Meta-Analysis of Radiotherapy in Lung Cancer

A meta-analysis based on individual patient data evaluating the role of altered fractionation on survival

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# CONTENTS

1. INTRODUCTION AND BACKGROUND ........................................................................................................... 4  
2. OBJECTIVES .................................................................................................................................................. 7  
3. TRIAL SELECTION CRITERIA ....................................................................................................................... 7  
   3.1 INCLUSION CRITERIA .......................................................................................................................... 7  
   3.2 EXCLUSION CRITERIA .......................................................................................................................... 8  
4. TRIAL SEARCH ............................................................................................................................................... 8  
5. DESCRIPTION OF TRIALS INCLUDED ....................................................................................................... 8  
6. CRITERIA OF EVALUATION ......................................................................................................................... 9  
   6.1 ENDPOINTS ........................................................................................................................................... 9  
   6.2 PROGNOSTIC FACTORS ......................................................................................................................... 9  
7. DATA COLLECTION AND QUALITY CONTROL ............................................................................................ 9  
8. STATISTICAL ANALYSIS PLAN ................................................................................................................... 10  
   8.1 ANALYSES BY TRIAL LEVEL CHARACTERISTICS (NSCLC trials only) .................................................. 11  
   8.2 ANALYSES BY PATIENT LEVEL CHARACTERISTICS ........................................................................ 12  
   8.3 SENSITIVITY ANALYSES .................................................................................................................... 13  
   8.4 SURROGATE ENDPOINT VALIDATION .............................................................................................. 13  
9. WORKING PARTIES IN THE META-ANALYSIS PROJECT ........................................................................ 13  
10. PRACTICAL CONSIDERATIONS ............................................................................................................... 14  
11. PUBLICATION POLICY ............................................................................................................................ 14  
12. REFERENCES ............................................................................................................................................... 15  
   12.1 REFERENCES OF RANDOMIZED TRIALS ELIGIBLE FOR THE META-ANALYSIS ......................... 17  
   12.2 REFERENCES OF ONGOING RANDOMIZED TRIALS ...................................................................... 18  
   12.3 REFERENCES OF EXCLUDED RANDOMIZED TRIALS ..................................................................... 19  
Appendix A: trial search strategy .................................................................................................................... 20  
Appendix B: Description of the trials ............................................................................................................... 21  
Appendix C: Classification of trials ................................................................................................................ 24  
Appendix D: Suggested coding ....................................................................................................................... 31
1. INTRODUCTION AND BACKGROUND

Worldwide, lung cancer accounts for the largest number of new cases of cancer and of deaths from cancer annually with around 1.35 million new cases and 1.18 million of deaths\(^1\). About 85% of these tumors are of non-small cell histological type\(^2\), including adenocarcinomas, squamous cell and large cell carcinomas. The remaining are small cell cancers (SCLC). For the period 2000-2002, in Europe, five-year survival relative survival in lung cancer was about 11% in Europe and 16% in USA\(^3\).

Although surgery is generally regarded as the optimal treatment, only about 30% of tumors 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 recent years, considerable interest has been raised about non-conventional fractionation schedules in radiation therapy for head & neck and lung cancers\(^5,6,7\). Two types of altered fractionation have been studied\(^7\):

- The first was hyperfractionation in which the dose per fraction was decreased, with two or three fractions per day given instead of one. The reduction of the dose per fraction was supposed to decrease the probability of late radiation induced morbidity, and by this means the total dose to the tumor could be increased.
- A second and more recent approach consisted of reducing the overall treatment time, thus accelerating radiotherapy by delivering to the tumor a high total dose in a much shorter overall time. Accelerated radiotherapy is often combined with hyperfractionation.

In both cases, the aim was to increase the loco-regional control rate, which may ultimately result in an overall survival benefit.

