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Evidence-based Series #7-4 Version 2 – ARCHIVED 2017

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

Evidence-Based Series 7-4 Version 2 was ARCHIVED in 2017 (See Section 3 for details). This means that the recommendations will no longer be maintained but may still be useful for academic or other information purposes.

This document is comprised of the following 3 sections and is available on the CCO Lung Cancer page:

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

December 8, 2017

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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. Natasha Leighl and Glenn G Fletcher, reviewers. Toronto (ON): Cancer Care Ontario; 2013 May [ARCHIVED 2017]. Program in Evidence-based Care Practice Guideline Report No.: 7-4 Version 2 ARCHIVED.

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 Sep 1997	1990-1997	Full Report	Web publication; Journal publication	NA
Updated version Apr 2002	1997-2002	New data added to original full report	Updated Web publication	NA
Version 2 May 2013	2002-2012	New data found (see Document Review Summary and Tool In Appendix A)	Updated Web publication	2002 recommendations are **ENDORSED**
Version 2 Reviewed Dec 2017	Until Aug 2017	New data found in Section 3: Document Review Summary and Tool	Updated Web publication	2002 recommendations are **ARCHIVED**

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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 ARCHIVED, which means that the recommendations are no longer maintained but may be of interest for educational or other information purposes. See Section 3 for rationale.

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

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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)

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 2-1.

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 2-1. Additional evidence is currently under review by the Lung DSG (4u-8u).

Table 2-1. 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

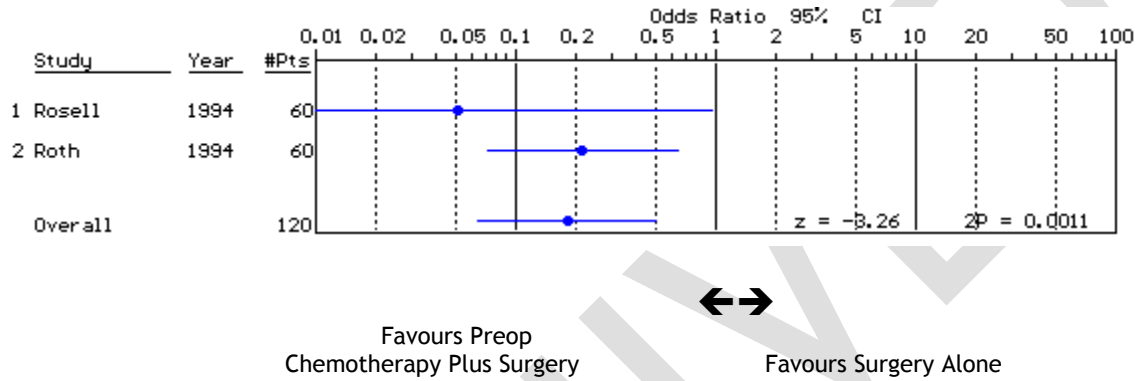
Original: September 1997

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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Update: April 2002

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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

Natasha Leighl, Glenn G. Fletcher, and the Lung Cancer Disease Site Group

December 8, 2017

The 2002 guideline recommendations are ARCHIVED

This means that the recommendations will no longer be maintained but may still be useful for academic or other information purposes.

Background

The original guideline was completed in 1997. The Inclusion criteria were "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". Ideally, trials would have both arms identical other than the use of neoadjuvant chemotherapy. It is unclear whether studies with radiotherapy in only one arm meet these criteria; however such studies would be considered confounded and would give only indirect information about the effect of chemotherapy. Some such studies are including in the previous versions of the guideline, however inclusion does not appear comprehensive.

Summary of Previous Versions

The initial version of the document was dated September 1997 and included two RCTs (Roth et al 1994 [1] and Rosell et al, 1994 [2]) and which evaluated chemotherapy + surgery versus surgery alone. It included two additional studies which did not have equivalent arms: one trial had (chemotherapy + surgery + chemotherapy) versus (surgery + radiotherapy), while the other had (chemotherapy + surgery + chemotherapy + radiotherapy) versus (radiotherapy + surgery + radiotherapy). The April 2002 version indicates that "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." The April 2002 version added 2 additional trials to Table 2-1; however, both were also confounded.

There was a literature search in March 2002 that found publications with longer term follow-up of the trials by Roth [3] and Rosell [4], as well as a trial by Depierre et al [5]. Two other trials were confounded by the use of radiotherapy in only one arm. All of these publications from the March 2002 search were included in the update reference list but data was not extracted and they were not incorporated into the guideline. It is stated that "evidence that has emerged since that time [January 2000] is currently being reviewed by the Lung Cancer DSG. The guideline will be revised in 2002 to incorporate the relevant new evidence." It would appear that this 2002 update did not take place.

The document assessment in 2012 (see Appendix A) included seven publications. It should be noted that several of these trials were confounded by use of radiotherapy and/or adjuvant chemotherapy and therefore do not directly answer the question regarding use of neoadjuvant chemotherapy. The new trials were not incorporated into the literature review, key evidence, or recommendations and the publications from the March 2002 search were not included. It is noted that the literature search strategy only resulted in 317 hits, in contrast to 1504 hits for the same time period in the current search, suggesting the search was not comprehensive. This version, approved October 2012, is the current version, although assigned a release date of May 16, 2013.

Recommendations in the 1997 and 2002 versions of this guideline are based primarily on 2 trials which included 120 patients. The guideline does not address the use of chemoradiotherapy, radiotherapy, whether surgery is required, timing of chemotherapy (neoadjuvant, adjuvant, or both), optimal chemotherapy, or use of immunotherapy or immuno-chemotherapy. The question of whether to use neoadjuvant chemotherapy together with surgery may be too restrictive given the wider range of data available and incorporated into other more recent guidelines.

In 2016, 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 (GF) conducted an updated search of the literature. A clinical expert (NL) reviewed and interpreted the new eligible evidence and proposed that the existing recommendations should be archived. An Expert Panel composed of members of the Lung Cancer Disease Site Group (Appendix 3-2) met on 8 Dec 2017 and agreed with the proposal to archive Guideline 7-4v2.

A summary of the 2017 assessment and review is provided in the Document Review Tool. The results of the current search are appended following this tool.

Document Review Tool

Number and Title of Document under Review	7-4v2 Use of Preoperative Chemotherapy With or Without Postoperative Radiotherapy in Technically Resectable Stage IIIA Non-Small Cell Lung Cancer
Current Report Date	May 16, 2013
Date Assessed (by DSG or Clinical Program Chairs)	Dec 16, 2016
Health Research Methodologist	Glenn Fletcher
Clinical Expert	Natasha Leighl
Approval Date and Review Outcome (once completed)	Dec 8, 2017 ARCHIVE

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 Selection Criteria:
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.

Recommendations (in 2002/2013 version)

- 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.

Previous Search Details:
Sept 1997 (original document): Medline Jan 1990-June 1997; ASCO proceedings May 1997

April 2002 (partial update): The guideline was reviewed monthly from June 1998 through December 1999. New information that emerged from updating activities prior to January 2000 was included in this report.

