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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Contents

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

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

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.

[1] Non-small Cell Lung Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. British Medical Journal 1995;311:899-909.

Box 2

Summary of Results of MAC3-LC[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

	Hazard Ratio	Confidence Interval	p-value	Heterogeneity p-value
Survival	0.89	0.81-0.98	0.02	0.16
Disease free survival	0.84	0.74-0.96	0.009	0.05

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.

[2] Auperin A, Le Pechoux C on behalf of the MAC3-LG Group. Meta-analysis of randomized trials evaluating cisplatin or carboplatin-based concomitant chemoradiation versus radiotherapy alone in locally advanced non-small cell lung cancer (NSCLC). Lung Cancer 2003;41(Suppl 2):S69.

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[6-8]. 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[9] 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 World Lung Cancer Conference 1997-2003
- Proceedings of the European Society of Medical Oncology (ESMO) 1996 - 2002
- Proceedings of the European Cancer Conference Organization (ECCO) 1995 - 2003
- 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[11]. 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;[12] 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. χ^2 heterogeneity tests[5] will be used to test for gross statistical heterogeneity, the I^2 statistic[13] will be used as a measure of consistency. Survival curves will be presented as simple (non-stratified) Kaplan-Meier curves[14]. 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

Meta-analysis Stage	WHO / ECOG	Karnofsky
Good	0, 1	100, 90, 80, 70
Poor	2, 3, 4	60 - 10

**Stage

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

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[15]. 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

Autumn 2004	Write to Trialists seeking collaboration
Autumn 2004-Summer 2005	Collate, check and verify incoming data, analyse individual trials
Autumn 2005	Analyses
Winter 2005	Present results to Trialists

Comparison 4

Radiotherapy vs radiotherapy + sequential chemotherapy

Trial	Period of recruitment	Drugs	Number of patients
Long term alkylating agent			
NRH NSC-26271[16]	1968-71	Cy	74
EORTC 08742[17]	1973-80	Cy, Lo, Mx	117
RTOG 7302a[18]	1973-78	Cy	111
RTOG 7302b[18]	1973-78	Cy	96
RTOG 7302c[18]	1973-78	Cy	104
MCL-1[19]	1980-84	A, Lo, Cy, Mx	52
Aviano[20]	1980-84	A, Cy, Mx, Pc	111
Platinum + vinca alkaloid / etoposide			
Brussels (neo-adjuvant)[21]	1981-84	C, Et, Vd	65
Essen[22] (neo-adjuvant)	1983-87	C, Vd	48
SLCSG[23] (neo-adjuvant)	1983-89	C, Et	327
WSLCRG/FI[24] (neo-adjuvant)	1984-89	C, Vd	79
Perugia (neo-adjuvant)[25]	1984-88	C, Et	66
CALGB 8433 (neo-adjuvant)[26]	1984-87	C, Vb	180
EORTC 08842[27] (neo-adjuvant + alternated)	1984-89	C, Vd	75
CEBI 138[28] (neo-adjuvant + adjuvant)	1983-89	C, Cy, Vd, Lo	353
SWOG 8300a (neo-adjuvant)	1984-88	5fu, Vc, Mi, Lo, C, A, Cy	128
SWOG 8300b (neo-adjuvant)	1984-88	5fu, Vc, Mi, Lo, C, A, Cy	126
*Seoul (neo-adjuvant)[29]	1988-92	C, Et, Vb	101
*CRC TU LU3001 (MIC 1) (neo-adjuvant)[30]	1988-96	C, Mi, If	461
*RTOG 8808 – ECOG 4588 (neo-adjuvant)[31]	1989-92	C, Vb	327
*Asan Med Center 1 [32] (adjuvant)	1991-93	C, Mi, Vb	32
*New Delhi (neo-adjuvant) [33]	1992-98	C, Mi, If	506
*BLT [34] (adjuvant)	1995-01	(C, Vd) or (C, Vn) or (C, Mi, If) or (C, Mi, Vn)	119
*BLT (neo-adjuvant) [34]	1995-01	(C, Vd) or (C, Vn) or (C, Mi, If) or (C, Mi, Vn)	169
*Lostau (alternated) [35]		C, Mi, If	57
Platinum + Taxane			
*CALGB 39801 (neo-adjuvant) (Cb, Px concomitant in both arms) [36]	1998-2002	Cb, Px	360
*Asan Med Center 2 [37] (adjuvant)	2000-01	C, Px	52
*GERCOR [38] (adjuvant)		Cb, Px	41
Other Platinum Regimens			
Buenos Aires [39] (adjuvant ?)	1981-85	C, A, Cy	81
FLCSG 2 [40] (neo-adjuvant + alternated + adjuvant)	1982-84	C, A, Cy	252
*MAOP 2192 (NCI-V92-0087) (neo-adjuvant + concomitant + adjuvant)		Rth alone vs [C, 5FU ci followed by Rth+5FU ci followed by 5FU]	25