In the past decades, several randomized trials on lung cancer have compared a conventional radiotherapy arm with hyperfractionated or accelerated radiotherapy arm(s). These trials contain relatively homogeneous series of patients mostly with locally advanced tumors, and generally a reference arm of conventional radiotherapy alone (60-70 Gy in 6-7 weeks for non-small cell cancer – NSCLC - and 40-50 Gy in 4-5 weeks for SCLC). In some of these trials, a significant improvement in loco-regional control or in overall survival was shown in favor of the modified fractionation arm, but in other trials no significant gain was observed. Therefore, it remains controversial whether modified fractionation may improve survival for lung cancer patients. However, to distinguish between ineffective treatment and moderate treatment effects a great number of patients must be studied. For instance, to detect a 5 to 10% reduction in mortality, more than one thousand patients have to be randomized. The size of most of the individual trials performed in lung cancer has not been large enough to detect such a moderate decrease in mortality. Indeed, none of these trials included more than 300 patients per arm. Increased evidence suggests that a moderate improvement in survival is generally the best that can be expected of new cancer treatments, but that may be clinically worthwhile\(^6,13\). Given the incidence of lung cancer, an improvement in survival of 5% could prolong the life of thousands of patients throughout the world, each year.

An individual patient data (IPD) meta-analysis on altered fractionated radiotherapy has been recently performed in head and neck cancer\(^13,15\). Its results, which demonstrate a small benefit on overall survival of altered fractionated radiotherapy, are summarized in Box 1.
Summary of the results of the Meta-Analysis of Radiotherapy in Carcinomas of Head & neck (MARCH)

The MARCH study included 15 randomized trials comparing hyperfractionated and/or accelerated radiotherapy with standard radiotherapy, and 6,515 patients with a median follow-up of 6.0 years. Tumors sites were mostly oropharynx and larynx; 5,221 (74%) patients had stage III–IV disease (International Union Against Cancer, 1987). The study showed that altered fractionated radiotherapy improves survival as compared with standard radiotherapy in patients with locally advanced head-and-neck cancer. The pooled HR was 0.92 (95% CI 0.86–0.97; 0.003), with a 3.4% absolute survival benefit at 5 years. The benefit was significantly higher with hyperfractionated radiotherapy (8% at 5 years) than with accelerated radiotherapy (2% with accelerated fractionation without total dose reduction and 1.7% with total dose reduction at 5 years, p=0.02).

Secondary endpoints

There was a benefit on loco-regional control in favor of altered fractionation versus conventional radiotherapy (6.4% at 5 years; p<0.0001), the investigational schedule was particularly efficient in reducing local failure, whereas the benefit on nodal control was less pronounced (see table below).\textsuperscript{13,14}

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|}
\hline
 & Hyperfractionation & Accelerated fractionation & Accelerated fractionation & Overall & \hline
 & without total dose reduction & without total dose reduction & & & \\
\hline
Locorregional control & 0.76 (0.66–0.87) & 0.79 (0.72–0.87) & 0.90 (0.80–1.02) & 0.45 & 0.92 (0.87–0.98) & <0.0001 \\
\hline
Local control & 0.75 (0.63–0.88) & 0.74 (0.67–0.83) & 0.81 (0.71–0.91) & 0.50 & 0.77 (0.71–0.83) & <0.0001 \\
\hline
Regional control & 0.83 (0.66–1.03) & 0.90 (0.77–1.04) & 0.87 (0.72–1.06) & 0.83 & 0.87 (0.72–0.97) & 0.02 \\
\hline
Metastatic control & 1.08 (0.76–1.53) & 0.83 (0.74–1.19) & 0.95 (0.68–1.32) & 0.77 & 0.91 (0.63–1.35) & 0.75 \\
\hline
\end{tabular}
\caption{Hazard ratio (95% CI) of altered fractionated radiotherapy versus conventional radiotherapy on overall population and by type of radiotherapy for loco-regional, local, regional, and metastatic control (n=7073)}
\end{table}

Variation of treatment effect with age

The effect of altered fractionated radiotherapy on overall survival decreased with increased age (see Table below). The proportion of deaths not due to head & neck cancer increased with age, from 18% at age 50 years to 41% at age ≥ 71 years in MARCH, and from 15% to 39% in the Meta-Analysis of Chemotherapy in Head and Neck Cancer (MACH-NC).