> There was a search of Medline to March 2002, CANCERLIT to March 2002, Cochrane (Issue 1 2002), ASCO proceedings 1998-2001. Publications were included in a reference list but data was not extracted or considered in the text. The DSG was to update in 2002, however no record of this was located.

May 2013 (2012 assessment): Apr 2002 to Feb 2012 Medline, Embase, ASCO conferences, clinicaltrials.gov. Attached as Section 3 of the document but the recommendations and systematic review (Sections 1 and 2) not updated.

Current Search (until Aug 2017) and Summary of New Evidence: appended following this table.

Clinical Expert Interest Declaration: None

1. Does any of the newly identified evidence contradict the current recommendations? (i.e., the current recommendations may cause harm or lead to unnecessary or improper treatment if followed)	No. None of the new evidence (e.g NATCH trial) contradicts the current recommendation. Use of radiotherapy was outside of the scope of the original guideline, yet included in the recommendations. Neoadjuvant chemoradiotherapy is stated in some guidelines/reviews to be standard of care. The role of surgery is still subject to debate, but was also outside of scope.
2. Does the newly identified evidence support the existing recommendations?	Yes. The NATCH study supports the existing recommendations, as do the other studies identified in the review. The evidence suggests neoadjuvant chemotherapy plus surgery is better than surgery alone. Surgery alone, though, may not be the appropriate comparison, and the guideline does not address use of radiotherapy or adjuvant chemotherapy either together with

	or instead of neoadjuvant chemotherapy.
3. Do the current recommendations cover all relevant subjects addressed by the evidence? (i.e., no new recommendations are necessary)	No. For historical reasons, the topic has been approached by very specific treatment modality and sequence which does not allow for a complete picture of the evidence and recommendations for this disease. It is proposed that we ARCHIVE this and other stage III guidelines and UPDATE using these clinical questions – 1. What is the optimal approach to resectable Stage III NSCLC? 2. What is the optimal approach to unresectable Stage III NSCLC? We will need to clarify how we determine resectability, how we select candidates for different approaches and evidence gaps.
Review Outcome as recommended by the Clinical Expert	Archive, with preparation of a new, more comprehensive guideline
If the outcome is UPDATE, are you aware of trials now underway (not yet published) that could affect the recommendations?	
DSG/GDG Commentary	The LUNG-ART trial will add to our current knowledge of potential approaches to resectable stage III NSCLC.

2017 Review

A literature search for randomized controlled trials (RCTs), systematic reviews or meta-analyses, and guidelines on neoadjuvant chemotherapy in lung cancer was conducted on August 28, 2017 using Medline and Embase (see Appendix 3-1 for search strategy). After removal of duplicates there were 3233 citations. An additional 24 publications were added from other sources such as website searches for guidelines or reference lists of publications. After excluding 3123 publications, there were 26 publications of guidelines, 30 systematic reviews or meta-analyses, 24 RCTs on chemotherapy + surgery versus surgery alone, and 54 other RCTs (described later). It is noted that there were also several very recent non-systematic reviews that address issues of neoadjuvant therapy and multimodality treatment of lung cancer.

Guidelines

The search found 26 publications of guidelines, representing 16 guidelines from 2012-2017 [6-23] (see Table 3-1) and 7 older guidelines [24-31]. Recommendations generally do not support the routine use of neoadjuvant chemotherapy plus surgery as treatment for resectable Stage IIIA NSCL, although it may be suitable for selected patients. These guidelines

are more recent and comprehensive than the PEBC/CCO guideline being reviewed. Additionally, the recent (2017) PEBC/CCO guideline [6] on treatment of stage III (N2 or N3) NSCLC deals with a partially overlapping patient population recommends definitive chemoRT or induction chemoRT plus surgery if potentially resectable. Some guidelines indicate that chemoRT (alone or prior to surgery) is the standard of care, and that surgery does not necessarily improve survival.

Systematic Reviews and Meta-analyses

In addition to the reviews in guidelines, several other systematic reviews and meta-analyses relevant to treatment of stage IIIA NSCLC were found. Those specifically on neoadjuvant chemotherapy plus surgery versus surgery alone surgery [32-39], are discussed in the next section. Additional topics covered are as follows:

- induction chemo + chemoRT vs chemoRT [40,41],
- chemo (+/- RT) + surgery versus chemoRT [42],
- chemo and/or RT + surgery vs surgery [43],
- induction (chemotherapy or chemoRT) then randomized to surgery vs RT [44],
- chemo/chemoRT then (surgery vs chemoRT/RT) [45],
- chemo + RT vs chemoRT (sequential vs concurrent) [46-49],
- chemoRT vs (chemotherapy or RT) [50-52],
- chemoRT vs surgery [53],
- neoadjuvant vs adjuvant chemotherapy [54,55],
- comparison of various chemotherapies [56,57],
- other topics [58-61]

Neoadjuvant chemotherapy + surgery vs surgery alone

For this comparison, only trials with both arms equivalent, other than for the use of neoadjuvant chemotherapy in one arm, are included. Trials with addition of radiotherapy in both arms were allowed. The most relevant and complete meta-analyses comparing neoadjuvant chemotherapy plus surgery versus surgery alone for stage IIIA disease are those by Song et al [38] and by Horita et al [36] (see Table 3-2. The Song et al meta-analysis was reported in the 2012 document assessment but not incorporated into the guideline. The meta-analysis included 1586 patients from 8 trials [1-5,62-66] in their sub-analysis of stage III disease (see Table 3-3). For patients with stage III NSLC they reported overall survival combined hazard ratio =0.84 (95% confidence interval 0.75 to 0.95; p=0.005). Horita et al included 1447 patients from six of the same trials [1-4,62-65] plus 1 other small trial [67]. For patients with stage III disease they reported a pooled hazard ratio for overall survival of 0.77 (95% CI, 0.68 to 0.87; p<0.001). Additional publications [68-70] for two of the trials were found in the literature search. An additional 10 trials conducted in patients with stage III or locally advanced disease, or which reported some data for this subgroup were also found and included 1229 patients [71-80] (see Table 3-3). While several trials do not distinguish between stages IIIA and IIIB, it is expected that due to the classification as resectable most patients would be stage IIIA.

Other Trial Designs

The above trials address whether neoadjuvant chemotherapy is beneficial for patients who would otherwise only receive surgery (or sometimes adjuvant chemotherapy as well). In order to determine whether neoadjuvant chemotherapy should be recommended in a broader patient population, other trial designs may be important. As the purpose of this review is only to help decide what should be done with the 2012 document, but not create an actual update, only a list (without data extraction) of 19 other study designs included in 54 publications is reported. If further work is done on this guideline or a related topic, it would be the task of a new working group to decide on the scope and thus relevance of these trials. Full-text review was not completed for these publications, and therefore it is recognized that some may not meet all inclusion criteria.

