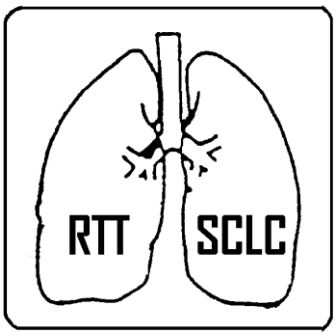

RadioTherapy Timing in Small Cell Lung Cancer

A *meta-analysis of randomised trials using individual patient data on the timing of chest radiotherapy in patients with limited stage small cell lung cancer*

April 2008

Updated in February 2014

Secretariat and Advisory Group

Secretariat

Dirk De Ruysscher, MD, PhD, Dpt of Radiotherapy, University Hospital Maastricht, the Netherlands.
e-mail: dirk.deruysscher@maastro.nl

Madelon Pijls-Johannesma, MSc, Dpt Radiation Oncology, MAASTRO clinic, Maastricht,
the Netherlands. e-mail: madelon.pijls@maastro.nl

Cécile Le Pechoux, MD, Dpt of Radiotherapy, Gustave Roussy, Villejuif, France.
e-mail: lepechoux@gustaveroussy.fr

Jean-Pierre Pignon, MD, PhD, Meta-analysis Unit, Gustave Roussy, Villejuif, France,
e-mail: jean-pierre.pignon@gustaveroussy.fr

Secretariat address:
RadioTherapyTiming in Small Cell Lung Cancer Collaborative group
c/o Service de Biostatistique et d'Epidémiologie
Gustave Roussy
114, rue Edouard Vaillant
94805 Villejuif cedex, France
fax: 33 1 42 11 45 65

List of the members of the advisory group

Paul Baas, MD, PhD
Dpt of Chest Oncology
Netherlands Cancer Institute –
Antoni van Leeuwenhoek Ziekenhuis (NKI-AVL)
Plesmanlaan 121
1066 CX Amsterdam
The Netherlands
Tel: 31 20-512 91 11
Fax: 31 20 512 25 73
e-mail: p.baas@nki.nl

Rodrigo Arriagada,MD
Gustave Roussy
Department of radiotherapy
114, rue Edouard Vaillant
94805 Villejuif cedex
France
Tel: 33 1 4211 5360
Fax: 33 1 4211 5299
e-mail: rodrigo.arriagada@gustaveroussy.fr

Lesley Seymour, MD
NCIC CTG
Cancer Research Institute
10 Stuart Street
Kingston ON K7L 3N6
Canada
Tel: 1 613-533-6430 ext. 78417
Fax: 1 613-533-2941
email : LSeymour@ctg.queensu.ca

Allan Price, MD
Dept of Radiation Oncology
University of Edinburgh
Western General Hospital
Crewe Road
Edinburgh EH4 2XU
UK
Tel: 44 (131) 537 2205
Fax: 44 (131) 537 2240
e-mail: aprice@staffmail.ed.ac.uk

Hak Choy, M.D.
The University of Texas Southwestern
Department of Radiation Oncology
5801 Forest Park Road
Dallas, TX 75390
USA
Tel: 1- 214-645-7600
Fax: 1- 214-645-9183
e-mail: Hak.Choy@utsouthwestern.edu

Contents

Introduction

Small cell lung cancer (SCLC) accounts for about 15-20% of all lung cancer cases, with only one third of the patients presenting with limited stage (LS) (1,2). Without treatment, tumour progression in patients with SCLC is rapid, with a median survival of 2–4 months. Chemotherapy has improved the median survival time substantially, but long-term survival remains rare after chemotherapy alone (3). Both a meta-analysis based on individual patient data, performed by the Institute Gustave Roussy (IGR) (4), as well as a meta-analysis based on published data (5) have shown an improvement of 5.4% in absolute survival at 2-years and 3-years, in patients who received chest irradiation and chemotherapy versus those receiving chemotherapy alone. The 5-year survival rate remained nevertheless disappointingly low at 10–15% (4). Although evidence for a significant survival benefit of adding chest radiotherapy was provided by these meta-analyses, no conclusions could be drawn regarding the optimal timing and sequencing of chemotherapy and radiation (6,7).

Two meta-analyses based on published data showed that delivering chest radiotherapy early after the beginning of chemotherapy improved survival (8,9). Using meta-analysis techniques, but based on published data, it appeared that a short time between the first day of chemotherapy and the last day of chest radiotherapy (Start of any treatment till the End of Radiotherapy, the so-called “SER”) was associated with improved survival in LS-SCLC (10). Furthermore, the results of two recently published meta-analyses, also based on published data, suggest that it is essential to ensure that the delivery of chemotherapy is optimal when administered with early chest radiotherapy (11,12).

Despite these recent findings, several issues about the administration of chest radiotherapy in LS-SCLC are still unresolved, including its timing with chemotherapy, the optimal overall treatment time of chest radiotherapy, the optimal dose and dose–intensity of chemotherapy, and whether or not to deliver radiotherapy concurrent with chemotherapy.

The main focus of this meta-analysis based on individual patient data is the best timing of chest radiotherapy with chemotherapy. Because it has become clear in recent years that the overall treatment time of radiation plays an important role in the outcome, this variable will also be examined (13-15). Since the type of chemotherapy delivered together with radiotherapy may affect outcomes, we will also stratify for this factor (6, 8-10,15).

The Maastricht group carried out two meta-analyses based on published data on the timing of chest radiotherapy in LS-SCLC and on the role of the SER (9,10,12). The results show that when platinum-based chemotherapy concurrently with chest RT is used, the 2-and 5-year survival rates of patients with LS-SCLC may be in favour of early chest radiotherapy, with a significant difference if the overall treatment time of chest radiation is less than 30 days (9,10,12).

The results thus showed that timing of chest radiotherapy (see summary of the results in box 1) may influence the 5-year survival. However, as the results were based only on published data, no firm conclusions could be drawn. A meta-analysis based on individual patient data would therefore be needed. The results would influence standard practice worldwide to a great extend.