Trial	Period of recruitment	Drugs	Number of patients
Vinca alkaloid only			
AZ-OC-1-80[41] (concomitant + adjuvant)	1981-85	Vb	52
Gwent 3 (adjuvant)	1981-85	Et	85
SECSG 81 LUN 375 [42] (concomitant + adjuvant)	1981-85	Vd	212
Taxane Only			
*Tax S1009 [43] (adjuvant)	1995-99	Dx	+/- 180
Other non-platinum regimens			
Gwent 1 [44] (adjuvant)	1974-76	A, 5fu	56
SWOG 7635 [45] (alternated)	1977-79	A	62
NCCTG 822451 [46] (neo-adjuvant + adjuvant)	1983-87	A, Cy, Mx, Lo	121
*Marburg [47] (neo-adjuvant) (concomitant C in both arms)	1986-89	If, Vd	85
		Total	**5548**

***Trials completed since 1995 Meta-analysis

Comparison 5

Radiotherapy vs radiotherapy + concomitant chemotherapy

Trial	Period of recruitment	Drugs	Number of patients
Platinum alone			
Soresi [48]	*1986-87*	*C*	*95 (not available)*
EORTC 8844 [49]	1984-89	C	330
HOG LUN 86 1 [50]	1986-92	C	237
Aviano [51]	1987-91	C	173
PMCI 88 C091 [52]	1989-95	Cb	208
CALGB-ECOG [53]induction C, Vb in both arms)	1991-94	Cb	282
NKB-CKVO 94 11 [54]	1994-98	Cb	160
*NPC 96-01 (induction Cb, Navelbine in both arms)	1996-2003	Cb	580
*Cakir [55]	1997-1999	C	187
Salamanca [56]		*Cb*	*38 (not available)*
Platinum + Eto			
Kragujevac 88 [57]	1988-89	Cb, Et	169
Kragujevac 90 [58]	1990-91	Cb, Et	131
NCCTG 90 24 51 [59]	1992-93	C, Et	74
RTOG 9701	*1997-99*	*Cb, Et*	*13 (not available)*
Platinum + Taxane			
*LAMP ACR 427 [60] (induction Cb, Px in both arms)	1998-2001	Cb, Px	166
Taxane only			
*Uluda [61]	1996-2001	Px	45
*Brocat Study Group CT/RT 99/97 [62] (induction Cb, Px in both arms)	1997-2002	Px	219
*GMMA Ankara [63]		Px	51
*Ramlau (European) [64] (induction C, Dx in both arms)		Dx	89
		Total	**3101**

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

Comparison 6

Radiotherapy + sequential chemotherapy vs radiotherapy + concomitant chemotherapy

Trial	Period of recruitment	Drugs	Number of patients
Platinum based regimens			
Osaka [65]	1992-94	C, Vd, Mi	320
Prague [66]	1997-2001	C, Vn	102
RTOG 9410 [67]	1994-98	C, Vb	+/-400
GLOT-GFPC NPC 95-01 [68]	1996-2000	C, Vn induction versus C, Et concomitant and C, Vn adjuvant	212
EORTC 08972	1999-2003	C, G induction versus C concomittant	150
CLB 8831 (induction C, Vb in both arms)		C, Vb adjuvant versus Cb conco	90
		Total	**1274**

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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 Ftorafur
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.
19	(lung adj cancer$).ab,ti.
20	(lung adj neoplasm$).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.

Patient Identifier

Preferably not name	
Type	character
Width	15

Date of Birth

Type	date
Width	8 or 6
Code	date in dd/mm/yyyy (recommended) or dd/mm/yy format

Age

Type	numeric
Width	3
Code	age in years unknown = 999

Sex

Type	numeric
Width	1
Code	1=male 2=female 9=unknown

Tumour stage used

Type	numeric
Width	1
Code	1=pTNM 2=AJCC 3=1986 ISS 4=1997 UICC

If pTNM used
Tumour Stage pTNM

Type	character		
Width	3		
Code	pT Stage	pN Stage	pM stage
	0=pT0	0=pN0	0=pM0
	X=pTX	1=pN1	1=pM1
	S=pTis	2=pN2	9=Unknown
	1=pT1	3=pN3	
	2=pT2	9=Unknown	
	3=pT3		
	4=pT4		
	9=Unknown		