- (chemo vs RT) then surgery [81]
- (chemoRT vs chemo) then surgery [82-84]
- chemo + chemoRT then (chemoRT vs surgery) [85]
- chemo + chemoRT vs chemoRT + chemo [order only]; surgery in both groups [86]
- chemo + chemoRT vs surgery + adjvant chemoRT [87]
- chemo + PDT vs chemo; surgery in both groups [88,89]
- chemo + surgery +chemo + RT vs RT + surgery +RT [90]
- chemo +chemoRT + surgery vs surgery + RT [91,92]
- chemo then (chemoRT vs surgery + chemo) [93]
- chemo then (RT + surgery vs chemoRT; different chemo in each arm) [94]
- chemo then (surgery vs RT) [95-101]
- chemo then [(chemoRT + surgery) vs (surgery + RT)] [102-104]
- chemoRT + surgery vs chemoRT [105]
- chemoRT then (surgery + chemo vs RT+chemo) [106]
- chemoRT then (surgery vs chemoRT) [107,108]
- comparison of different neoadjvuant chemo or immunotherapies [109-121]
- neoadjuvant vs adjuvant [122-125]
- timing: chemo + (early vs late chemoRT) + surgery [126,127]
- Initially unresectable, but some resectable after neoadjuvant treatment [128-134]

Table 3-1: Guidelines

Source	Organization	Topic	Relevant recommendations	Notes
Swaminath, 2017 [6]	Cancer Care Ontario (CCO)	Treatment of stage III (N2 or N3) NSCLC	Definitive chemoRT or induction chemoRT + surgery if potentially resectable Primary surgical resection + adjuvant therapy generally not recommended, except in special circumstances	Includes T1-3N2 (plus N3 which is outside current scope); excludes T3N1 and T4N0-1
Kris, 2017 [9]	American Society for Clinical Oncology/ Cancer Care Ontario (ASCO/CCO)	Adjuvant systemic and RT therapy for resected NSCLC	Adjuvant cisplatin-based chemo recommended for routine use in stage IIIA disease with complete resection; PORT on individual basis for N2 disease	Excluded trials of neoadjuvant chemo
Schild, 2017 [7]	UpToDate	Management, stage III NSCLC	Resection if mediastinal nodes are negative (stage III N0 or N1); definitive RT if technically resectable but not surgical candidate. Definitive chemo RT or bi/tri-modality therapy if mediastinal nodes positive. T3N1: surgical resection then adjuvant chemo if completely resected, or chemoRT if complete resection not technically feasible Superior sulcus (Pancoast) with hilar LN involvement or N0: chemoRT then surgery T4N0-1: usually chemoRT; resection for small subset Clinical stage I/II but pathological stage III: resection + adjuvant chemo (+ RT if positive margins)	Adjuvant chemo using platinum-based doublet regimens prolongs OS in pts with completely resected stage III disease and is std of care PORT in special cases: positive margins, inadequate lymph node sampling and suspected mediastinal node involvement, N2 involved nodes found at surgery
Postmus, 2017 [8]	European Society for Medical Oncology (ESMO)	Early and locally advanced NCSLC	Stage III: If resectable (single station N2, T4N0, after induction therapy when there is nodal downstaging and pneumonectomy can be avoided) evaluate in multidisciplinary team If N2 found intraoperatively then give adjuvant chemo; PORT not	Has recommendations according to stage No clear benefit of one local therapy over another in several trials

Source	Organization	Topic	Relevant recommendations	Notes
			routine but option for some pts If N2 preoperatively use resection + adjuvant chemo OR neoadjuvant chemo + surgery OR neoadjuvant chemoRT + surgery; PORT not a standard but may be an option If multistation N2 or N3: concurrent definitive chemoRT Potentially resectable superior sulcus tumours or selected T3 or T4 central tumours: concurrent chemoRT then definitive surgery For curative-intent management , systemic therapy should be platinum-based (preferably cisplatin)	
Ettinger, 2017 [10]	National Comprehensive Cancer Network (NCCN)	NSCLC	Superior sulcus tumor, T3 N0-1 or T4 N0-1 resectable: chemoRT + surgery + chemo T3 N1, negative mediastinal nodes: resection + adjuvant chemo OR neoadjuvant chemo + resection T3/4N0-1 resectable: either • (1) surgery (preferred); adjuvant chemo if negative margins or if positive margins use either resection + chemo or chemoRT or reresction + chemoRT; or • (2) chemoRT or chemo then surgery; reresection if positive margins T1-3 N2 (other than invasive): chemo RT or chemo +/- RT then surgery: if no progression then use +/- chemo +/- RT (if not given previously); if progression use RT +/- chemo or chemo IIIA with separate pulmonary nodules in same lobe (T3 N0-1) or ipsilateral non-primary lobe (T4 N0-1): surgery then either (1) adjuvant chemo of N0-1; (2) adjuvant chemo or chemo + RT if N2 negative margins; or (3) adjuvant chemoRT if margins positive	
Cancer Council Australia, 2017 [11]	Cancer Council Australia	Lung cancer treatment	Stage III operable: Patients with resectable stage III NSCLC, who are being considered for preoperative chemotherapy and surgery or surgery and postoperative chemotherapy, should have their treatment plan reviewed in a lung cancer-specific multidisciplinary meeting.	Has questions and recommendations by stage The guideline does not address the issue of

Source	Organization	Topic	Relevant recommendations	Notes
			If neoadjuvant chemoRT used: • Unselected pts with biopsy confirmed stage IIIA (N2) are best treated with chemoRT without surgery • Selected pts with cIIIA (N2) disease may be treated with chemoRT + surgery provided the pt does not require a pneumonectomy • In selected patients (excellent performance status and cardio respiratory reserve) with stage cIIIA (N2) NSCLC, planned for surgery that will entail less than pneumonectomy, it is reasonable to offer neoadjuvant chemoradiotherapy. It is recommended to consider pre-operative administration of 2-3 cycles of platinum doublet-based, third-generation chemotherapy as a treatment option in good performance status patients with operable clinical stage IIIA non-small cell lung cancer. Patients whose tumours respond to preoperative chemotherapy may derive additional survival benefit from postoperative chemotherapy. Patients who have a good performance status (WHO 1, 2) and completely resected stage III non-small cell lung cancer should be offered adjuvant cisplatin-based chemotherapy PORT not recommended routinely but consider in selected pts with pN2 disease	whether neoadjuvant or adjuvant treatment is better.
Villar Alvarez, 2016 [12] [13]	Thoracic Surgery and Thoracic Oncology groups of the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR)	Diagnosis and treatment of NSCLC	In resectable stage III without N2 involvement, proposed treatment is surgical resection with adjuvant CT/RT (Grade 1A) In potentially resectable stage IIIA without N2 lymph node involvement, proposed treatment is neoadjuvant CT/RT, surgical resection, and adjuvant treatment (Grade 2C). In stage IIIA due to T3N1, surgery within a multidisciplinary therapeutic setting is recommended in patients with potentially resectable NSCLC (Grade 1B) In stage IIIA with intra-operative (occult) N2 involvement, treatment is surgical resection and adjuvant CT/RT (Grade 1A/2C)	