The following therapeutic comparison will be studied: Early chest Radiotherapy vs. Late chest Radiotherapy whatever the type of chemotherapy. In this case, two types of trials will be considered: 1) Trials where the timing of chest radiation was different between both arms, but with the same radiotherapy in both arms; 2) Trials where the timing of chest radiation was different between both arms, but with different radiotherapy type in both arms. The impact of the second categories of trials on the results will be explored.

Box 1

Summary of Results of the meta-analysis based on published data on the timing of chest irradiation in LS-SCLC[12]

The main objective of the meta-analysis was to investigate the effect of timing of chest radiotherapy (early, i.e. within 30 days after the initiation of chemotherapy vs. late) on survival. The meta-analysis is based on 7 trials and 1514 patients.

Results

Comparison (number of trials)	Odds Ratio	Confidence Interval	p-value
Early versus late chest irradiation: 2-3 year survival (n=7)			
Platinum-based chemotherapy during radiotherapy (n=6)	0.73	0.57-0.94	0.01
Non-platinum-based chemotherapy during radiotherapy (n=1)	1.93	1.10-3.37	0.02
Early versus late chest irradiation: 5 year survival (n=5)			
Platinum-based chemotherapy during radiotherapy (n=4)	0.65	0-45-0.93	0.02
Non-platinum-based chemotherapy during radiotherapy (n=1)	2.10	0.95-4.66	0.07
Early versus late chest irradiation: 2-3 year survival as a function of overall treatment time of chest radiotherapy (n=5)			
Overall treatment time of radiotherapy < vs. ≥ 30 days	0.79	0.61-1.02	0.07
Early versus late chest irradiation: 5 year survival as a function of overall treatment time of chest radiotherapy (n=3)			
Overall treatment time of radiotherapy < vs. ≥ 30 days	0.57	0.38-0.85	0.005

A further objective was to assess what the effect of timing was on haematological, lung and oesophageal toxicity and whether the results were influenced by the compliance to chemotherapy. Oesophageal toxicity was higher in the early or accelerated arms, whereas other toxicity was similar. Compliance with chemotherapy had no effect on the outcome parameters.

Conclusions

When platinum-based chemotherapy concurrently with chest RT is used, the 2-and 5-year survival rates of patients with LS-SCLC may be in favour of early chest radiotherapy.

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.

Objectives

Assessment of the role of the timing of radiotherapy in small cell lung cancer by studying the following questions:

Main question

Role of the timing of radiotherapy on the **survival** of patients with small cell lung cancer by comparing:

Early chest radiotherapy

↗
↘

Late chest radiotherapy

Secondary questions

- Effect of radiotherapy timing on loco-regional control, distant control, recurrence-free survival,
- Comparison of observance, acute toxicity and late toxicity between the two radiotherapy modalities
- Investigation of the interaction between the treatment effect and the type of radiotherapy or chemotherapy (indirect comparison).
- Investigation of the interaction between the treatment effect and the prognostic factors and patient characteristics (subgroup analyses).

Eligibility criteria

Trials must

• Be properly randomised in a way which precludes prior knowledge of treatment assigned
• Be not confounded, except for the modalities of radiotherapy
• The timing of chest radiotherapy should be different between the treatment arms, but both trials with same radiotherapy modalities and those with different modalities will be included. The impact of the later on the results will be studied.
• Have commenced randomisation on or after January 1, 1970
• Have completed accrual before December 31, 2005 (ongoing trials will be listed but no data collected)
• Include patients with limited stage small cell lung cancer. Limited stage is defined as: cancer confined to one hemi-thorax including contralateral mediastinal and hilar lymph nodes as well as ipsilateral and/or bilateral supraclavicular involvement, but excluding malignant pleural effusion.
• Include only patients with a reasonably good performance status (WHO 0-2)
• Include patients in first line therapy
• Not use orthovoltage radiotherapy

• Use a radiotherapy dose of 30 Gy or more
• Investigate combined radiotherapy and chemotherapy
• Chemotherapy schedule (drugs, doses, number of cycles) should be the same in all treatment arms

Patients must

- Have unresected disease
- Be suitable for radical thoracic radiotherapy
- Have not received prior radiotherapy to the chest

Identification of trials

There is good evidence that investigators and journals alike are more likely to publish trials with positive results (15-18). 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 (19) will be modified (**Appendix A**).

- To specifically retrieve RCTs of radiotherapy for LS-SCLC
- 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 - 2007

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) 1993-2007
- Proceedings of the World Lung Cancer Conference 1997-2007
- Proceedings of the European Society of Medical Oncology (ESMO) 1996 - 2007
- Proceedings of the European Cancer Conference Organization (ECCO) 1995 - 2007
- 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.

Description of trials included

The eligible trials (24-35) are described in **Appendix B.** In total, twelve trials including more than 2,500 patients studied the role of radiotherapy timing in patients with small cell lung cancer. Table 1-B summarizes the potential confounding factors in each trial.

Endpoints and covariates

The main endpoint will be **overall survival**, because of its importance and because of the reliability of the measurement.

Secondary endpoints such as time to first event (local or distant failure), event–free survival will be also considered. Observance, acute and late toxicity will be also studied, if possible.

The prognostic factors and patient characteristics that will be considered are:

- Age.
- Sex.
- Stage.
- Performance status.

Data Collection and quality control

For all 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 (extensive versus limited stage) if TNM not available)
- Involvement of lymph nodes: no versus supra-clavicular / mediastinal lymph nodes
- Date of randomisation
- Treatment allocated (specify each arm of radiotherapy)
- Date start chemotherapy
- Number of chemotherapy cycles received
- Compliance of chemotherapy: percentage of planned dose, if available, per cytotoxic drug
- Radiotherapy started / not started
- Date first day chest radiotherapy
- Date last day chest radiotherapy
- Total administered dose of radiotherapy
- Number of fractions of radiotherapy
- QD vs. BID schedule
- If BID schedule: Time between the two daily fractions
- Chest irradiation concurrent with chemotherapy: yes/ no
- Prophylactic Cranial Irradiation (PCI): yes/ no
- Survival status
- Date of last follow-up
- Vital status
- Cause of death
- Local recurrence status
- Date of local recurrence
- Distant recurrence status
- Date of distant recurrence
- Second malignancy status
- Date of second malignancy
- Acute toxicity (neutropenia, thrombocytopenia, anemia, oesophageal and pulmonary) + specification of toxicity grading system used
- Late toxicity (oesophageal and pulmonary) + specification of toxicity grading system used
- Whether excluded from trial analysis
- Reason for exclusion

Appendix C gives the suggested format and coding of the form to be sent to the Secretariat.

