Chemotherapy in Non-Small Cell Lung Cancer: An Update

A meta-analysis of randomised trials using individual patient data

Protocol D

Comparison 4
Radiotherapy vs Radiotherapy + Sequential Chemotherapy

Comparison 5
Radiotherapy vs Radiotherapy + Concomitant Chemotherapy

Comparison 6
Radiotherapy + Sequential Chemotherapy vs Radiotherapy + Concomitant Chemotherapy

Conducted by the Non-small Cell Lung Cancer Collaborative Group (NSCLCCG)
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NSCLC Collaborative Group

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Introduction

More than a million new cases of lung cancer are diagnosed each year\(^1\). About 80% of these tumours are of non-small cell histological type\(^2\), including adenocarcinomas and squamous cell and large cell carcinomas. Non-small cell lung cancer (NSCLC) is the main cause of deaths from cancer and five-year survival across all stages of disease is about 14%\(^3\).

Surgery is generally regarded as the best treatment option, but only about 20% of tumours are suitable for potentially curative resection\(^4\). A further 20% of patients, usually those presenting with locally advanced disease, undergo radical thoracic radiotherapy. The remaining 50% of patients, with late stage or metastatic disease are usually treated palliatively.

In 1991, the British Medical Research Council’s Cancer Trials Office (MRC), Cambridge; the Institut Gustave Roussy (IGR), Villejuif, France; and the Instituto Mario Negri (IMN), Milan, Italy initiated an individual patient data (IPD) meta-analysis to assess the role of chemotherapy in the treatment of NSCLC. At that time, despite over thirty years of research involving more than 9000 patients in over 50 randomised clinical trials (RCTs) the efficacy of chemotherapy, when combined with local treatment or supportive care, was unclear. With few exceptions, most trials were too small to reliably detect moderate treatment effects. Consequently, although a few trials reported significant results, both for and against chemotherapy, most trials were inconclusive.

This IPD approach to meta-analysis and systematic review involved the central collection, validation and analysis of the original trial data. It did not rely on data extracted from publications. At the outset, the secretariat contacted the investigators responsible for each trial and established the NSCLC Collaborative Group on whose behalf the meta-analysis was carried out and published in the British Medical Journal in 1995\(^5\). This has become a 'landmark publication' and was cited nearly 900 times between 1995-2003.

The meta-analysis concluded that despite previous scepticism and controversy, modern chemotherapy could have a role in treating NSCLC. In particular, there was strong evidence that for more advanced disease, chemotherapy given in addition to radical radiotherapy and given in addition to best supportive care, prolonged survival. The results for early stage disease, although in favour of chemotherapy, were less clear-cut. A fuller presentation of the results of the meta-analysis published in 1995 is given in Box 1.

The results suggested survival benefits are moderate (~ 5%) but potentially important and that there was no good evidence that any subgroup of patients (age, sex, stage, histology, performance status) benefits more or less than any other group.

Modern cisplatin-based regimens may offer the first effective adjuvant treatment in NSCLC and this should be evaluated in a prospective large-scale trial. New agents may offer further advantages and should be explored.

Since the meta-analysis was published, there has been renewed enthusiasm for investigations of chemotherapy in NSCLC and a considerable number of new RCTs have been completed. The total number of patients randomised has approximately doubled from 9 387 to around 23 000 patients. In particular, there have been many new trials in the surgical setting including trials of neoadjuvant chemotherapy. A number of new agents and timings have been investigated in all settings. As the aim of the NSCLC Collaborative Group is to provide an up to date and reliable review of the role of chemotherapy, both to act as a sound basis for evidence based medicine and to help guide future research, it is now timely to undertake a major update and re-evaluation of the 1995 meta-analysis.
The IGR also carried out an individual patient data meta-analysis of concomitant platin-based chemo-radiotherapy in locally advanced non-small cell lung cancer. The results showed that concomitant chemo-radiotherapy may improve survival but the available data are insufficient to accurately define the size of such a potential treatment benefit and the optimum schedule of chemotherapy. The results are given in Box 2. In addition to the update of the comparison on sequential radio-chemotherapy versus radiotherapy alone, this meta-analysis will be updated and a meta-analysis on the direct comparison of these two types of radio-chemotherapy, sequential versus concomitant, will be performed.