Source	Organization	Topic	Relevant recommendations	Notes
			In preoperative stage IIIA-N2, treatment may be definitive CT/RT or induction therapy and surgery (Grade 1A). In preoperative stage IIIA-N2, initial surgical resection and adjuvant therapy is NOT recommended (with exceptions) (Grade 1C). After induction therapy, pneumonectomy should be avoided, particularly on the right side,given the high post-operative mortality, except in highly experienced centers (Grade2C). In a multidisciplinary therapeutic setting, surgery is recommended in NSCLC with T4 involvement with ipsilateral tumor nodules in different lobes (Grade 1B)	
Rodrigues, 2015 [14] [15]	American Society for Radiation Oncology (ASTRO)	Definitive and PORT in locally advanced NSCLC	RT alone superior to observation or chemo for overall survival, but side-effects of esophagitis and pneumonitis Concurrent (chemoRT) has improved OS, local control, and response rate compared to sequential chemo then RT. If a pt cannot tolerate chemoRT, sequential chemo + RT is better than RT alone. Chemo then chemoRT has no advantage over chemoRT, though may be considered for bulky tumours for treatment planning PORT does not improve survival but may improve local control in completely resected N2 NSCLC and results in inferior survival in N0-N1 pts with complete resection Adjuvant chemo may improve survival and should be given before RT (if RT is used) in pts with complete resection PORT may be appropriate if residual disease and may be used concurrently or consecutively with chemo There is no level 1 evidence for use of induction RT or chemoRT followed by surgery for resectable stage III NSCLC. If used, preoperatively planned lobectomy (as opposed to pneumonectomy) is preferable	The Intergroup (INT) 0139 Phase III randomized clinical trial, comparing trimodality therapy to the definitive concurrent chemoradiotherapy, demonstrated no survival advantage to the trimodality arm (median survival, 23.6 months vs. 22.2 months), with improved progression-free survival of 12.8 versus 10.5 months. Exploratory unplanned analysis of the INT 0139 data, demonstrating that patients who underwent lobectomy after induction chemoradiotherapy, experienced an

Source	Organization	Topic	Relevant recommendations	Notes
				improved survival
Garcia-Campelo, 2015 [16]	Spanish Society of Medical Oncology (SEOM)	Treatment of NSCLC	In patients with R0 resected NSCLC and an incidental N2 metastases found on final pathology examination of the resection specimen, adjuvant chemotherapy should be given. PORT (PORT) may be considered and should be administered after adjuvant chemo. In patients with N2 documented intra-operatively, surgery should be followed by adjuvant chemotherapy +/- PORT. Neoadjuvant therapy + surgery is better than surgery alone in potentially resectable IIIA (N2) disease. Patients could be treated with induction chemotherapy followed by surgery, induction chemoradiotherapy followed by surgery or concurrent definitive chemoradiotherapy. Trimodality treatment is preferably planned in patients in whom a complete resection by lobectomy is expected.	
Eberhardt, 2015 [17]	ESMO consensus conference	Locally advanced stage III NSCLC	If, despite adequate mediastinal staging procedures, N2 disease is only documented intra-operatively, surgery should be followed by adjuvant chemotherapy. In case of complete resection, addition of post-operative radiotherapy is not routinely recommended, but may be an option following individual risk assessment. Preoperative diagnosis of IIIA(N2): Possible strategies include several options: induction chemotherapy followed by surgery, induction chemoradiotherapy followed by surgery, or concurrent definitive chemoradiotherapy. No recommendation can yet be made; however, an experienced multidisciplinary team is of paramount importance in any complex multi-modality treatment strategy decision. If induction chemotherapy alone is given preoperatively, post-operative radiotherapy is not standard treatment but may be an option based on critical evaluation of locoregional relapse risks Potentially operable IIIA(N2) disease and selected IIIB disease but at high risk of incomplete resection: In potentially resectable superior sulcus tumours, concurrent chemoradiotherapy induction followed by definitive surgery is the treatment of choice. The same strategy may be applied for potentially resectable T3 or T4 central tumours in highly selected cases and experienced centres. In both situations, surgery should be carried out within 4 weeks after the end of	

Source	Organization	Topic	Relevant recommendations	Notes
			radiotherapy	
Sculier, 2014 [18]	European Lung Cancer Working Party (ELCWP)	Management of resectable NSCLC	Question 9 is of direct relevance, and asks " In case of clinical stage IIIA or B, if surgical indication is retained, should we do an induction treatment, and if so, which one?"	The guideline is in French and was not obtained.
Healthcare Improvement Scotland, 2014 [19]	Scottish Intercollegiate Guidelines Network (SIGN)	Management of lung cancer	Patients with proven early N2 NSCLC may be considered for surgery as part of multimodality treatment. All of these cases must be discussed at the multidisciplinary team meeting. [SIGN 80] Patients with good performance status (PS 0-1) who have completely resected NSCLC (stage II to IIIa) should be offered platinum based postoperative systemic anticancer therapy. [SIGN 80] Patients with NSCLC who have had complete tumour resection should not receive postoperative radiotherapy, except as part of a randomised trial. [SIGN 80] Concurrent chemoradiotherapy should be administered to patients with locally advanced NSCLC (suitable for radical radiotherapy) who have a good performance status (PS 0-1).	This is a very broad guideline, and therefore of limited relevance to the current topic. Several sections, including resection in stage III cancer, comes from SIGN 80 (2005); the original supporting evidence was not re-appraised and the text and recommendations are reproduced verbatim.
Ramnath, 2013 [20]	American College of Chest Physicians (ACCP)	Stage III NSCLC, diagnosis and management	In patients with discrete N2 involvement by NSCLC identified preoperatively (IIIA), • we recommend the treatment plan should be made with the input from a multidisciplinary team (Grade 1C) • either definitive chemoradiation therapy or induction therapy followed by surgery is recommended over either surgery or radiation alone (Grade 1A) • primary surgical resection followed by adjuvant therapy is not recommended (except as part of a clinical trial) (Grade 1C) . In patients with NSCLC undergoing surgical resection, systematic mediastinal lymph node sampling or complete mediastinal lymph node dissection is recommended (Grade 1B) . In patients with NSCLC who have incidental (occult) N2 disease (IIIA) found at surgical resection despite thorough preoperative staging and	There are several other recommendations for infiltrative stage III (N2,3)NSCLC; surgery is not recommended for these pts.