All data will be checked for internal consistency and consistency with the trial protocol and published report. Range checks will be performed and extreme values will be checked with the trialists. Each trial will be analyzed individually, and the resulting survival analyses and trial data will be sent to the trialists for verification.

Statistical Analysis

Trial characteristics will be reported in tabular form, information will include patient numbers, period of recruitment, treatment details and median follow-up. Median follow-up will be computed using the reverse Kaplan-Meier method (20).

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, as it is expected that the overwhelming mortality will be due to recurrence of small cell lung cancer. Additional analyses will be performed on the endpoints of time to local recurrence, time to distant recurrence and overall recurrence-free survival, if sufficient data are available. Toxicity will be compared between early and late chest irradiation.

All analyses 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 (21). 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 to early chest radiotherapy compared to those who were not. X^2 heterogeneity tests will be used to test for gross statistical heterogeneity; the I^2 statistic (22) will be used as a measure of consistency. Stratified survival curves were estimated for control and experimental groups using annual death rates and hazard ratio (23). They were used to calculate absolute benefit at 3-years, and 5-years with their 95% confidence interval (23). All p-values will be two-sided.

Analyses by trial level characteristics

The main results will be presented with the overall results and the results according to the 3 groups defined in Table A-1, same radiotherapy and platinum during radiotherapy, same radiotherapy and other chemotherapy schedules, and different radiotherapy schedules whatever the chemotherapy schedule. The corresponding test of interaction will be performed.

Type of radiotherapy

Radiotherapy was applied in different ways in the trials. To explore this further, providing that there are sufficient data available, trials will be grouped according to some characteristics of radiotherapy. The groups will be compared by interaction test to determine whether there are any differences in treatment effect between these groups. The trials in which the radiotherapy characteristic studied is different between the two arms will be excluded from the corresponding analysis.

Trials will be compared on the basis of following radiotherapy characteristics: 1) hyperfractionated radiotherapy (more than one fraction per day) versus standard (once-daily) fractionation; 2) fraction size of radiotherapy below 1.8 Gy versus standard fraction sizes (1.8 Gy-2.4 Gy) versus high doses per fraction (superior or equal to 2.5 Gy); 3) overall treatment time of chest radiotherapy more than 30 days versus less or equal than 30 days.

As an exploratory analysis, the difference between the SER between trial arms will be calculated in order to explain survival differences. The trials will be divided in three groups according to the start of chest radiotherapy in relation to the first day of chemotherapy administration: < 30 days, 30 - 60 days and > 60 days.

Type of chemotherapy
It is neither 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.
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, administered during chest radiotherapy
This group corresponds to the trials where platinum based chemotherapy, i.e. platinum (either cisplatin or carboplatin) + any other chemotherapeutic drug, was given during radiotherapy. Therefore, trials where non-platinum chemotherapy was given outside of chest radiation, but platinum-containing regimes during radiotherapy, are thus part of this group.

Compliance with the treatment
Chemotherapy compliance
Provided that there will be sufficient data available, we will investigate whether the treatment effect is dependent on the compliance with chemotherapy. The compliance analysis will be performed by comparing the compliance between the treatment arms of each trial.

Radiotherapy compliance
Also for radiotherapy, we will investigate what the compliance was. The compliance analysis will be performed by comparing the compliance between the treatment arms of each trial.

Concurrent chest radiotherapy and chemotherapy
In some trials or study arms, chest radiotherapy will not be delivered concurrently with chemotherapy. This may affect the outcome. We will therefore investigate whether the delivery of chest radiotherapy concurrently with chemotherapy has an influence on the outcome, and whether this is independent from the timing of thoracic radiotherapy.

Administration of Prophylactic Cranial Irradiation (PCI)
In all studies, PCI was administered to a subgroup of patients. We will analyse the influence of PCI on the survival of the subgroup having received PCI versus those who did not.

Sensitivity Analyses
Analysis will be performed without the trials that used different modalities of radio-chemotherapy in the two arms (e.g. concurrent versus sequential or alternating versus sequential). In trial of Takada (26) the timing of chest radiotherapy differed but in one arm no concurrent chemo-radiation was delivered. A sensitivity analysis will be carried out with or without this study. Hazard ratios for overall survival will also be calculated excluding any trials that are clear outliers.

Sensitivity with or without trials where the timing of chest radiation was different between both arms, but with different radiotherapy type in both arms, will be performed.

Hazard ratios for overall survival will also be calculated using a random effects model if the heterogeneity has a p-value < 0.10.

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 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 early chest radiotherapy.

The subgroups are as follows:
Age (<60, 60-64, ≥ 65)
Sex (Male, Female)
Performance Status * (0, 1, ≥ 2)
Stage (mediastinal and/ or supraclavicular lymph nodes involved or not)

*Performance Status

WHO / ECOG	Karnofsky (%)
0	100, 90
1	80, 70
2, 3, 4	60 - 10

Project Administration

Working parties in the meta-analysis

In order to complete the meta-analysis successfully, three groups with specific functions will be created: 1) the Secretariat 2) the Advisory Group 3) The RadioTherapy Timing in Small Cell Lung Cancer (RTT-SCLC) Collaborative Group. The Secretariat is in charge of the coordination of the meta-analysis. It is responsible for completing the trial register and for inviting investigators to provide data available on patients. The Secretariat is also in charge of checking, processing and analyzing the data. Finally, the Secretariat is responsible for preparing reports, publications and works in very close collaboration with the Advisory Group.

The Advisory Group will include international experts in the field of oncology and radiotherapy, involved in lung cancer, and experts in meta-analysis. The list of its members is given at the beginning of the protocol. The Advisory Group will support the Secretariat with medical and methodological expertise, help determine trials relevant to the overview, and promote contact between investigators and all the collaborators.

The RadioTherapy Timing in Small Cell Lung Cancer (RTT-SCLC) Collaborative Group will include the investigators responsible for trials included in the meta-analysis.