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|}
\hline
Age (y) & No. of patients & Hazard ratio (95% CI) & Test for trend (p) \\
\hline
≥50 & 131 & 6.78 (0.65–0.94) & 0.007 \\
51–60 & 2300 & 6.93 (0.83–1.09) \\
61–70 & 2346 & 6.92 (0.81–1.06) \\
≥71 & 1085 & 1.08 (0.89–1.30) \\
\hline
\end{tabular}
\caption{Altered fractionated RT vs. standard RT}
\end{table}

Lastly, preliminary analyses indicate that event-free survival and locoregional control can be used as a surrogate for overall survival to evaluate the treatment effect in randomized trials of radiotherapy of patients with head and neck cancer.\textsuperscript{15}
Therefore, the most effective method to establish whether there is any reliable evidence of a survival benefit attributable to a modified schedule of radiotherapy fractionation is to perform an IPD based meta-analysis (or a quantitative overview) that combines the results from similar and unconfounded randomized clinical trials\textsuperscript{16}. It has the advantage of taking into account all available information and of providing evidence based on a large number of patients.

A collaborative overview has therefore been initiated by the Institut Gustave-Roussy. This project will concern the two radiotherapy modalities (hyperfractionated or accelerated schedules) of altered fractionation.

The methodology will be similar to that used in the Early Breast Cancer Overview\textsuperscript{8}, the Small Cell Lung Cancer Meta-analysis\textsuperscript{9}, the Prophylactic Cranial Irradiation Overview\textsuperscript{11}, the MACH-NC\textsuperscript{13}, and the Non Small Cell Lung Cancer Overview\textsuperscript{10}. The latter study has been recently updated and collected data from more than 100 trials on chemotherapy in lung cancer\textsuperscript{17-19}, in particular 43 trials on radio-chemotherapy combinations in locally advanced disease\textsuperscript{18,19}. It concluded that both sequential and concomitant chemo-radiotherapy improves survival compared to radiotherapy alone. Direct comparison of these two radio-chemotherapy modalities was in favor of the concomitant treatment\textsuperscript{19}. We will constitute a similar collaborative group comprising all investigators involved in randomized trials on modified radiotherapy fractionation in lung cancer and the meta-analyses will be conducted and reported on its behalf.

Both published and unpublished randomized trial will be included in the meta-analysis since there is evidence that both investigators and journal editors are more likely to publish trials with positive results\textsuperscript{20}. Basic survival and prognostic information will be collected for all patients randomized in each study because this allows a more reliable and flexible approach, a more sensitive analysis and avoids the potential bias of post-randomization exclusion\textsuperscript{21,22}. Updated follow-up information will be sought which will enable us to report on long-term survival and treatment effects.

The main purpose of this meta-analysis is to evaluate the role of modified fractionation on the survival of patients with lung cancer (separately in SCLC and NSCLC). In order to answer this question, we intend to combine the data of trials comparing conventional radiotherapy to modified radiotherapy fractionation (Appendix A).

This IPD meta-analysis aims to provide the most comprehensive and reliable summary of the effect of modified fractionated radiotherapy in lung cancer. It is also hoped that the meta-analysis will stimulate future international collaboration and will lead to a valuable exchange of ideas and will ultimately be of benefit to the patients.
2. OBJECTIVES

Assessment of the role of altered fractionated radiotherapy in lung cancer, separately in NSCLC and SCLC, by studying the following questions:

MAIN QUESTION

Role of altered fractionated radiotherapy on the survival of patients with lung cancer by comparing:

- Conventional radiotherapy
- Hyperfractionated and/or accelerated radiotherapy

SECONDARY QUESTIONS

- Effect of altered fractionated radiotherapy on loco-regional control, distant control, event-free survival, lung cancer mortality and non-lung cancer mortality
- 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 (indirect comparison).
- Investigation of the interaction between the treatment effect and the prognostic factors and patient characteristics (subgroup analyses).
- Study of the treatment effect on loco-regional control, and event-free survival as surrogate endpoints of overall survival.

3. TRIAL SELECTION CRITERIA

3.1 INCLUSION CRITERIA

All trials must satisfy the following criteria:

Trials must

- Be randomized in a way that precludes prior knowledge of treatment assignment.
- Be unconfounded, i.e. trials should differ only on radiotherapy modalities.
- Have started randomization on or after January 1st 1970.
- Have completed accrual before December 31st, 2005.
- If chemotherapy is associated to radiotherapy, the same chemotherapy should be administered in both arms.
- Include patients with lung cancer (SCLC or NSCLC).
- Not include patients with metastatic disease.
Patients should

- Undergo a first line therapy.
- Not have received prior radiotherapy.
- Be suitable for radical thoracic radiotherapy.
- Be randomized to receive conventional radiotherapy or hyperfractionated and / or accelerated radiotherapy.
- Not be treated by orthovoltage radiotherapy.
- Receive a planned radiotherapy dose of 30 Gy or more.
- Not receive prior chemotherapy, except induction chemotherapy administered before randomization.
- Have unresected disease.
- Undergo a potentially curative loco-regional treatment.