Source	Organization	Topic	Relevant recommendations	Notes
			in whom complete resection of the lymph nodes and primary tumor is technically possible, completion of the planned lung resection and mediastinal lymphadenectomy is suggested (Grade 2C) . In patients with resected NSCLC (R0) who were found to have incidental (occult) N2 disease (IIIA) despite thorough preoperative staging and who have good performance status, adjuvant platinum-based chemotherapy is recommended (Grade 1A) . In patients with R0 resected NSCLC who were found to have incidental (occult) N2 disease (IIIA) despite thorough preoperative staging, sequential adjuvant radiotherapy is suggested when concern for a local recurrence is high (Grade 2C) . In patients with NSCLC who were found to have incidental (occult) N2 disease (IIIA) despite thorough preoperative staging and were incompletely resected (R1,2), combined postoperative concurrent chemotherapy and radiotherapy is suggested (Grade 2C) .	
Expert Panel on Radiation Oncology-Lung [21]	American College of Radiology (ACR)	Induction and adjuvant therapy for N2 NSCLC	PORT with a dose of 45–54 Gy is an appropriate therapy following completion of adjuvant chemotherapy in patients with incidental pN2 disease (IIIA-1, -2). The therapeutic benefits of PORT in patients undergoing induction chemotherapy and surgery for clinical N2 disease remain to be fully defined. In patients with clinical N2 disease (IIIA-3) who are potential candidates for a lobectomy, both definitive concurrent chemotherapy and radiation therapy (60–70 Gy) and induction concurrent chemotherapy and radiation therapy (45–50 Gy) are usually appropriate treatment options while induction chemotherapy alone followed by surgery +/- PORT may also be appropriate. In patients with clinical N2 disease (IIIA-3) who would require a pneumonectomy, definitive concurrent chemotherapy and radiation therapy (60–70 Gy) is most appropriate, whereas induction chemotherapy and radiation therapy may be appropriate in expert hands. For postoperative, preoperative, and definitive radiation therapy, 3-D	The current clinical question is whether neoadjuvant therapy offers any advantages over adjuvant therapy. At this time, induction therapy with chemotherapy alone for stage IIIA disease should be considered investigational.

Source	Organization	Topic	Relevant recommendations	Notes
			conformal techniques and IMRT are most appropriate.	
Brodowicz, 2012 [22]	Central European Cooperative Oncology Group (CECOG)	Systemic treatment of NSCLC	Neoadjuvant (induction) chemotherapy may be considered in stage III disease [II,B]. Adjuvant chemotherapy after complete tumor resection should be offered to patients with stage II and III [I,A] disease and may be considered for selected patients based on tumor size with stage IB disease. Chemotherapy should consist of cisplatin plus a third-generation cytotoxic drug, preferentially vinorelbine [I,B].	
Alberta Health Services, 2012 [23]	Alberta Health Services	Stage III NSCLC	Treatment for Operable Disease (T3N1, selected T4N0-1) • Surgical resection is recommended. • Extended pulmonary resection may be performed in selected lesions. These include peripheral lesions invading the chest wall, apical lung carcinomas, central lesions with limited mediastinal invasion, or focal pericardial or phrenic nerve invasion. Carinal tumours and those within 2 cm of the carina occasionally may be amenable to resection with airway reconstruction. • Platinum-based chemotherapy regimens are recommended as post-operative adjuvant therapy in the management of patients with completely resected stage IIIA NSCLC. Cisplatin-based treatment is preferred, although carboplatin-based regimens can be used as an alternative if there is a contraindication to cisplatin. • Adjuvant radiotherapy after surgical resection is not routinely recommended. However, this treatment could be considered when there is microscopic involvement of the resection margin, including the bronchial resection margin. Treatment for T1-3N2 Disease • Concurrent chemo-radiation is recommended for pre-operatively diagnosed N2 disease. Cisplatin-based chemotherapy (with either etoposide or vinorelbine) and thoracic radiation of 55 Gy in 25 fractions to 66 Gy in 33 fractions is the recommended treatment option. Additional cycles of chemotherapy can be considered for bulky disease.	

Source	Organization	Topic	Relevant recommendations	Notes
			• In select patients, neoadjuvant chemoradiotherapy followed by lobectomy can be considered. Pre-operative pathologically diagnosed N2 disease is not recommended to undergo surgical resection alone. • For patients with N2 disease discovered intra-operatively where complete resection of the lymph nodes and primary tumour is technically possible, completion of the planned lung resection is recommended. • In patients with N2 disease discovered intra-operatively, platinum-based adjuvant chemotherapy is recommended. Adjuvant radiotherapy can be considered in select patients.	

Chemo, chemotherapy; chemoRT, concurrent chemotherapy plus radiotherapy; PORT, post-operative radiotherapy; RT, radiotherapy

Table 3-2. Meta-Analyses of Neoadjuvant Chemotherapy plus Surgery versus Surgery

Meta-analysis [36,38]	Patients	Trials included	Notes
Song, 2010 [38]	Resectable NSCLC (3224 pts), subgroup analysis for stage III (1586 pts and 1172 deaths)	13 trials, including 8 for separate stage III meta-analysis [1-5,62-66]*	Included in 2012 assessment reference list but not in tables or text (found in literature search but not used) OS in stage III NSCLC: combined HR=0.84, 95% CI 0.75 to 0.95; p=0.005
Horita, 2013 [36]	Resectable NSCLC (3728 pts), subgroup analysis for stage III (1447 pts and 1068 deaths)	16 trials, including 7 for separate stage III meta-analysis [1-4,62-65,67]*	OS in stage III NSCLC: pooled HR=0.77, 95% CI, 0.68 to 0.87; p<0.001

*Additional publications [68-70] for two of the trials were found in the literature search

Table 3-3. Randomized Controlled Trials of Neoadjuvant Chemotherapy plus Surgery versus Surgery

Trial name, location, publication	Recruitment	Meta-analysis	Stage	# pts (stage III or IIIA)	Additional stage or pt information	Treatment	Survival outcome data	Notes
MD Anderson; Roth, 1994, 1998 [1,3]	1987-1993	[36,38]	IIIA	60		Chemo + surgery vs surgery 6 cycles cyclophosphamide + etoposide + cisplatin	Median survival 21 months vs 14 months, p=0.056 log rank, p=0.048 Breslow-Gehan-Wilcoxon 3-y OS 43% vs 19% 5-y OS 36% vs 19% OS: 9/19 vs 5/32 (to median of 82 months after randomization) Subgroup with complete resection: 3-y OS 59% vs 24% 5-y OS 53% vs 24%	Sept 1997 version has original publication [1] but not updated data [3] Terminated early based on ethical considerations, the magnitude of the treatment effect, and the high degree of statistical significance attained
Spain; Rosell, 1994,1995, 1999 [2,4,68]	1989-1991	[36,38]	IIIA	60		Chemo + surgery vs surgery 3 cycles mitomycin + ifosfamide + cisplatin	7 year assessment: Median survival 22 months vs 10 months, p=0.005 3-y OS 20% vs 5%	Sept 1997 version has original publication [2] but not updated data [4] or k-ras