The members of the Secretariat and the Advisory Group will also be included in this group. The trialists will be responsible for providing the Secretariat with data on patients and for discussing the reports prepared by the Advisory Group and the Secretariat.

Practical considerations

The Secretariat, located in the Biostatistics Department at Institut Gustave Roussy, will be responsible for liaising with trialists. The main database will be run by the Secretariat. All data, updating and correction should be sent there. All supplied data will remain confidential and used exclusively for the meta-analysis. A meeting of all group members will be organized by the Secretariat to discuss the preliminary results.

Contacting Trialists

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

Publication Policy

The results of the meta-analyses will be published and presented in the name of the RadioTherapy Timing in Small Cell Lung Cancer (RTT-SCLC) 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. One author from each trial will be co-author, and when appropriate other people who made a significant contribution to this study.

Timetable

Letter to all trialists for their collaboration: June 2008
Data collected in IGR and checked for consistency: December 2008
Analysis performed in IGR: January-April 2009
RTT-SCLC Collaborative Group meeting: May-June 2009
Submission for ASCO 2010: January 2010
Submission to an international journal: March-April 2010

Acknowledgments
We are grateful to Anne-Sophie Veillard for assistance in preparing the protocol.

References

1. Bunn Jr PA, Carney DN. Overview of chemotherapy for small cell lung cancer. Semin Oncol 1997;24(2 Suppl. 7):S769–74.

2. Stupp R, Monnerat C, Turrisi 3rd AT, Perry MC, Leyvraz S. Small cell lung cancer: state of the art and future perspectives. Lung Cancer 2004;45:105–17.

3. Kelly K. New chemotherapy agents for small cell lung cancer. Chest 2000;117(4 Suppl. 1):156S–62S.

4. Pignon JP, Arriagada R, Ihde DC, et al. A meta-analysis of thoracic radiotherapy for small-cell lung cancer. N Engl J Med 1992;327(23):1618–24.

5. Warde P, Payne D. Does thoracic irradiation improve survival and local control in limited-stage small-cell carcinoma of the lung? A meta-analysis. J Clin Oncol 1992;10(6):890–5.

6. Kumar P. The role of thoracic radiotherapy in the management of limited-stage small cell lung cancer: past, present, and future. Chest 1997;112(4 Suppl.):259S–65S.

7. De Ruysscher D, Vansteenkiste J. Chest radiotherapy in limited stage small cell lung cancer: facts, questions, prospects. Radiother Oncol 2000;55(1):1–9.

8. Fried DB, Morris DE, Poole C, et al. Systematic review evaluating the timing of thoracic radiation therapy in combined modality therapy for limited-stage small-cell lung cancer. J Clin Oncol 2004;22:4785-93

9. De Ruysscher D, Pijls-Johannesma M, Vansteenkiste J, et al. Systematic review and meta-analysis of randomised controlled trials of timing of chest radiotherapy in patients with limited stage small cell lung cancer. Ann Oncol 2006;17: 543–552

10. De Ruysscher D, Pijls-Johannesma M, Bentzen SM, et al. Time between the first day of chemotherapy and the last day of chest radiation is the most important predictor of survival in limited disease small-cell lung cancer. J Clin Oncol 2006;24:1057–63.

11. Spiro SG, James LE, Rudd RM, et al. Early compared with late radiotherapy in combined modality treatment for limited disease small-cell lung cancer: a London Lung Cancer Group multicenter randomized clinical trial and meta-analysis. J Clin Oncol 2006;24:3823–30.

12. Pijls-Johannesma M, De Ruysscher D, Vansteenkiste J, Kester A, Rutten I, Lambin P. Timing of chest radiotherapy in patients with limited stage small cell lung cancer: A systematic review and meta-analysis of randomised controlled trials. Cancer Treat Rev. 2007;33 :461-473.

13. Bentzen SM, Thames HD. Clinical evidence for tumor clonogen regeneration: interpretations of the data. Radiother Oncol 1991;22:161–6.

14. Withers HR, Taylor JM, Maciejewski B. The hazard of accelerated tumor clonogen repopulation during radiotherapy. Acta Oncol 1988;27:131–46.

15. Harari PM, Mehta MP, Ritter MA, Petereit DG. Clinical promise tempered by reality in the delivery of combined chemoradiation for common solid tumors. Semin Radiat Oncol 2003;13:3–12.

16. Dickersin K. The existence of publication bias and risk factors for its occurrence. JAMA 1990; 263:1385-9.

17. Easterbrook PJ, Berlin JA, Gopalan R, Matthews DR. Publication bias in clinical research. Lancet 1991; 337:867-72.

18. Dickersin K, Min Y-I, Meinert CL. Factors influencing publication of research results. JAMA 1992; 267(3):374-8.

19. Lefebvre C, Clarke MJ. Identifying Randomised Trials. In: Egger M, Smith GD, Altman DG, Eds. Systematic Reviews in Healthcare. 2nd edition. London: BMJ Publishing Group, 2002: 69-87.

20. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. Controlled clinical trials 17: 343–346, 1996.

21. Parmar MKB, Machin D. Survival analysis: a practical approach. John Wiley & Sons Ltd, 1995.

22. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Statistics in Medicine 2002; 21:1539-58.

23. Early Breast Cancer Trialists' Collaborative Group. Systemic treatment of early breast cancer by hormonal, cytotoxic or immune therapy: 133 randomised trials involving 31,000 recurrences and 24,000 death among 75,000 women. Lancet 1992;1–15.

References of randomized trials eligible for the meta-analysis

National Cancer Institute of Canada Clinical Trials Group (NCI-C)
24. Murray N, Coy P, Pater JL, et al. Importance of timing for thoracic irradiation in the combined modality treatment of limited-stage small-cell lung cancer. The National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 1993;6-344

Yugoslavia
25. Jeremic B, Shibamoto Y, Acimovic L, et al. Initial versus delayed accelerated hyperfractionated radiation therapy and concurrent chemotherapy in limited small-cell lung cancer: a randomized study. J Clin Oncol 1997;5:893-900

Japan Clinical Oncology Group (JCOG)
26. Takada M, Fukuoka M, Kawahara M, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with cisplatin and etoposide for limited-stage small-cell lung cancer: results of the Japan Clinical Oncology Group Study 9104. J Clin Oncol 2002;20:3054-3060

London Lung Cancer Group (LLCG), UK
27. Spiro SG, James LE, Rudd RM, et al. Early compared with late radiotherapy in combined modality treatment for limited disease small-cell lung cancer: a London Lung Cancer Group multicenter randomized clinical trial and meta-analysis. J Clin Oncol 2006;24:3823–30.

