cancer, MDCP=Moderate dose cisplatin, HDCP=High dose cispaltin, CT=Chemotherapy, RT=Radiotherapy, P=Primary, S=Secondary, CR=Complete Response, PR=Partial Response, OS=Overall Survival, DFS=Disease Free Survival, RR=Response Rate
†Study was stopped prematurely due to poor recruitment of patients

1. Does any of the newly identified evidence, on initial review, contradict the current recommendations, such that the current recommendations may cause harm or lead to unnecessary or improper treatment if followed? Answer Yes or No, and explain if necessary, citing newly identified references:	1. NO If Yes, the document will be immediately removed from the PEBC website, and a note as to its status put in its place. **Go to 2**.
2. On initial review, a. Does the newly identified evidence support the existing recommendations? b. Do the current recommendations cover all relevant subjects addressed by the evidence, such that no new recommendations are necessary? Answer Yes or No to each, and explain if necessary:	2. Yes and Yes If both are Yes, the document can be ENDORSED. If either is No, go to 3.
3. Is there a good reason (e.g., new stronger evidence will be published soon, changes to current recommendations are trivial or address very limited situations) to postpone updating the guideline? Answer Yes or No, and explain if necessary:	3. Not applicable If Yes, a final decision can be **DELAYED** up to one year. If No, **go to 4.**
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?	4. Not applicable If Yes, the document needs an **UPDATE**. It can be listed on the website as IN REVIEW for one year. If a full update is not started within the year, it will be automatically **ARCHIVED**. If NO, go to 5.
5. If Q2, Q3, and Q4 were all answered NO, this document should be **ARCHIVED** with no further action.	

Review Outcome	ENDORSE
DSG/GDG Approval Date	1 October 2012
DSG/GDG Commentary	None

New References Identified (Alphabetic order):

1. Berghmans T, Paesmans M, Meert AP, Mascaux C, Lothaire P, Lafitte JJ, et al. Survival improvement in resectable non-small cell lung cancer with (neo)adjuvant chemotherapy: results of a meta-analysis of the literature. Lung Cancer. 2005;49(1):13-23.
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Literature Search Strategy:

Medline

1. meta-Analysis as topic.mp. [mp=ti, ab, ot, nm, hw, ps, rs, ui, tx, ct, 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 synthes?s or quantitative overview?).tw.

5. (systematic adj (review$ or overview?)).tw.

6. (exp Review Literature as topic/ or review.pt. or exp review/) and systematic.tw.

7. or/1-6

8. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.

9. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual 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. (neoadjuvant or preoperative or before surgery or neo adjuvant).tw.

47. (chemotherapy or systemic therapy).mp.

48. 46 and 47

49. 45 and 48

50. 40 and 49

51. (200212: or 2003: or 2004: or 2005: or 2006: or 2007: or 2008: or 2009: or 2010: or 2011: or "2012").ed.

52. 50 and 51

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 synthes?s 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.

26. practice guideline.pt.

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 letter/ or case study/

30. 28 not 29

31. limit 30 to english

32. Animal/

33. Human/

34. 32 not 33

35. 31 not 34

36. exp lung neoplasms/

37. (cancer? or carcinoma? or neoplasms? or tumor?).tw.

38. non small cell lung.tw.

39. 37 and 38

40. 36 or 39

41. (neoadjuvant or preoperative or before surgery or neo adjuvant).tw.

42. (chemotherapy or systemic therapy).tw.

43. 41 and 42

44. 40 and 43

45. 35 and 44

46. (200212$ or 2003$ or 2004$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$).ew.

47. 45 and 46

ASCO Annual Meeting - searched http://www.ascopubs.org/search with keywords: neoadjuvant AND (Lung cancer)

Clinicaltrials.gov – searched http://clinicaltrials.gov/ct2/home with keywords: neoadjuvant AND (Lung cancer)

OUTCOMES DEFINITIONS

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

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

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

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