Trial name, location, publication	Recruitment	Meta-analysis	Stage	# pts (stage III or IIIA)	Additional stage or pt information	Treatment	Survival outcome data	Notes
							5-y OS 17% vs 0%	subgroups [68]
Sichuan (China); Li, 2003 [62] [Chinese, English abstract]	1990-1995	[36,38]	III	137		Chemo + surgery vs surgery CAP (CTX + ADM + DDP) and EP (DDP + Vp-16)	1-y OS 62.3% vs 63.3% 3-y OS 45.5% vs 43.3% 5-y OS 23.3% vs 21.7% 7-y OS 1.3% vs 1.6%, p> 0.05	
JCOG 9209. (Japan); Nagai, 2003 [63]	1993-1998	[36,38]	IIIA	62		Chemo + surgery vs surgery 3 cycles cisplatin + vindesine	Median follow-up 6.2 y Median OS 17 vs 16 months 1-y OS 68% vs 65% 3-y OS 23% vs 26% 5-y OS 10% vs 22%, p=0.5274	Terminated due to slow accrual
Sichuan (China); Zhou, 2001 [64] [Chinese; English abstract]	1990-2001	[36,38]	III	624	93% stage IIIA	Chemo + surgery vs surgery 2 cycles, various chemo: MVP in 68 cases, CAP in 36 cases, EP in 67 cases, VIP in 20 cases, Gem+ DDP in 30 cases, NVB+ DDP in 32 cases, Taxol+ NVB in 30 cases, and Taxol+ DDP in 10 cases	Resection rate 87.69% vs 91.94% 1-y OS 89.35% vs 87.53% 3-y OS 67.46% vs 51.54% 5-y OS 34.39% vs 51.54% 10-y OS 29.34% vs 21.64%, p<0.01	
Chongqing (China); Yao, 2004 [65] [Chinese, English abstract]	1990-2002	[36,38]	III	456		Chemo + surgery vs surgery 2 cycles, various chemo: Gem+DDP in 47 cases, NVB+DDP in 35 cases, MVP in 86 cases, and EP in 66 cases	Resection rate 87.02% vs 83.78% 1-y OS 76.07% vs 69.82% 3-y OS 52.99% vs 41.44% 5-y OS 34.18% vs 22.97%, p<0.01	
Tianjin (China); Zhou, 2011 [71] [abstract]	1990-2006		III	624	Pts with Muc-1 mRNA expression	Chemo + surgery vs surgery; 2 cycles neoadjuvant Gem DDP in 214 cases and NVB DDP in 100 cases Adjuvant chemo 3-4 cycles CP or NP regimen in all pts (both groups)	Resection rate 94.90% vs 90.65% 1-y OS 78.30% vs 64.53% 3-y OS 51.46% vs 40.54% 5-y OS 27.31% vs 14.19% 10-y OS 20.35% vs 12.64%, p<0.01 Subgroup without micromets: 1-y OS 89.62% vs 77.23% 3-y OS 67.46% vs 54.34% 5-y OS 39.61% vs 24.89% 10-y OS 31.75% vs 20.87%, p<0.01	
Guangzhou (China);	1999-2004		IIIA	40		Chemo + surgery vs surgery	Median follow-up 28.5 months	Terminated due to

Trial name, location, publication	Recruitment	Meta-analysis	Stage	# pts (stage III or IIIA)	Additional stage or pt information	Treatment	Survival outcome data	Notes
Yang, 2005 [72] [abstract]						2 cycles gemicimbine + carboplatin or cisplatin; 2 additional cycles post-surgery for responding pts	OS 58% vs 43%	slow accrual
Guangzhou (China); Wu, 2002 [67] [abstract]	1999-2004 (until 2002 in abstract)	[36]	IIIA	48 (55)	48 pts in published abstract; 55 in individual pt meta-analysis [33]	Chemo + surgery vs surgery 2 cycles docetaxel + carboplatin	OS 81% vs 64%	
Jiangsu (China) Li, 2009 [73]	2000-2004		IIIA	56		Chemo + surgery vs surgery; Neoadjuvant chemo arm: 2 cycles cisplatin + vinorelbine Adjuvant chemo; RT + adjuvant chemo if incomplete resection	Resection rate 78.6% vs 60.7% Median OS 30 vs 16 months, p=0.04 Median DFS 24 vs 11 months, p=0.048 3-y OS 49.7% vs 29.2% 5-y OS 31.9% vs 3.6%	
Dalian (China) Li, 2007 [74] [Chinese, with English abstract and data tables]	2001-2004		Locally advanced stage III	92	82 pts stage IIIA, 10 pts stage IIIB	Chemo + surgery vs surgery Neoadjuvant chemo for 2 cycles by bronchial artery infusion (BAI) of cisplatin + etoposide Both groups: adjuvant chemo with MVP regimen (mitomycin, vindesine, cisplatin) or NP (vinorelbine + cisplatin); pts with incomplete resection also received RT	Resection rate 89.7% vs 72.5%, p<0.05 1-y OS 100.0% vs 94.1% 2-y OS 80.6% vs 60.0%	
Kashmir (India); Lone, 2010 [75] [abstract]	2006-2009		Locally advanced	100		Chemo + surgery vs surgery 2 cycles neoadjuvant chemo	Resection 85% vs 64% 48 months follow-up OS 80% vs 72%, p>0.05	
Wuhan (China); Li, 2012 [76]	2007-2010		Locally advanced	115	67 pts stage IIIa, 48 pts stage IIIb	Chemo (2 cycles) + surgery* + chemo (2 cycles) vs surgery + chemo (4 cycles)	1-y DFS 76.2% vs 71.2%, p>0.05 2-y DFS 57.1% vs 36.5%, p<0.05	

Trial name, location, publication	Recruitment	Meta-analysis	Stage	# pts (stage III or IIIA)	Additional stage or pt information	Treatment	Survival outcome data	Notes
						*pts who progressed on chemo were excluded and given RT + chemo Neoadjuvant chemo: 2 cycles gemcitabine + cisplatin		
Keio (Japan); Kobayashi, 2000 [77] [Japanese; English abstract, tables, figures]	1990-1993		I-III (clinical)	28	47 pts; pathological stage: 11 stage I, 1 stage II, 16 stage IIIA 12 stage IIIB 6 stage IV	Chemo-immunotherapy + surgery vs surgery; Preoperative: 1 cycle of CDDP + VDS + OK-432 Postoperative (all pts): 1 cycle CDDP +VDS, plus chemo-immunotherapy for one year	<u>All stages (resectable pts only, n=34):</u> 3-y DFS 59.8% vs 36.3% 5-y DFS 53% vs 28.7%, p=0.05 Cumulative survival rates at 3 years were 58.2% vs 37.6% and at 5 years were 38.2% vs 26.9%, RR=0.47, p=0.05	Stage IIIA not reported separately.
MIP-91. France; Depierre, 2002 [5]; Westeel, 2010 [69] [abstract]; Milleron, 2005 [70]	1991-97	[38] ([36], stage III data not reported)	I-IIIA	167	355 pts, of which 167 (47%) were stage IIIA	Chemo + surgery (+ adjuvant chemo in responders) vs surgery. Chemo: mitomycin + ifosfamide + cisplatin (2 cycles neoadjuvant + 2 additional cycles adjuvant in responders) Postoperative RT in both groups if pT3 or pN2	<u>All stages (n=373)</u>: Median survival 37 vs 26 months, p=0.15 At median 80 months follow-up: 1-y OS 77.1% vs 73.3% 2-y OS 59.2% vs 52.3% 3-y OS 51.6% vs 41.2% 4-y OS 43.9% vs 35.3%, ns Median DFS 26.7 vs 12.9 months 3-y DFS 44% vs 33% DFS RR=0.76, p=0.033 DFS adjusted for stage: RR=0.74, p0.001 10-y OS 29.4% vs 20.8%, p=0.12 In multivariate analysis, neoadjuvant chemo significantly correlated with OS, HR=0.78, 95% CI 0.61—0.99, p=0.038	2002 publication indicates benefit was confined to patients with N0-N1 diseases, with RR=0.68 (95% CI 0.49-0.96, p=0.027) in N0/N1 disease and RR=1.04 (95% CI 0.68-1.60, p=0.85) in N2 disease Data in the Song et al meta-analysis [38] appears to be for N2 (not IIIA) disease, and some numbers for this trial may be incorrect 2010 publications shows small but not