Seven therapeutic comparisons will be explored:

1. surgery vs surgery + adjuvant chemotherapy
2. surgery vs neoadjuvant chemotherapy + surgery
3. surgery + radiotherapy vs surgery + radiotherapy + adjuvant chemotherapy
4. radiotherapy vs radiotherapy + sequential chemotherapy (neo-adjuvant –before radiotherapy- and/or adjuvant –after radiotherapy–) or alternated radio-chemotherapy
5. radiotherapy vs radiotherapy + concomitant chemotherapy
6. radiotherapy + sequential chemotherapy vs radiotherapy + concomitant chemotherapy
7. supportive care vs supportive care + chemotherapy

Three of these comparisons (2, 5 and 6) are new; this reflects changes in practice and interest since the 1995 Meta-analysis and ensures that this systematic review is as inclusive and comprehensive as possible.

For clarity a separate protocol has been produced for each individual comparison, each of which can be considered as an independent meta-analysis, but when considered together will allow us to evaluate the overall picture of chemotherapy in non-small cell lung cancer.

This protocol relates to comparisons 4, 5 and 6 of the meta-analysis, copies of all protocols are available on request or can be downloaded from http://www.ctu.mrc.ac.uk/download.asp or http://www.igr.fr/php/index.php?ids_path=2.51.70.127.567

The meta-analyses will be jointly run by the Medical Research Council and the Institut Gustave Roussy. See Appendix D for further meta-analyses completed by these two groups.
Box 1

Summary of Results of 1995 Meta-analysis\(^1\)

The main objective of the meta-analysis was to investigate the effect of chemotherapy on survival when given in addition to appropriate local treatment:

**Early disease**
- surgery versus surgery + chemotherapy
- surgery + radiotherapy versus surgery + radiotherapy + sequential chemotherapy

**Locally advanced disease**
- radical radiotherapy versus radical radiotherapy + chemotherapy

**Advanced disease**
- supportive care versus supportive care + chemotherapy

Trials were classified as belonging to one of four pre-specified categories of chemotherapy:
- Regimens containing cisplatin
- Regimens using long-term alkylating agents (but not cisplatin)
- Regimens containing etoposide or vinca alkaloids (but not cisplatin)
- Other regimens

### Results

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Hazard Ratio</th>
<th>Confidence Interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery vs surgery + chemotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long-term alkylating agents</td>
<td>1.15</td>
<td>1.04-1.27</td>
<td>0.005</td>
</tr>
<tr>
<td>Other drugs</td>
<td>0.89</td>
<td>0.72-1.11</td>
<td>0.30</td>
</tr>
<tr>
<td>Cisplatin based</td>
<td>0.87</td>
<td>0.74-1.02</td>
<td>0.08</td>
</tr>
<tr>
<td>Surgery + RT vs surgery + RT + chemotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long-term alkylating agents</td>
<td>1.35</td>
<td>0.83-2.20</td>
<td>0.23</td>
</tr>
<tr>
<td>Cisplatin based</td>
<td>0.94</td>
<td>0.79-1.11</td>
<td>0.46</td>
</tr>
<tr>
<td>Radical RT vs radical RT + chemotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long-term alkylating agents</td>
<td>0.98</td>
<td>0.83-1.16</td>
<td>0.81</td>
</tr>
<tr>
<td>Vinca-alkaloids</td>
<td>0.87</td>
<td>0.70-1.09</td>
<td>0.23</td>
</tr>
<tr>
<td>Other drugs</td>
<td>0.98</td>
<td>0.74-1.29</td>
<td>0.88</td>
</tr>
<tr>
<td>Cisplatin based</td>
<td>0.87</td>
<td>0.79-0.96</td>
<td>0.005</td>
</tr>
<tr>
<td>Supportive care vs supportive care + chemotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long-term alkylating agents</td>
<td>1.26</td>
<td>0.96-1.66</td>
<td>0.095</td>
</tr>
<tr>
<td>Vinca-alkaloids / etoposide</td>
<td>0.87</td>
<td>0.64-1.20</td>
<td>0.40</td>
</tr>
<tr>
<td>Cisplatin based</td>
<td>0.73</td>
<td>0.63-0.85</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

A further objective was to assess whether any possible effects were consistent in the subgroups of age, sex, extent of disease, tumour stage, histology and performance status. Subgroup analysis of trials using cisplatin based regimens found no indication that any particular type of patient benefited more or less from chemotherapy.