3.2 EXCLUSION CRITERIA:

- Randomized trials without a conventional radiotherapy arm:
  Conventional radiotherapy is defined as a radiotherapy with one 1.8-2 Gy fraction per day, 5 days a week with a minimum dose of 40 Gy for SCLC and 60 Gy for NSCLC.
- Randomized trials comparing hypofractionated (dose per fraction above 2.5 Gy) radiotherapy versus conventional radiotherapy.
- Associated loco-regional chemotherapy.

4. TRIAL SEARCH

Data from all published and unpublished randomized trials investigating the above mentioned comparisons in lung cancer patients will be sought using electronic database searching (Medline, Cancerlit, Embase), hand searching (review articles, meeting proceedings) and by contacting experts in the field. Trials registries (PDQ, ClinProt...) will be also consulted. All investigators who take part in the meta-analysis will be asked to help to identify more trials. The detail of the initial search and its results are given in appendix A.

5. DESCRIPTION OF TRIALS INCLUDED

Pages 16 and 17 give the references of the eligible trials, and page 18 the references of the excluded trials. Appendices B & C describe the material available to date for the meta-analysis. In total, eleven trials (12 therapeutic comparisons as one trial with a 2x2 design was divided in two parts) including more than 2,000 patients studied the role of altered fractionations in patients with lung cancer; The 11 trials (approximately 2,400 patients) completed their accrual before December 31st, 2005, and one will start in 2008. There were 2 trials (678 patients) and 9 trials (1782 patients) in NSCLC.
6. CRITERIA OF EVALUATION

6.1 ENDPOINTS

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 (for the surrogate validation project), lung cancer mortality, non-lung cancer mortality will be also considered. The two latter endpoints will be analyzed if both disease failure and cause of death are available. Observance, acute and late toxicity will be also studied, if possible.

6.2 PROGNOSTIC FACTORS

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

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

7. DATA COLLECTION AND QUALITY CONTROL

For each eligible trial, the main investigator will be asked to provide the following basic data for survival and prognostic factors for all randomized patients.

- Date of birth or age.
- Sex.
- Performance status
- Histology.
- Stage TNM for NSCLC (if not available stage; information on classification used), for SCLC, limited disease yes/no, node extension yes/no.
- Allocated treatment.
- Date of randomization.
- Date chemotherapy start
- Number of chemotherapy cycles received
- Radiotherapy started / not started
- Date first day thoracic radiotherapy
- Date last day thoracic radiotherapy
- Total administered dose of radiotherapy
- Total number of fractions of radiotherapy
- Number of daily fraction, if multiple daily fraction, time between fractions
- Prophylactic Cranial Irradiation (PCI): yes/ no
- Date of last follow-up.
- Survival status.
o Cause of death.
o Date of loco-regional failure, distant failure, and second primary.
o Acute toxicity (neutropenia, thrombocytopenia, anemia, cardiac, esophageal
and pulmonary)
+ Specification of toxicity grading system used
o Late toxicity (esophageal, cardiac and pulmonary) +
specification of toxicity grading system used
o Whether excluded from trial analysis.
o Reason for exclusion (if applicable).

Appendix D 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.

8. STATISTICAL ANALYSIS PLAN

Trial characteristics will be reported in tabular form, information will include patient
numbers, period of recruitment, population description, treatment details and median follow-
up. Median follow-up will be computed using the reverse Kaplan-Meier method23.

Trials in SCLC (n=2, 678 patients) and NSCLC (n=9, 1782 patients) will be analyzed
separately. The ultimate aim will be to obtain and analyze data from all randomized patients
included in all relevant randomized trials on an intention-to-treat basis. With around 1,900
patients (or 1,500 deaths) it would be possible to detect, with a power of 90%, an absolute
improvement in survival from 15 % to 20 % at 3-years (two-sided logrank test, type I error =
5%).