Hellenic Cooperative Oncology Group (HeCOG), Greece
28. Skarlos DV, Samantas E, Briassoulis E, et al. Randomized comparison of early versus late hyperfractionated thoracic irradiation concurrently with chemotherapy in limited disease small-cell lung cancer: a randomized phase II study of the Hellenic Cooperative Oncology Group (HeCOG). Ann Oncol 2001;12:1231–8.

Cancer and Leukemia Group B (CALGB)
29. Perry MC, Herndon JE, Eaton WL, et al. Thoracic radiation therapy added to chemotherapy for small-cell lung cancer: an update of Cancer and Leukemia Group B Study 8083. J Clin Oncol 16:2466-2467, 1998

Aarhus Lung Cancer Group (ALCG), Denmark
30. Work E, Nielsen OS, Bentzen SM, et al. Randomized study of initial versus late chest irradiation combined with chemotherapy in limited-stage small-cell lung cancer. Aarhus Lung Cancer Group. J Clin Oncol 1997;30-3037

Petites Cellules Group, France
31. Lebeau B, Urban T, Brechot JM, et al. A randomized clinical trial comparing concurrent and alternating thoracic irradiation for patients with limited small cell lung carcinoma. ‘‘Petites Cellules Group”. Cancer 1999;86:1480–7.

EORTC
32. Gregor A, Drings P, Burghouts J, et al. Randomized trial of alternating versus sequential radiotherapy/chemotherapy in limited-disease patients with small-cell lung cancer: a European Organization for Research and Treatment of Cancer Lung Cancer Cooperative Group Study. J Clin Oncol 1997;15:2840–9.

USA : Turrisi et al
33. Turrisi AT, Kim K, Blum R, et al. Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. N Engl J Med 1999;65-271

USA: Blackstock et al
34. Blackstock AW, Bogart JA, C. Matthews C, et al. Split-course versus continuous thoracic radiation therapy for limited-stage small-cell lung cancer: final report of a randomized phase III trial. Clin Lung Cancer 2005;6:287-292.

South-Korea
35. Park SK, Kim GH, Jeong SS, et al. The effects according to the timing of thoracic radiotherapy in limited stage small cell lung cancer. Tuberculosis and Respiratory Diseases 1996;43:903−915.

References of excluded randomized trials

The reasons for exclusion were:

The timing of chest radiation as well as the overall treatment time were the same in both trial arms
USA: Bonner et al
36. Bonner JA, Sloan JA, Shanahan TG, et al. Phase III comparison of twice-daily split-course irradiation versus once-daily irradiation for patients with limited stage small-cell lung carcinoma. J Clin Oncol 1999;17(9):2681–91.

Orthovoltage was used in some patients
Germany
37. Heilmann HP, Arnal ML, Bünemann H, Calavrezos A, Engel J, Franke HD, Hain E, Jüngst G, Kohl FV, Koschel G, Seysen U, von Wichert P. Kombinierte Chemotherapie-Radiotherapie-Studie des kleinzelligen Bronchuskarzinoms (CCR-Studie): Chemo-/Radiotherapie gegen Radio-/Chemotherapie. Strahlentherapie 1983;159 (3):152-155.

Appendix A: *Search Strategy for Medline*

("Lung Neoplasms/radiotherapy"[MeSH] AND Randomized Controlled Trial[ptyp])
OR ("Lung Neoplasms/radiotherapy"[MeSH] AND "Randomized Controlled Trials"[MeSH Terms])
OR ("Lung Neoplasms/radiotherapy"[MeSH] AND random*[Title/Abstract])

OR ("Lung Neoplasms/radiotherapy"[MAJR] AND Randomized Controlled Trial[ptyp])
OR ("Lung Neoplasms/radiotherapy"[MAJR] AND "Randomized Controlled Trials"[MeSH Terms])
OR ("Lung Neoplasms/radiotherapy"[MAJR] AND random*[Title/Abstract])

OR ("Lung Neoplasms"[MAJR] AND (radiother*[Title] OR radiat*[Title]) AND Randomized Controlled Trial[ptyp])
OR ("Lung Neoplasms"[MAJR] AND (radiother*[Title] OR radiat*[Title]) AND "Randomized Controlled Trials"[MeSH Terms])
OR ("Lung Neoplasms"[MAJR] AND (radiother*[Title] OR radiat*[Title]) AND random*[Title/Abstract])

OR (lung[Title] AND (radiother*[Title] OR radiat*[Title]) AND Randomized Controlled Trial[ptyp])
OR (lung[Title] AND (radiother*[Title] OR radiat*[Title])] AND "Randomized Controlled Trials"[MeSH Terms])
OR (lung[Title] AND (radiother*[Title] OR radiat*[Title]) AND random*[Title/Abstract])

AND ("1980"[PDAT] : "3000"[PDAT])

An initial research has been made in 2007, and then updated. Research on PubMed MEDLINE was made on January 11th 2007 and led to 905 results (+138 references from other sources). The search made on February 21st 2014, lead to 1,285 results on PubMed. Only one new trial was appropriate to be included in the meta-analysis in a sensitivity analysis using published data (Sun et al. *Ann Oncol* 2013)