If AJCC used
Tumour Stage AJCC

Type	numeric
Width	1
Code	1=stage 1

2=stage 2
3=stage 3
4=metastatic
9=unknown

If ISS used

Tumour Stage 1986 ISS

Type numeric
Width 1
Code 1=stage 1
2=stage 2
3=stage 3A
4=stage 3B
5=stage 4
9=unknown

If 1997 staging used

Tumour Stage 1997 UICC

Type numeric
Width 1
Code 1=stage 1A
2=stage 1B
3=stage 2A
4=stage 2B
5=stage 3A
6=stage 3B
7=stage 4
9=unknown

Histology

Type numeric
Width 1
Code 1=small cell
2=adenocarcinoma
3=squamous
4=mixed
5=large cell undifferentiated
6=NSC unspecified
7=other
9=unknown

*Performance Status (**Karnofsky**)*

Type numeric
Width 3
Code 10-100
999=unknown

*Performance Status (**WHO/ECOG**)*

Type numeric
Width 1
Code 1-4
9=unknown

Treatment Allocated

Type numeric
Width 1
Code **In comparison 4 and 5**
1=radiotherapy
2=radiotherapy + chemotherapy
If more than 1 regimen of chemotherapy used, please specify and use 3,4,5 etc for each different regimen
In comparison 6

		1=radiotherapy + sequential chemotherapy 2=radiotherapy + concomitant chemotherapy
Date of Randomisation		
	Type	date
	Width	8 or 6
	Code	date in dd/mm/yyyy (recommended) or dd/mm/yy format
Started radiotherapy (only for comparison 6)		
	Type	numeric
	Width	1
	Code	0=not started radiotherapy 1=started radiotherapy 9=unknown
Survival Status		
	Type	numeric
	Width	1
	Code	0=alive 1=dead
Date of Death / Last Follow-up	Type	date
	Width	8 or 6
	Code	date in dd/mm/yyyy (recommended) or dd/mm/yy format
Cause of Death		
	Type	numeric
	Width	1
	Code	1=lung cancer 2=treatment related 3=other 9=unknown
Local Recurrence Status		
	Type	numeric
	Width	1
	Code	0=no recurrence 1=recurrence 9=unknown
Date of Local Recurrence		
	Type	date
	Width	8 or 6
	Code	date in dd/mm/yyyy (recommended) or dd/mm/yy format
Distant Recurrence Status		
	Type	numeric
	Width	1
	Code	0=no recurrence 1=recurrence 9=unknown
Date of Distant Recurrence		
	Type	date
	Width	8 or 6
	Code	date in dd/mm/yyyy (recommended) or dd/mm/yy format
Recurrence Status (unspecified local or distant)		
	Type	numeric
	Width	1
	Code	0=no recurrence

	1=recurrence
	9=unknown

Date of Recurrence (unspecified local or distant)

Type	date
Width	8 or 6
Code	date in dd/mm/yyyy (recommended) or dd/mm/yy format

Acute toxicity scale used (only for comparison 6)

Type	numeric
Width	1
Code	1=RTOG
	2=CTC - NCI
	3=WHO
	4=Other

Highest grade of acute haematological toxicity (only for comparison 6)

Type	numeric
Width	1
Code	0 to 5
	9=unknown

Highest grade of acute pulmonary toxicity (only for comparison 6)

Type	numeric
Width	1
Code	0 to 5
	9=unknown

Highest grade of acute oesophageal toxicity (only for comparison 6)

Type	numeric
Width	1
Code	0 to 5
	9=unknown

Late toxicity scale used (only for comparison 6)

Type	numeric
Width	1
Code	1=RTOG / EORTC criteria
	2=SOMA evaluation
	3=CTC - NCI
	4=Other

Highest grade of late oesophageal toxicity (only for comparison 6)

Type	numeric
Width	1
Code	0 to 5
	9=unknown

Excluded

Type	numeric
Width	1
Code	0=included in analysis
	1=excluded from analysis
	9=unknown

Reason for Exclusion

Type	character
Width	25

Appendix D

Completed Meta-analyses by IGR and MRC

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

Pignon J-P, Arriagada R, Ihde DC, Johnson DH, Perry MC, Souhami RL, et al. A meta-analysis of thoracic radiotherapy for small-cell lung cancer. New England Journal of Medicine 1992;327:1618-24.

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Meta-analysis Group, Medical Research Council, UK

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