### Conclusions

The results were consistent across primary treatment settings and they tended to show a benefit of modern cisplatin-based chemotherapy regimens although essential drugs were not identified.

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Box 2

Summary of Results of MAC3-LC\textsuperscript{2}

The main objective of the meta-analysis was to investigate the effect of platin-based concomitant chemotherapy on survival of patients with locally advanced non-small cell lung cancer treated with radical thoracic radiotherapy.

The meta-analysis was based on 9 trials and 1764 patients.

Results

<table>
<thead>
<tr>
<th></th>
<th>Hazard Ratio</th>
<th>Confidence Interval</th>
<th>p-value</th>
<th>Heterogeneity p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival</td>
<td>0.89</td>
<td>0.81-0.98</td>
<td>0.02</td>
<td>0.16</td>
</tr>
<tr>
<td>Disease free survival</td>
<td>0.84</td>
<td>0.74-0.96</td>
<td>0.009</td>
<td>0.05</td>
</tr>
</tbody>
</table>

These results must be interpreted with caution because there was some heterogeneity across trials and sensitivity analyses led to inconsistent results.

A further objective was to assess whether any possible effects were consistent in the subgroups of age, sex, stage of disease, histology and performance status. Subgroup analysis found some indications that patients younger than 60 years and patients with stage IIIB could benefit less from concomitant chemotherapy.

Conclusions

Concomitant platin-based chemoradiotherapy may improve survival of patients with locally advanced NSCLC. However, the available data are insufficient to accurately define the size of such a potential treatment benefit and the optimum schedule of chemotherapy.

Methods

Design

A systematic review and quantitative meta-analysis based on updated individual patient data will be carried out. This approach involves the central collection, validation and analysis of data from all patients from all relevant randomised trials.

Treatment comparisons

Seven meta-analyses will be carried out over three main clinical settings, corresponding to the stage of disease and to the primary treatment

Surgery
1. surgery vs surgery + adjuvant chemotherapy
2. surgery vs neoadjuvant chemotherapy + surgery
3. surgery + radiotherapy vs surgery + radiotherapy + adjuvant chemotherapy

Radiotherapy
4. radiotherapy vs sequential radiotherapy + sequential chemotherapy (neo-adjuvant – before radiotherapy- and/or adjuvant –after radiotherapy–) or alternated radio-chemotherapy
5. radiotherapy vs radiotherapy + concomitant chemotherapy
6. radiotherapy + sequential chemotherapy vs radiotherapy + concomitant chemotherapy

Supportive care
7. supportive care vs supportive care + chemotherapy

Identification of trials

There is good evidence that investigators and journals alike are more likely to publish trials with positive results. In order to avoid such publication bias, both published and unpublished trials will be included in the meta-analysis. To identify as many relevant trials as possible, systematic searches of a number of trial sources will be carried out and updated during the course of the project, ensuring a comprehensive and up-to-date database of trials.

Electronic Databases

The optimum search strategy for retrieving randomised controlled trials (RCTs) from Medline, developed by the Cochrane Collaboration will be modified (Appendix B).
- To specifically retrieve RCTs of chemotherapy for NSCLC
- And used to search Medline

In addition the following electronic bibliographic databases will be searched.
- The Cochrane Central Register of Controlled Trials (CENTRAL)
- Proceedings of ASCO 1995 - 2003

Trial Registers

Trial registers will be used to supplement searches of electronic databases with trials that may not (yet) be published or are still recruiting patients:
- UKCCCR Trials Register
- ClinicalTrials.gov
- Physicians Data Query Protocols (open and closed)
- Current Controlled Trials 'metaRegister' of controlled trials
Hand Searches
The following hand searches will be carried out with the aim of identifying trials that may have only been reported as abstracts or that might have been missed in the searches described above:

- Proceedings of the American Society for Clinical Oncology (ASCO) 1993-2003
- Proceedings of the European Society of Medical Oncology (ESMO) 1996 - 2002
- Bibliographies of all identified trials and review articles will be searched

Experts in the field
All participating trialists will be asked to review and supplement a provisional list of trials
Eligibility criteria