Appendix B: Description of the trials

Table 1-A. Characteristics of the potentially eligible randomized trials

See abbreviations at the end of the table

Study	Number of Patients	Inclusion period	Start of chest radiation (day)	Concurrent CT	PCI	Chemotherapy (mg/m²)	Number of CT cycles (before RT, during RT, after RT)	Radiotherapy dose (Gray) / Number of fractions / duration (weeks)
Same radiotherapy and platinum during radiotherapy								
Murray [24]	332	1985-88	Day 22 Day 106	Early: Yes Late: Yes	Yes, only if CR	Early : P : 25 mg/m² x 3days, weeks 4,11,17 E : 100 mg/m², weeks 4,11,17 alternating with C : 1000 mg/m², wks 1,8,14 A : 50mg/m², wks 1,8,14 V : 2 mg, wks 1,8,14 Late : P : 25 mg/m² x 3days, weeks 4,10,16 E : 100 mg/m², weeks 4,10,16 alternating with C : 1000 mg/m², wks 1,7,13 A : 50mg/m², wks 1,7,13 V : 2 mg, wks 1,7,13	Early : 6 cycles (1 before RT, 1 during RT, 4 after RT) Late : 6 cycles (5 before RT, 1 during RT)	40 Gy in 15 fractions (2.7 Gy) / 3 weeks
Jeremic [25]	107	1988-92	Day 1 Day 36	Early: Yes Late: Yes	Yes, only if CR or PR	During RT : Early : Cb : 30 x 5 mg/m², wks 1 to 4 E : 30 x 5 mg/m², wks 1 to 4 Late : Cb : 30 x 5 mg/m², wks 6 to 9 E : 30 x 5 mg/m², wks 6 to 9 Outside RT : Early: P : 30 x 3 mg/m², wks 6,9,12,15 E : 120 x 3 mg/m², wks 6,9,12,15 Late : P : 30 x 3 mg/m², wks 1,4,11,14 E : 120 x 3 mg/m², wks 1,4,11,14	Early : 4 cycles (1 injection x 5 per week during RT, 4 after RT) Late: 4 cycles (2 before RT, 1 injection x 5 per week during RT, 2 after RT)	54 Gy in 36 fractions (1.5 Gy twice daily) / 3.6 weeks

Study	Number of Patients	Inclusion period	Start of chest radiation (day)	Concurrent CT	PCI	Chemotherapy (mg/m²)	Number of CT cycles (before RT, during RT, after RT)	Radiotherapy dose (Gray) / Number of fractions / duration (weeks)
Takada [26]	231	1991-95	Day 2 Day 85	Early: Yes Late: No	Yes, only if CR or "near CR"	Early*: P : 80 mg/m², wks 1,5,9,13 E : 100 x 3 mg/m², wks 1,5,9,13 Late: P : 80 mg/m², wks 1,4,7,10 E : 100 x 3 mg/m², wks 1,4,7,10	Early : 4 cycles (1 during RT, 3 after RT) Late : 4 cycles (4 before RT)	45 Gy in 30 fractions (1.5 Gy twice daily) / 3 weeks
Spiro [27]	325	1993-99	Day 22 Day 106	Early: Yes Late: Yes	Yes, only if CR	P : 25 x 3 mg:m², wks 4,10,16 E : 100 x 3 mg/m², wks 4,10,16 alternating with C : 1000 mg/m², wks 1,7,13 A : 50 mg/m², wks 1,7,13 V : 2 mg, wks 1,7,13	Early : 6 cycles (1 before RT, 1 during RT, 4 after RT) Late : 6 cycles (5 before RT, 1 during RT)	40 Gy in 15 fractions (2.7 Gy) / 3 weeks
Skarlos [28]	86	1993-99	Day 1 Day 57	Early: Yes Late: Yes	Yes, only if CR	Cb : 6 AUC, wks 1,4,7,10,13,16 E : 100 x 3 mg/m², wks 1,4,7,10,13,16	Early : 6 cycles (1 during RT, 5 after RT) Late : 6 cycles (3 before RT, 1 during RT, 2 after RT)	45 Gy in 15 fractions (1.5 Gy twice daily) / 3 weeks
Same radiotherapy and other chemotherapy schedules								
Perry [29]	426**	1981-84	Day 1 Day 64	Early: Yes Late: Yes	Yes	C : 1000 mg/m², every 3 weeks V : 1.4 mg/m², every 3 weeks E : 80 x 3 mg/m², every 3 weeks Starting at cycle 7 for odd-numbered cycles : C : 1000 mg/m², every 3 weeks V : 1.4 mg/m², every 3 weeks A : 50 mg/m², every 3 weeks	About 26 cycles	50 Gy in 24 fractions (2.08 Gy ?) / 5 weeks

Study	Number of Patients	Inclusion period	Start of chest radiation (day)	Concurrent CT	PCI	Chemotherapy (mg/m²)	Number of CT cycles (before RT, during RT, after RT)	Radiotherapy dose (Gray) / Number of fractions / duration (weeks)
Work [30]	199	1981-89	Day 1 Day 127	Early: No Late: No	Yes***	Early : P : 60 mg/m², wks 3,8,23 E : 120 x 3 mg/m², wks 3,8,23 alternating with C :1000 mg/m², wks 11,14,17,20,26,29 A : 45 mg/m², wks 11,14,17,20,26,29 V : 1.4 mg/m², wks 11,14,17,20,26,29 Late : P : 60 mg/m², wks 1,4,21 E : 120 x 3 mg/m², wks 1,4,21 alternating with C :1000 mg/m², wks 7,10,13,16,28,31 A : 45 mg/m², wks 7,10,13,16,28,31 V : 1.4 mg/m², wks 7,10,13,16,28,31	Early : 9 cycles (1 in alternance with RT, 8 after RT) Late : 9 cycles (6 before RT, 1 in alternance with RT, 2 after RT)	20 Gy in 11 fractions (1.8 Gy) / 2 weeks 3 weeks break 22.5 Gy in 11 fractions (2 Gy) / 2 weeks ****
Different radiotherapy schedules whatever the chemotherapy schedule								
Lebeau [31]	164	1988-94	Concurrent : Day 30 Alternating : Day 36	Conc : Yes Alt : No	Yes only if CR	C : 1000 mg/m², wks 1,13,17,21 A : 45 mg/m², wks 1,13,17,21 E : 150 x 2 mg/m², wks 1,13,17,21 C : 1000 mg/m², wks 5,9 Vd : 3 mg/m², wks 5,9 E : 150 x 2 mg/m², wks 5,9	Conc : 6 cycles (2 before RT, 1 during RT, 3 after RT) Alt : 6 cycles (2 before RT, 2 in alternance with RT, 2 after RT)	Conc : 50 Gy in 20 fractions (2.5 Gy) / 5 weeks Alt : 20 Gy in 8 fractions (2.5 Gy) / 2 weeks 2 weeks break 20 Gy in 8 fractions (2.5 Gy) / 2 weeks 2 weeks break 15 Gy in 6 fractions (2.5 Gy) / 1.5 weeks