Trial name, location, publication	Recruitment	Meta-analysis	Stage	# pts (stage III or IIIA)	Additional stage or pt information	Treatment	Survival outcome data	Notes
							<u>Subgroups, 10-year data</u> Stage I-II: 10-y OS 37.6% vs 23.1%, p=0.04 Stage IIIa: 10-y OS 21.7% vs 18.7%, not significant	significant survival advantage for stage IIIA
Shanghai (China); Liao, 2003 [66] [Chinese; English abstract]	1995-97	[38] ([36], stage III data not reported)	I-IIIA	65	211 pts, of which 65 (31%) were stage IIIA	Chemo + surgery vs surgery 1-2 cycles neoadjuvant chemo: mitomycin + cisplatin + (doxorubicin or vincristine or vinblastine) Adjuvant chemo for stage II-IIIA (total 4 cycles)	Stage IIIA: 37 pts chemo first, 28 pts surgery first 1-y survival 75.68% vs 85.71% 3-y survival 32.43% vs 53.57% 5-y survival 14.55% vs 15.31% Median survival 21.5 vs 38.4 months, p=0.225	Follow-up until 2002. Pts did same or worse with neoadjuvant chemo compared to surgery first (significantly worse for stage II pts)
Shanghai (China); Chen, 2013 [78]	1995-2001		I-IIIA	122	356 pts, of which 122 pts were stage IIIA	Chemo + surgery vs surgery; Neoadjuvant: 1-2 cycles mitomycin + cisplatin + vindesine 4-6 cycles adjuvant chemo in both arms	All stages: 5-y OS 34% vs 48% 10-y OS 28% vs 33% 15-y OS 24% vs 21% Median survival 45.42 vs 57.59 months, p=0.016, HR=1.67 Stage II: 5-y OS 27% vs 48% 10-y OS 22% vs 33% 15-y OS 22% vs 21% Median survival 40.86 vs 80.81 months, p=0.044 Stage III: OS, p=0.051 [no data reported]; PFS, HR=1.332 (95% CI 0.877-2.023, p=0.179	Follow-up until 2012. Authors noted mitomycin-cisplatin-vindesine regimen is no longer used for first-line therapy in NSCLC
Shanghai (China); Yi, 2003 [79]	1998-2001	([36], stage III data not	I-III	43	84 pts, of which 43 (51%)	Chemo + surgery + chemo vs surgery	Stage III: OS 75.00% vs 42.11%, p=0.037	

Trial name, location, publication	Recruitment	Meta-analysis	Stage	# pts (stage III or IIIA)	Additional stage or pt information	Treatment	Survival outcome data	Notes
[Chinese, English abstract & tables]		reported)			were stage III; stage III reported separately	Neoadjuvant group : 2 cycles MVP (mitomycin, vinblastine, cisplatin) before surgery and 2-4 cycles after surgery		
NATCH; Felip, 2010 [80]	2000-2007	([36], stage III data not reported)	IA-IIIA (T3N1 only for stage IIA)	9 T3N1	409 pts, of which 9 (2%) T3N1 (stage IIIA)	Chemo + surgery vs surgery Also third arm of surgery + postoperative chemotherapy Neoadjuvant: 3 cycles paclitaxel + carboplatin Adjuvant: 3 cycles paclitaxel + carboplatin	Stage II or T3N1 combined -neoadjuvant vs surgery alone: DFS 39% vs 25%, HR=0.81 (0.64-1.02); 5-y OS 41.3% vs 34.5%, HR=0.88 (0.69-1.12, p=0.31) -adjuvant vs surgery alone: DFS 34% vs 25%, HR=0.87 (0.54-1.34); 5-y OS 36.6% vs 34.5%, HR=1.01 (0.62-1.65, p=0.97)	

Stage III or IIIA pts; some separate data reported for stage III pts

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Appendix 3-1: Search Strategy

Database(s): Embase 1996 to 2017 August 28, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R)

#	Searches	Results
1	exp Lung cancer/ or exp lung tumor/ or exp non small cell lung cancer/ or (non-small-cell lung or NSCLC).mp. or ((lung$ or pulmon: or bronchio:) and (cancer$ or carcinoma$ or adenocarcinoma or neoplasm$ or tumor$ or tumour$)).mp.	791548
2	exp neoadjuvant therapy/ or exp induction chemotherapy/ or ((Neoadjuvant or neo adjuvant or preoperative or induction or before surgery or prior to surgery).mp. and (exp adjuvant chemotherapy/ or exp chemoradiotherapy/ or (chemotherap: or radiochemotherap: or chemoradiation: or chemoradiotherap: or systemic treatment or systemic therapy).mp.))	169775
3	1 and 2	20533
4	exp Randomized Controlled Trial/ or Clinical Trial, Phase III/ or Clinical Trial, Phase IV/ or Phase 3 Clinical Trial/ or Phase 4 Clinical Trial/ or ((exp Clinical Trial/ or Prospective Study/ or Prospective Studies/) and Random$.tw.) or exp Randomized Controlled Trials as topic/ or Clinical Trials, Phase III as Topic/ or Clinical Trials, Phase IV as Topic/ or exp "Randomized Controlled Trial (Topic)"/ or "Phase 3 Clinical Trial (Topic)"/ or "Phase 4 Clinical Trial (Topic)"/ or ((exp Clinical Trials as Topic/ or exp "Clinical Trial (Topic)"/) and random$.tw.) or Random Allocation/ or Randomization/ or Single-Blind Method/ or Double-Blind Method/ or Single Blind Procedure/ or Double Blind Procedure/ or Triple Blind Procedure/ or Placebos/ or Placebo/ or ((singl$ or doubl$ or tripl$) adj3 (blind$3 or mask$3 or dummy)).tw. or (random$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw. or (((phase II or phase 2 or clinic$) adj3 trial$) and random$).tw. or (placebo? or (allocat$ adj2 random$)).tw. or (random$ adj3 trial$).mp. or "clinicaltrials.gov".mp.	1987614
5	exp meta analysis/ or exp "meta analysis (topic)"/ or exp meta-analysis as topic/ or exp "systematic review"/ or exp "systematic review (topic)"/ or ((exp "review"/ or exp "review literature as topic"/ or review.pt.) and ((systematic or selection criteria or data extraction or quality assessment or jaded scale or methodologic$ quality or study) adj selection).tw.) or meta-analysis.mp. or (meta-analy: or metaanaly: or meta analy:).tw. or (systematic review or systematic overview).mp. or ((cochrane or medline or embase or cancerlit or hand search$ or hand-search$ or manual search$ or reference list$ or bibliograph$ or relevant journal$ or pooled analys$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes?s or quantitative overview$ or systematic) adj2 (review$ or overview$)).tw. or (medline or med-line or pubmed or pub-med or embase or cochrane or cancerlit).ab.	677388
6	exp evidence based practice/ or exp practice guideline/ or exp consensus development conference/ or guideline.pt. or practice parameter$.tw. or practice guideline$.mp. or (guideline: or recommend: or consensus or standards).ti. or (guideline: or recommend: or consensus or standards).kw.	1711331
7	3 and 4	3353