Eligibility criteria common to the 3 meta-analyses

Trials must
- be properly randomised in a way which precludes prior knowledge of treatment assigned
- be unconfounded
- have commenced randomisation on or after January 1st 1965
- have completed accrual before December 31st 2002 (ongoing trials will be listed but no data collected)
- include patients with non-small cell lung cancer
- include patients in first line therapy
- not use orthovoltage radiotherapy
- use a radiotherapy dose of 30Gy or more
- use the same radiotherapy in the compared arms

Patients must
- have unresected disease
- be suitable for radical thoracic radiotherapy
- not have received prior radiotherapy

Eligibility criteria specify to the 3 meta-analyses

4 radiotherapy vs radiotherapy + sequential chemotherapy

Trials
- must not give chemotherapy only during radiotherapy
- could use additional same concomitant chemotherapy in the compared arms
- could not have additional neo-adjuvant or adjuvant chemotherapy in both arms (for example, a design like neo-adjuvant chemotherapy in both arms and randomisation on adjuvant chemotherapy is not eligible)

Patients must
- be randomised to receive radical radiotherapy or radical radiotherapy plus sequential chemotherapy (before or/and after radiotherapy or/and alternated design)

5 radiotherapy vs radiotherapy + concomitant chemotherapy

Trials
- must use platin-based chemotherapy or new agents (taxane, gemcitabine, CPT-11, vinorelbine)\(^{10}\)
- must give chemotherapy during radiotherapy
- could use additional same sequential chemotherapy in both arms

Patients must
- be randomised to receive radical radiotherapy or radical radiotherapy plus concomitant chemotherapy

6 radiotherapy + sequential chemotherapy vs radiotherapy + concomitant chemotherapy

Trials must
- give chemotherapy before and/or after radiotherapy in one arm
- give chemotherapy mainly during radiotherapy in the other arm

Patients must
- be randomised to receive radical radiotherapy plus sequential chemotherapy or radical radiotherapy plus concomitant chemotherapy
Data Collection

New Trials
For all new trials, basic survival and baseline characteristics will be sought for all patients randomised into each trial. Up to date follow-up will be requested in order to report on both short and longer-term outcomes.

patient identifier (preferably not patient name)
date of birth or age at randomisation
sex
performance status
tumour TNM (or stage if TNM not available)
histology
date of randomisation	
treatment allocated (specify each arm of chemotherapy if several regimens used)
radiotherapy started / not started (only for comparison 6)
survival status
date of last follow-up
date of death
cause of death
local recurrence status
date of local recurrence
distant recurrence status
date of distant recurrence
acute toxicity (haematological, oesophageal and pulmonary) (only for comparison 6)
late oesophageal toxicity (only for comparison 6)
whether excluded from trial analysis
reason for exclusion

Trials already included in the 1995 Meta-analysis
Trials of long-term alkylating agents will not be updated as these are old trials that provided mature data for the 1995 analysis.

For the remaining trials of sequential chemotherapy included in the 1995 meta-analysis, we will seek data on the additional endpoints of local and distant recurrence. Where possible we will also obtain updated follow-up information for those patients that were alive at the time of the previous data submission.

Suggested coding conventions for these data are provided (Appendix C) and although using them will facilitate data transfer, it is not essential. Data will be accepted in whatever format is most convenient for the individual trial investigator or data centre and can be supplied by email, computer disk, on data collection forms or as a computer printout. We will also ask for a limited amount of information on trial design as well as the original trial protocol, associated on-study forms and publications.

A final copy of the data from each trial will be returned to the trialists for verification. The data collation and checking for this comparison will be done by the IGR. Copies of the final agreed database of all trials included in all comparisons will be held by the MRC and the IGR. All trial data will be held securely and will not be used, circulated or distributed in any way that allows access to individual trial data, without first seeking permission from trial investigators.
Analysis

The ultimate aim will be to obtain and analyse data from all randomised patients included in all of the relevant randomised trials.

The principal analysis will be performed on the endpoint of overall survival. Additional analyses will be performed on the endpoints of local recurrence-free survival, distant recurrence-free survival and overall recurrence-free survival, if sufficient data are available. In comparison 6, toxicity will be compared between sequential and concomitant chemotherapy. The number of patients who have at least one radiotherapy fraction (radiotherapy started / not started) will be described in comparison 6.