Study	Number of Patients	Inclusion period	Start of chest radiation (day)	Concurrent CT	PCI	Chemotherapy (mg/m²)	Number of CT cycles (before RT, during RT, after RT)	Radiotherapy dose (Gray) / Number of fractions / duration (weeks)
Gregor [32]	349	1989-95	Alternating : Day 43 Sequential : Day 99	Early: No Late : No	Yes only if CR *****	Alt : C : 1.0 mg/m², wks 1,5,9,13,17 A : 45 mg/m², wks 1,5,9,13,17 E : 100 x 3 mg/m², wks 1,5,9,13,17 Seq : C : 1.0 mg/m², wks 1,4,7,10,13 A : 45 mg/m², wks 1,4,7,10,13 E : 100 x 3 mg/m², wks 1,4,7,10,13	Alt : 5 cycles (2 before RT, 3 in alternance with RT) Seq : 5 cycles (5 before RT)	Alt : 50 Gy in 20 fractions (2.5 Gy) / 4 one week course with 3 weeks break Seq : 50 Gy in 20 fractions (2.5 Gy) / 4 consecutive weeks
Turrisi [33]	417	1989-92	RT in both arms: Day 1 SER arm 1: 3 weeks SER arm 2: 5 weeks	Both arms: Yes	Yes, only if CR	P : 60 mg/m², wks 1,4,7,10 E :120 x 3 mg/m², wks 1,4,7,10	4 cycles (1 during RT, 3 after RT)	Arm 1 : 45 Gy in 30 fractions (1.5 Gy twice daily) / 3 weeks Arm 2 : 45 Gy in 25 fractions (1.8 Gy) / 5 weeks
Blackstock [34]	114	1987-92	SER arm 1 : 5 weeks SER arm 2 : 7 weeks	Yes	Yes, only if CR	C : 750 mg/m², wks 7,10,16 A : 60 mg/m², wks 7,10,16 V : 2 mg, wks 7,10,16 alternating with P : 60 mg/m², wks 1,4,13 E : 120 x 3 mg/m², wks 1,4,13	Arm 1 : 6 cycles (2 during RT, 4 after RT) Arm 2 : 6 cycles (3 in alternance with RT, 3 after RT)	Arm 1 : 50 Gy in 25 fractions (2 Gy) / 5 weeks Arm 2 : 20 Gy in 8 fractions (2.5 Gy) / 2 weeks 1 week break 20 Gy in 8 fractions (2.5 Gy) / 2 weeks 1 week break 10 Gy in 4 fractions (2.5 Gy) / 1 week

Study	Number of Patients	Inclusion period	Start of chest radiation (day)	Concurrent CT	PCI	Chemotherapy (mg/m²)	Number of CT cycles (before RT, during RT, after RT)	Radiotherapy dose (Gray) / Number of fractions / duration (weeks)
Park [35]	51	Not mentioned in abstract	Concurrent : Day 1 ? (3 weeks) Sequential : Day 137 ? (5-6 weeks)	Early : Yes Late : No	Not mentioned in abstract	C : not available A : V : alternating with P : E :	Early : 6 cycles (1 during RT, 5 after RT) Late : 6 cycles (6 after RT)	Early : 45 Gy in 30 fractions (1.5 Gy twice daily) / 3 weeks Late : 40-50 Gy in ? fractions / 5-6 weeks

* Chemotherapy concomitant to radiotherapy for early arm only
** All 3 arms considered (the third arm (n = 138) in which patients only received chemotherapy will not taken up in this review).
*** At first, PCI was given to patients randomized to receive early radiotherapy. After October 1984, all patients received PCI independent of the timing of the radiotherapy.
**** Before October 1984, the dose of radiotherapy was 40 Gy and after this date, the dose was 45 Gy. In the early arm, 45 patients received a dose of 40 Gy and 54 patients received a dose of 45 Gy. In the late arm, 41 patients received a dose of 40 Gy and 59 patients received a dose of 45 Gy.
***** Patients who achieved complete response were eligible for inclusion in the UKCCCR/EORTC trial UK02 (randomized to PCI or no PCI)

Abbreviations: E: early chest radiation arm, L: late chest radiation arm. PCI: Prophylactic Cranial Irradiation; CR: complete remission. PR: partial remission. CT: Chemotherapy. RT: chest radiotherapy. SER: Time from the start of any treatment to the end of chest radiotherapy, AUC : Area Under the Curve
Alt=Alternating, Seq=Sequential, Conc=Concurrent
C: Cyclophosphamide, A: Adriamycin, E: Etoposide, Cb: Carboplatin, P: Cisplatin, V: Vincristine, Vd: Vindesine

Table 1-B. Distribution of the eligible trials according to the potential confounding variables.

Trials	N° patients	Hyperfractionated radiotherapy	Fraction size of radiotherapy	Concurrent chemotherapy in both arms	Overall treatment time of chest radiotherapy	Platinum during radiotherapy	PCI planned in the protocol
Murray	332	No	superior or equal to 2.5 Gy	Yes	Less or equal than 30 days	Yes	Yes
Jeremic	107	Yes	Below 1.8 Gy	Yes	Less or equal than 30 days	Yes	Yes
Takada	231	Yes	Below 1.8 Gy	Yes	Less or equal than 30 days	Yes	Yes
		Yes	Below 1.8 Gy	No	Less or equal than 30 days	No	Yes
Spiro	325	No	superior or equal to 2.5 Gy	Yes	Less or equal than 30 days	Yes	Yes
Skarlos	86	Yes	Below 1.8 Gy	Yes	Less or equal than 30 days	Yes	Yes
Perry	426	No	1.8 Gy – 2.4 Gy	Yes	More than 30 days	No	Yes
Work	199	No	1.8 Gy – 2.4 Gy	No	More than 30 days	No	Yes
Lebeau	164	No	superior or equal to 2.5 Gy	No	More than 30 days	No	Yes
		No	superior or equal to 2.5 Gy	Yes	More than 30 days	No	Yes
Gregor	349	No	superior or equal to 2.5 Gy	No	More than 30 days	No	Yes
		No	superior or equal to 2.5 Gy	No	Less or equal than 30 days	No	Yes
Turrisi	417	No	1.8 Gy – 2.4 Gy	Yes	More than 30 days	Yes	Yes
		Yes	Below 1.8 Gy	Yes	Less or equal than 30 days	Yes	Yes
Blackstock	114	No	1.8 Gy – 2.4 Gy	Yes	More than 30 days	Yes	Yes
		No	superior or equal to 2.5 Gy	No	More than 30 days	No	Yes
Park	51	Yes	Below 1.8 Gy	Yes	Less or equal than 30 days	Yes	?
		No	?	No	More than 30 days	No	?