The main analysis will be performed on the endpoint of overall survival. Additional analyses
will be performed on the endpoints of loco-regional failure rate, distant failure rate, lung
cancer mortality and non-lung cancer mortality, if sufficient data are available. Proportion of
patients who have received at least one radiotherapy fraction (radiotherapy started / not
started), the percentage of the planned total dose of radiotherapy, acute and late toxicity rates
will be also studied.

All analyses will include all randomized patients and will be carried out on an intention-to-
treat basis that is patients will be analyzed 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 model24. Thus, the time 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 altered fractionated radiotherapy compared with those
who were allocated conventional radiotherapy. For comparing toxicity rates, overall pooled
odds ratio stratified by trials will be calculated by a fixed-effect model.
Lung cancer and non-lung cancer mortality using method similar to that used in the Lung Adjuvant Cisplatin Evaluation (LACE)\textsuperscript{25} will be studied. An unbiased, although potentially diluted, logrank analysis of lung cancer mortality was obtained indirectly by subtracting the logrank statistic for non-lung cancer mortality from the logrank statistic for mortality from all causes (i.e., the two observed values, the two expected values, and the two variances are each subtracted from each other)\textsuperscript{26}. Non-lung cancer mortality was defined as death of known cause without recurrence and not considered as a lung cancer death. Lung cancer mortality included death of any cause with prior recurrence, death from lung cancer and death from unknown cause.

The $\chi^2$ heterogeneity tests\textsuperscript{10,13} will be used to test for gross statistical heterogeneity, the $I^2$ statistic\textsuperscript{27} will be used as a measure of consistency among trials. Stratified survival curves will be estimated for control and experimental groups using annual death rates and hazard ratios\textsuperscript{28}. They will be used to calculate absolute benefit at 3-years, and 5-years with their 95\% confidence intervals\textsuperscript{28}. All p-values will be two-sided.

ANALYSES BY TRIAL LEVEL CHARACTERISTICS (NSCLC trials only)

The effect of altered fractionated radiotherapy may vary across trials in the meta-analysis because the treatments might be applied in different ways. To explore this further, providing that there are sufficient data available, analyses are planned in which trials, or arms within trials, will be grouped according to the type of altered fractionated radiotherapy to determine whether there is any difference in treatment effect among these groups.

Among the 9 trials, four groups of trials (Appendix B) have been identified according to the type of radiotherapy. One small trial (Sun) with atypical design will be excluded of this analysis. The analysis will take into account these groups of trials and study the interaction between the observed effect of the treatment on survival and the type of radiotherapy. The hazard ratio of the three groups of trials will be compared by a chi-square test for heterogeneity. The following exploratory analyses will be performed to take into account the multidimensional aspect of the difference between new fractionation schedules:

A fixed effects survival model will be fitted using all the NSCLC trials, including indicator variables for each trial, and an overall hazard ratio between conventional and alternative radiotherapy will be calculated. Heterogeneity of treatment effects will be assessed by investigating the treatment by trial interaction.

Additionally, a more detailed model will be fitted which also includes indicator variables to represent the different aspects of the radiotherapy (acceleration, total dose, hyperfractionation). Hazard ratios will be calculated from this model to assess the impact of the various methods of altering conventional radiotherapy. Any identifiability problems caused by the small number of trials will be fully explored when fitting the model.
Example of setting up indicator variables. Using this, all six variables would be zero for conventional radiotherapy.

<table>
<thead>
<tr>
<th>Acceleration</th>
<th>Acc1</th>
<th>Acc2</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-13%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>14-49%</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>50%+</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total dose</th>
<th>Tot1</th>
<th>Tot2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identical</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lower</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Higher</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hyperfractionation</th>
<th>Hyp1</th>
<th>Hyp2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1.25-1.75Gy</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>&lt;1.25Gy</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Results will be also compared, between trials with the use of combined chemotherapy (n=3, 472 patients) and those without (n=6, 1310 patients), and according to the dose of radiotherapy in the control arm (less than 60 Gy, 60-69 Gy and 70 + Gy).

These analyses will be performed for the main endpoint, overall survival and for the secondary endpoints.