All analyses will be of randomised patients and will be carried out by intention to treat, that is, patients will be analysed according to the treatment allocated, irrespective of whether they received that treatment. Survival analyses will be stratified by trial, and the log-rank expected number of deaths and variance will be used to calculate individual and overall pooled hazard ratios by the fixed-effect model. Thus, the times to death for individual patients will be used within trials to calculate the hazard ratio, representing the overall risk of death for patients who were allocated chemotherapy compared to those who were not.

Results will also be presented as absolute differences at relevant time points calculated from the hazard ratio and baseline event rate for patients not receiving chemotherapy; proportional hazards are assumed. Confidence intervals for absolute differences will be similarly calculated from the baseline event rate and the hazard ratio at the 95% CI boundary values. \( \chi^2 \) heterogeneity tests will be used to test for gross statistical heterogeneity, the \( I^2 \) statistic will be used as a measure of consistency. Survival curves will be presented as simple (non-stratified) Kaplan-Meier curves. All p-values are two-sided.

Analyses by trial level characteristics

The effect of chemotherapy may vary across trials in the meta-analysis because they have each applied treatment in different ways. To explore this further, providing that there are sufficient data available, analyses are planned whereby trials, or arms within trials, will be grouped according to the type of chemotherapy regimen to determine whether there are any differences in treatment effect between these groups.

Trial characteristics will be reported in tabular form, information will include patient numbers, period of recruitment, treatment details and proportion of patients who received second-line treatment.

Type of chemotherapy

It is not practical to look at groups of trials using only exactly the same regimens, nor is it appropriate or sensible to look overall at all trials. We therefore plan to split trials into broad groupings according to the type of chemotherapy used. This will build on the groupings used in the 1995 meta-analysis, which revealed that old trials using long-term oral alkylating agents had a detrimental effect whereas trials using modern regimens showed a beneficial effect.

Within each main treatment comparison, trials will be grouped by the type of chemotherapy regimen. If there are insufficient numbers of patients within any categories, categories may be combined.

*Platinum based regimens*  
platinum + vinca alkaloid / etoposide  
platinum + anti-metabolic agent (e.g. tegafur, uft)
platinum + taxane
other platinum regimen

Non-platinum based regimens
vinca alkaloid / etoposide only
anti-metabolic agent only
taxane only
other non-platinum regimen

Long-term alkylating agents
Owing to the results of the 1995 meta-analysis, long-term alkylating agents will be considered separately from other trials. Owing to their antiquity, these will not be updated and results will remain unchanged but will be included for completeness.

For these analyses a hazard ratio will be calculated for each trial and a pooled hazard ratio calculated for each treatment category. A test for interaction will be used to investigate if there are any substantial differences in the effect of treatment between these treatment categories. If there is no clear evidence of heterogeneity, results may also be combined over categories.

Timing of chemotherapy
In comparison 4, the timing of sequential chemotherapy will be studied. The effect of treatment will be compared between trials using neo-adjuvant chemotherapy, adjuvant chemotherapy, both and other timing (alternated or concomitant plus adjuvant chemotherapy).

Other analyses by trial level characteristics
In comparison 5, a test for interaction will be used to investigate if there are any substantial differences in the effect of concomitant chemotherapy between trials including patients treated with radiotherapy +/- concomitant chemotherapy and those including patients treated with neo-adjuvant chemotherapy followed by radiotherapy +/- concomitant chemotherapy.

In comparison 6, the effect of treatment will be compared between trials using the same agents for sequential and concomitant chemotherapy and trials using different agents.

Sensitivity Analyses
Hazard ratios for overall survival will also be calculated using a random effects model.
Hazard ratios for overall survival will also be calculated excluding any trials that are clear outliers.

Analyses by patient level characteristics
Providing there are sufficient data available, we will investigate whether any observed treatment effect is consistent across well-defined patient subgroups. These analyses will be carried out on all trials (except trials of long-term alkylating agents) and will be stratified by trial. If there are substantial heterogeneity and differences of effect between treatment categories, then subgroup analyses will be done within treatment categories.