Appendix 3-2: Members of the Expert Panel (Lung Disease Site Group)

Name	Affiliation	Declarations of Interest
Abdollah Behzadi	Surgeon Peel Regional Cancer Centre	none
Penny Bradbury	Medical Oncologist Queen's Suniversity	none
Adrien Chan	Medical Oncologist Thunder Bay Regional Health Sciences Centre	none
Susanna Cheng	Medical Oncologist Odette Cancer Centre	none
Peter Ellis	Medical Oncologist Juravinski Cancer Centre	Received honoraria from Abbvie for advisory role
Medhat El-Mallah	Radiation Oncologist Lakeridge Health Corporation	none
Conrad Falkson	Radiation Oncologist Cancer Centre of Southeastern Ontario	none
Ron Feld	Medical Oncologist Princess Margaret Hospital	Worked for the University Health Network and retired in June 2017
John Goffin	Medical Oncologist Juravinski Cancer Centre	none
Richard Gregg	Medical Oncologist Cancer Centre of Southeastern Ontario	none
Don Jones	Surgeon Peel Regional Cancer Centre	none
Jaro Kotalik	Bioethicist Centre for Health Care Ethics at Lakehead University	none
Swati Kulkarni	Medical Oncologist Windsor Regional Cancer Centre	Received a travel reimbursement from Astra Zeneca to attend the World Lung Cancer Conference in 2017
Sara Kuruvilla	Medical Oncologist London Regional Cancer Program	none
Scott Laurie	Medical Oncologist The Ottawa Hospital Regional Cancer Centre	none
Robert MacRae	Radiation Oncologist The Ottawa Hospital Regional Cancer Centre	none
Richard Malthaner	Surgeon London Health Sciences Centre	none
Donna Maziak	Surgeon	none

	The Ottawa Hospital	
Andrew Pearce	Radiation Oncologist Sudbury Regional Hospital	none
Kevin Ramchandar	Radiation Oncologist Thunder Bay Regional Health Sciences Centre	none
Andrew Robinson	Medical Oncologist Sudbury Regional Hospital	• Received more than $5000 from Merck for speaking and as an advisory board member • Received grants from multiple clinical trials with Merck, BMS, Roche, Astra-Zeneca
Alex Sun	Radiation Oncologist Princess Margaret Hospital	none
Anand Swaminath	Radiation Oncologist Juravinski Cancer Centre	none
Mojgan Taremi	Radiation Oncologist Southlake Regional Health Centre	none
Yee Chung Ung	Radiation Oncologist Odette Cancer Centre	none
Mark Vincent	Medical Oncologist London Regional Cancer Centre	none
Kazuhiro Yasufuku	Surgeon Toronto General Hospital	none
Edward Yu	Radiation Oncologist London Regional Cancer Program	none
Robert Zeldin	Surgeon Toronto East General Hospital	none

DEFINITIONS OF REVIEW OUTCOMES

1. **ARCHIVE** – ARCHIVE means that a Clinical Expert and/or Expert Panel has reviewed new evidence pertaining to the guideline topic and determined that the guideline is out of date or has become less relevant. The document 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 with the words "ARCHIVE."

2. **ENDORSE** – ENDORSE means that a Clinical Expert and/or Expert Panel has reviewed new evidence pertaining to the guideline topic and determined that the guideline is still useful as guidance for clinical decision making. A document may be endorsed because the Expert Panel 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. **UPDATE** – UPDATE means the Clinical Expert and/or Expert Panel recognizes that the new evidence pertaining to the guideline topic 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 Expert Panel advises that an update of the document be initiated. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making, unless the recommendations are considered harmful.

APPENDIX A: Previous Document Review, October 1, 2012

Ontario
Cancer Care Ontario
Action Cancer Ontario

Evidence-based Series #7-4 Version 2

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

These guideline recommendations have been ARCHIVED, which means that the recommendations are no longer maintained but may be of interest for educational or historical reasons. Please see December 2017 assessment in Section 3 for rationale.

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	Reference
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	Berghma et al 200
	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)	Nakamu et al 200
	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 2010

Randomized control trials not included in the meta-analysis above

Intervention	Population	Median follow up (mo)	Outcomes	Brief results	Reference
CT + Surgery or RT Vs.	Patients with stage IIIA or locally	12 overall	**P**:Median survival **S**:Median	• Median survival was 14.8 months in the docetaxel group and 12.6 months in the control group (difference not statistically	Mattson e al 2003

Surgery or RT alone	treatable IIIB NSCLC Median age, 62 yrs (n=274)		time to disease progression, CR, PR and toxicity	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 (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	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	†Elias et al 2002

	nodal involvement (N2) Median age, 60 yrs (n=50)			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.	
CT + RT + Surgery Vs. CT + Surgery + RT	Patients with stage IIIA–IIIB NSCLC and invasive mediastinal assessment Median age, 59 yrs (n=558)	70	**P:** PFS **S:** OS and the proportion of patients undergoing surgery	• In patients with complete resection, the proportion of those 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%])	Thomas et al 2008
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%,	†Tada et al 2009 (Abstract)

				respectively • There have been 37 deaths to date.		

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. Gemcitabine/cisplatin + surgery	Erlotinib Versus Gemcitabine/Cisplatin as (Neo)Adjuvant Treatment in Non-small Cell Lung Cancer	Recruiting	NCT01407822	August 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

4. 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**.
5. 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.
6. 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.**
7. 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.
2. Burdett S, Stewart LA, Rydzewska L. A systematic review and meta-analysis of the literature: chemotherapy and surgery versus surgery alone in non-small cell lung cancer. Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer. 2006;1(7):611-21.
3. Elias AD, Kumar P, Herndon J, 3rd, Skarin AT, Sugarbaker DJ, Green MR. Radiotherapy versus chemotherapy plus radiotherapy in surgically treated IIIA N2 non-small-cell lung cancer. Clinical Lung Cancer. 2002;4(2):95-103.
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9. Thomas M, Rube C, Hoffknecht P, Macha HN, Freitag L, Linder A, et al. Effect of preoperative chemoradiation in addition to preoperative chemotherapy: a randomised trial in stage III non-small-cell lung cancer. Lancet Oncology. 2008;9(7):636-48.

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)