**ANALYSES BY PATIENT LEVEL CHARACTERISTICS**

Provided that there will be 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 category, categories will be combined. Chi-squared tests for interaction or trend will be used to test whether there is any evidence that a particular type of patients benefit more or less from altered fractionated radiotherapy.

The subgroups to be analyzed will be as follows:

- **Age** (<60, 60-69, 70+)
- **Sex** (Male, Female)
- **Performance Status** *(Good, Mild, Poor)*
- **Histology** (Adenocarcinoma, Squamous, Other) in NSCLC
- **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</td>
<td>100, 90</td>
</tr>
<tr>
<td>Mild</td>
<td>1</td>
<td>80, 70</td>
</tr>
<tr>
<td>Poor</td>
<td>2, 3, 4</td>
<td>60 – 10</td>
</tr>
</tbody>
</table>

**Stage for Non Small Cell Lung Cancer**

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

Stage for Small Cell Lung Cancer: limited versus extensive and if limited, mediastinal and/ or supraclavicular lymph nodes involved or not.

**SENSITIVITY ANALYSES**

Hazard ratios for overall survival will also be calculated excluding any trials that are clear outliers. One trial (n=106) is difficult to classify as the experimental arm used simultaneous boost (Sun et al), resulting in an arm with a moderate acceleration and a lower total dose. The impact of the exclusion of the Sun et al trial on the results will be studied.

**SURROGATE ENDPOINT VALIDATION**

The study of the usefulness of loco-regional failure rate, and event-free survival as surrogate endpoints of overall survival will imply to analyze the data at the individual and trial level. At the individual level, the rank correlation coefficient ρ between the surrogate endpoint (locoregional failure rate, or event-free survival) and overall survival will be estimated from the bivariate distribution of these endpoints. At the trial level, the correlation coefficient R between treatment effects (estimated by log hazard ratios) on the surrogate endpoint and overall survival will be estimated from a linear regression\textsuperscript{15,29-31}.

**9. WORKING PARTIES IN THE META-ANALYSIS PROJECT**

In order to complete the meta-analysis successfully, three groups with specific functions have been created: 1) the Secretariat, 2) the Advisory Board and 3) the MAR-LC Trialists' Collaborative Group (MAR-LC-CG).
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 patient data. The Secretariat is also in charge of checking, processing and analyzing the data. Finally, the Secretariat is responsible for preparing reports and publications.

The Advisory Board is a small group of international experts that will support the Secretariat with medical and statistical expertise.

The Trialists' Collaborative Group (MAR-LC-CG) will include the investigators responsible for the trials included in the meta-analyses. The members of the Secretariat and the Advisory Board will also be included in this group. They will be responsible for providing the Secretariat with data on patients and for discussing the reports prepared by the Secretariat.

10. PRACTICAL CONSIDERATIONS

The Secretariat is located in the Biostatistics Department of the Institut Gustave Roussy. This Department will be responsible for liaising with trialists, running the main database. All data, updates and corrections should be sent there. The Secretariat will collect and check the data checking and perform the analysis.

All supplied data will remain confidential and will be used exclusively for these meta-analyses.

11. PUBLICATION POLICY

The Secretariat will prepare the manuscript and will submit it for revision to all members of the Group. Any publication arising from this project will be made in the name of the MAR-LC Collaborative Group and will include a list of all collaborators.

Acknowledgments

We are grateful to Audrey Mauguen and Denise Avenell for assistance in preparing the protocol.
12. REFERENCES

7. Horiot JC, Bontemps P, van den Bogaert W, Le Fur R, van den Weijngaert D, Bolla M, Bernier J, Lusinchi A, Stuschke M, Lopez-Torreilla J, Begg AC, Pierart M, Collette L. Accelerated fractionation (AF) compared to conventional fractionation (CF) improves loco-regional control in the radiotherapy of advanced head and neck cancers: results of the EORTC 22851 randomized trial. Radiother Oncol. 1997 ;44:111-121.


21 Stewart LA, Parmar MKB. Meta-analysis of the literature or of individual data: is there a difference? Lancet 1993;341:418-422.