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, 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.

Variable	Format/Coding
Patient Identifier	Type string **(Preferably not name)** – Width 15
Date of Birth	Type date – Width 8 or 6 Code date in dd/mm/yyyy (recommended) or dd/mm/yy format
Age (at study entrance)	Type numeric – Width 3 Code age in years, unknown = 999
Sex	Type numeric – Width 1 1=male, 2=female, 9=unknown
Tumour stage used	Type numeric – Width 1 1=limited vs. extensive, 2=AJCC, 3=1986 ISS, 4=1997 UICC
For Small cell Lung cancer, the three items below are recommended	
Limited vs. extensive	0=limited disease, 1=extensive disease
Mediastinal nodes involved	Type numeric - Width 1 0=no, 1=yes, 9=unknown
Supra-clavicular	Type numeric - Width 1 0=no, 1=yes, 9=unknown
If possible, provide both complete TNM and stage	
TNM	**T**: 0 to 4, 5=X, 6=in situ, 9=unknown **N**: 0 to 3, 4=X, 9=unknown **M**: 0, 1, 2=X, 9=unknown
If AJCC used *Tumour Stage AJCC* or *TNM*	Type numeric - Width 1 1=stage I, 2=stage II, 3=stage III, 4=metastatic, 9=unknown Type numeric - Width 1 for T, 1 for N, 1 for M
If ISS used *Tumour Stage 1986 ISS* or *TNM*	Type numeric - Width 1 1=stage I, 2=stage II, 3=stage IIIA, 4=stage IIIB, 5=stage IV, 9=unknown Type numeric - Width 1 for T, 1 for N, 1 for M
If 1997 staging used *Tumour Stage 1997 UICC* or *TNM*	Type numeric - Width 1 1=stage IA, 2=stage IB, 3=stage IIA, 4=stage IIB, 5=stage IIIA, 6=stage IIIB, 7=stage IV, 9=unknown Type numeric - Width 1 for T, 1 for N, 1 for M
Histology	Type numeric - Width 1 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 = 1= late radiotherapy, 2 = early radiotherapy
Date of Randomisation	Type date - Width 8 or 6 Code date in dd/mm/yyyy (recommended) or dd/mm/yy format
Start chemotherapy	Type numeric - Width 1 0=not started chemotherapy,1=started chemotherapy, 9=unknown
Date of start of chemotherapy	Type date - Width 8 or 6 Code date in dd/mm/yyyy (recommended) or dd/mm/yy format
Number of chemotherapy cycles received	Type numeric - Width 1
If available, percentage of planned dose, per cytotoxic drug	
Drug 1 (%)	Type numeric - Width 3
Drug 2 (%)	Type numeric - Width 3
Drug 3 (%)…..	Type numeric - Width 3
Start radiotherapy	Type numeric - Width 1 0=not started radiotherapy,1=started radiotherapy, 9=unknown
Date of start of radiotherapy	Type date - Width 8 or 6 Code date in dd/mm/yyyy (recommended) or dd/mm/yy format
Date of end radiotherapy	Type date - Width 8 or 6 Code date in dd/mm/yyyy (recommended) or dd/mm/yy format
Total dose of radiotherapy (Gy)	Type numeric - Width 2
Total number of fractions of radiotherapy	Type numeric - Width 2
Number of daily fractions	Type numeric – Width 1
If multiple daily fraction, time between fractions (hours)	Type numeric – Width 1
PCI	Width 1 0= No, 1=yes, 9=unknown
Survival Status	Type numeric - Width 1 0=alive, 1=dead , 9 unknown
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 1=lung cancer, 2=treatment related, 3=other, 9=unknown
Local Recurrence Status	Type numeric - Width 1 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 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 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
Second Malignancy status	Type numeric – Width 1 0=no second malignancy, 1=second malignancy , 9=unknown

Date of Second Malignancy	Type date – Width 8 or 6 Code date in dd/mm/yyyy (recommended) or dd/mm/yy format
Acute toxicity scale used	Type numeric - Width 1 1=RTOG, 2=CTC – NCI, 3=WHO, 4=Other
Highest grade of acute haemoglobin toxicity	Type numeric - Width 1 Code 0 to 5 , 9=unknown
Highest grade of acute neutrophils toxicity	Type numeric - Width 1 Code 0 to 5, 9=unknown
Highest grade of acute platelets toxicity	Type numeric - Width 1 Code 0 to 5, 9=unknown
Highest grade of acute pulmonary toxicity	Type numeric - Width 1 Code 0 to 5, 9=unknown
Highest grade of acute cardiac toxicity	Type numeric - Width 1 Code 0 to 5, 9=unknown
Highest grade of acute oesophageal toxicity	Type numeric - Width 1 Code 0 to 5, 9=unknown
Late toxicity scale used	Type numeric - Width 1 1=RTOG / EORTC criteria, 2=SOMA evaluation, 3=CTC – NCI, 4=Other
Highest grade of late pulmonary toxicity	Type numeric - Width 1 Code 0 to 5, 9=unknown
Highest grade of late cardiac toxicity	Type numeric - Width 1 Code 0 to 5, 9=unknown
Highest grade of late oesophageal toxicity	Type numeric - Width 1 Code 0 to 5, 9=unknown
Excluded	Type numeric - Width 1 0=included in analysis, 1=excluded from analysis, 9=unknown
Reason for Exclusion	Type string - Width 25