If there are insufficient numbers of patients within any patient categories, categories will be combined. Chi-squared tests for interaction or trend will be used to test whether there is any evidence that particular types of patients benefit more or less from chemotherapy.
The subgroups are as follows:

**Age** (<60, 60-64, 65-69, 70+)

**Sex** (Male, Female)

**Performance Status** *(Good, Poor)*

**Histology** (Adenocarcinoma, Squamous, Other)

**Stage** **See below for calculation**

*Performance Status*

<table>
<thead>
<tr>
<th>Meta-analysis Stage</th>
<th>WHO / ECOG</th>
<th>Karnofsky</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>0, 1</td>
<td>100, 90, 80, 70</td>
</tr>
<tr>
<td>Poor</td>
<td>2, 3, 4</td>
<td>60 - 10</td>
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</table>

**Stage**

<table>
<thead>
<tr>
<th>Meta-analysis Stage / ISS 1986</th>
<th>(p)TNM Classification</th>
<th>AJCC Stage</th>
<th>UICC stage 1997</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>0,1,2,X,S</td>
<td>I</td>
<td>IA, IB</td>
</tr>
<tr>
<td>II</td>
<td>0,1,2,X,S</td>
<td>1</td>
<td>IIA, IIB without T3N0</td>
</tr>
<tr>
<td>IIIA</td>
<td>a) 3</td>
<td>a) 0-1</td>
<td>III non metastatic</td>
</tr>
<tr>
<td></td>
<td>b) 1-3</td>
<td>b) 2</td>
<td>IIA + T3N0</td>
</tr>
<tr>
<td>IIIB</td>
<td>4, Any N</td>
<td>3, Any T</td>
<td>III non metastatic</td>
</tr>
<tr>
<td>IV</td>
<td>Any</td>
<td>Any 1</td>
<td>Any metastatic</td>
</tr>
</tbody>
</table>

**Alternative exploratory analysis**

Given the large number of trial and patient characteristics of interest, there may be interactions between them that could potentially confound these analyses. If we encounter substantial heterogeneity within any of the seven main meta-analyses we will further explore the potential influence of these factors using multi-level modelling techniques.

This modelling aspect of the project will be developed in collaboration with Dr Julian Higgins from the MRC Biostatistics Unit, who is a member of the International Advisory Group.
Publication Policy

The results of the meta-analyses will be published and presented in the name of the NSCLC Collaborative Group comprising trialists contributing data for analysis, the Secretariat and Advisory Group. Following publication in a peer reviewed journal, the meta-analyses will be submitted to the Cochrane Library to appear in the Cochrane Database of Systematic Reviews.

The seven meta-analyses will be analysed separately. We aim to have one collaborators meeting, at which the results will be presented, but the comparisons may be published separately.

The IGR carried out an individual patient data meta-analysis of concomitant chemotherapy (cisplatin or carboplatin) and radiotherapy in locally advanced non-small cell lung cancer. The results were presented at the 2003 World Conference on Lung Cancer in the name of the MAC3-LC (meta-analysis of cisplatin/carboplatin based concomitant chemotherapy in non-small cell lung cancer) Group. This study will be published in the name of this group. The update of this meta-analysis as well as the updating of the comparison on sequential radio-chemotherapy versus radiotherapy alone (comparison 4) and the direct comparison of these two types of radio-chemotherapy (comparison 6) will be published in the name of the current collaborative group.

Project Administration

As for the 1995 Meta-analysis, the MRC and the IGR will share project administration.

Comparisons 1, 2 & 7
The MRC will be responsible for all contact, data collection, verification and analysis for these comparisons.

Comparisons 3, 4, 5 & 6
The IGR will be responsible for all contact, data collection, verification and analysis for these comparisons.

Contacting Trialists

New trials
Trialists will be contacted, informed of the project, invited to collaborate and asked to supply data as outlined in the methods section.

Trials already included in the previous meta-analyses
Trials of long-term alkylating agents will not be updated as these are old trials that provided mature data for the 1995 analysis.

For remaining trials, trialists will be contacted and asked to provide recurrence data and additional follow-up as appropriate. Where possible we will also obtain updated follow-up information for those patients that were alive at the time of the previous data submission.

Timetable

<table>
<thead>
<tr>
<th>Timetable</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autumn 2004</td>
<td>Write to Trialists seeking collaboration</td>
</tr>
<tr>
<td>Autumn 2004-Summer 2005</td>
<td>Collate, check and verify incoming data, analyse individual trials</td>
</tr>
<tr>
<td>Autumn 2005</td>
<td>Analyses</td>
</tr>
<tr>
<td>Winter 2005</td>
<td>Present results to Trialists</td>
</tr>
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</table>
## Comparison 4

### Radiotherapy vs radiotherapy + sequential chemotherapy

<table>
<thead>
<tr>
<th>Trial</th>
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*Trials completed since 1995 Meta-analysis
## Comparison 5

Radiotherapy vs radiotherapy + concomitant chemotherapy

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*Trials completed since the MAC3-LC (meta-analysis of concomitant platin-based chemotherapy)
## Comparison 6

Radiotherapy + sequential chemotherapy vs radiotherapy + concomitant chemotherapy

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References


43. Mattson KV, Abratt RP, ten Velde G, Krofta K. Docetaxel as neoadjuvant therapy for


57. Jeremic B et al Randomized trial of hyperfractionated radiation therapy with or without concurrent chemotherapy for stage III non small cell lung cancer. J Clin Oncol


Appendix A

Glossary of Drugs

A  Doxorubicin
B  Bleomycin
Bu  Busulphan
C  Cisplatin
Cb  Carboplatin
Cy  Cyclophosphamide
Dx  Docetaxel
E  Epirubicin
Et  Etoposide
G  Gemcitabine
If  Ifosfamide
Lo  Lomustine / CCNU
Me  Mesna
Mi  Mitomycin C
Mx  Methotrexate
Mxa  Mitoxantrone
NM  Nitrogen Mustard
OF  Oral Florafur
Pc  Procarbazine
Pe  Pepleomycin
Pm  Porfiromycin
Pr  Prednisolone
Px  Paclitaxel
Tg  Tegafur
Ti  Tirapazamine
Tn  Teniposide
U  UFT (Tegafur + uracil)
Vb  Vinblastine
Vc  Vincristine
Vd  Vindesine
Vn  Vinorelbine
Appendix B

Search Strategy for Medline

1. Randomized Controlled Trial.pt.
2. exp Randomised Controlled Trials/
3. exp Random Allocation/
4. exp Double-Blind Method/
5. exp Single-Blind Method/
6. 1 or 2 or 3 or 4 or 5
7. clinical trial.pt.
8. exp Clinical Trials/
9. clin$ with trial.ab,ti.
10. (sing$ or doubl$ or trebl$ or tripl$ with blind$ or mask$).ab, ti.
11. exp Placebos/
12. placebo$.ab,ti.
13. random$.ab,ti.
14. exp Research Design/
15. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16. exp Carcinoma/
17. exp Lung Neoplasms/
18. (lung adj carcinoma$).ab,ti.
20. (lung adj neoplasm$).ab,ti.
21. cancer with lung.ab,ti.
22. carcinoma with lung.ab,ti.
23. 16 or 17
24. 18 or 19 or 20 or 21 or 22
25. exp Drug Therapy/
26. drug therapy.ab,ti.
27. chemotherapy.ab,ti.
28. 25 or 26 or 27
29. exp radiotherapy/
30. radiotherapy.ab,ti.
31. 29 or 30
32. exp surgery/
33. surgery.ab,ti.
34. 32 or 33
35. 28 or 31 or 34
36. 6 or 15
37. 36 and 24 and 35
Appendix C

Suggested coding

Please provide data on all patients randomised. You may complete data forms (provided on request) or supply your data as a computer printout, on floppy disk (formatted for PC) or by email. Data can be in almost any format (ASCII, Excel, Dbase, FoxPro etc.), but please indicate which format has been used. It would be helpful if you used the coding suggested, however you may code the data in the way that is most convenient for you. Please supply us with full details of the data coding system used. If sending data via email, please encrypt the data and let us know how it has been encrypted in a separate email.

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  - 3 = stage 3A
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  - 9 = unknown

If 1997 staging used
*Tumour Stage 1997 UICC*

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  - 6 = stage 3B
  - 7 = stage 4
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- **Code:**
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  - 2 = adenocarcinoma
  - 3 = squamous
  - 4 = mixed
  - 5 = large cell undifferentiated
  - 6 = NSC unspecified
  - 7 = other
  - 9 = unknown

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  - 999 = unknown

**Performance Status (WHO/ECOG)**

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**Treatment Allocated**

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- **Code:**
  - In comparison 4 and 5
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28
Protocol D

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1=radiotherapy + sequential chemotherapy
2=radiotherapy + concomitant chemotherapy
**Protocol D**

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Appendix D

Completed Meta-analyses by IGR and MRC

Service de Biostatistique et d'Epidemiologie, Institut Gustave-Roussy


Meta-analysis Group, Medical Research Council, UK