REFERENCES OF RANDOMIZED TRIALS ELIGIBLE FOR THE META-ANALYSIS

**ECOG/RTOG/SWOG**

**NCCTG sclc**

**RTOG 88-08, ECOG 4588**


**Australia, Ball et al**

**Fu et al**

**CHART**


**NCCTG 90-24-51**

**Sun et al**

**NCCTG Schild et al**
**ECOG 2597**


**Zajusz et al**


**REFERENCES OF ONGOING RANDOMIZED TRIALS**

1. Christie Hospital NHS Foundation Trust; Feb 2007 not yet recruiting

Cisplatin, Etoposide, and Two Different Schedules of Radiation Therapy in Treating Patients With Limited Stage Small Cell Lung Cancer


Consulted on 29 November 29, 2007.
REFERENCES OF EXCLUDED RANDOMIZED TRIALS

The reason for exclusion were:

Absence of arm with conventional radiotherapy (RTOG 83-11)


Control arm with hypofractionated radiotherapy


Patients received neoadjuvant and concomitant chemotherapy in both arms, but the proportions per arm were different in particular for neoadjuvant chemotherapy


Trial with hypofractionated radiotherapy (2.5 Gy) in both arm and comparing two doses and durations.


Trials comparing different doses and durations of conventional or hypofractionated (3 or 4 Gy) radiotherapy (RTOG 7301 and 7302)


Randomized phase I


Intra-arterial associated chemotherapy

## Appendix A: trial search strategy

<table>
<thead>
<tr>
<th>Base</th>
<th>Search strategy</th>
<th>Limites</th>
<th>References</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cochrane Central Register of Controlled Trials</td>
<td>There are 5 results out of 479462 records for: &quot;lung cancer radiotherapy and randomized in Publication Type not PubMed, from 1980 to 2007 in The Cochrane Central Register of Controlled Trials&quot;</td>
<td>2007-1980</td>
<td>1</td>
<td>11-janv.-07</td>
</tr>
<tr>
<td>ASTRO Annual Meeting</td>
<td><a href="http://www.redjournal.org/content/astro_abstracts">Link</a></td>
<td>2006-2005</td>
<td>8</td>
<td>12-Jan-07</td>
</tr>
<tr>
<td>ASCO's comprehensive database of abstracts</td>
<td><a href="http://www.asco.org">Link</a> search for lung in Title and randomized in Title and radiotherapy in Title within selected meetings returned 14 items.</td>
<td>2006-1995</td>
<td>14</td>
<td>12-Jan-07</td>
</tr>
</tbody>
</table>
## Appendix B: Description of the trials
comparing conventional radiotherapy with radiotherapy with altered fractionation

See references and page 16 and 17.

### TABLE A-2 : Randomized trials of hyperfractionated versus conventional radiotherapy in lung cancer

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of patients randomized</th>
<th>Inclusion period</th>
<th>Histology</th>
<th>RT dose (Gray)/ fraction/ duration (weeks) compared*</th>
<th>CT dose**</th>
<th>Patients characteristics***</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turrisi 1989</td>
<td>417</td>
<td>1989-1992</td>
<td>SCLC</td>
<td>Standard: 45 Gy / 25 fr / 5 w Experimental: 45 Gy / 30 fr / 3 w bid</td>
<td>Cisplatin 60 mg/m² d₁, Etoposid 120 mg/m² d₁,₂,₃ 4 cycles (3 w)</td>
<td>PS 0-2</td>
</tr>
<tr>
<td>Schild 1990 NCCTG</td>
<td>261</td>
<td>1990-1996</td>
<td>SCLC</td>
<td>Standard: 50.4 Gy / 28 fr / 5.5 w Experimental: 48 Gy / 32 fr / 5.5 w sc bid</td>
<td>Cisplatin 30 mg/m² d₁,₂,₃ Etoposide 130 mg/m² d₁,₂,₃ 6 cycles (4 w)</td>
<td>PS 0-2</td>
</tr>
<tr>
<td>Sause RTOG 88-08 ECOG 4588</td>
<td>306§</td>
<td>1989-1992</td>
<td>NSCLC</td>
<td>Standard: 60 Gy / 30 fr / 6 w Experimental: 69.6 Gy / 58 fr / 6 w bid</td>
<td>None</td>
<td>KPS &gt;=70 II-III</td>
</tr>
<tr>
<td>Ball 1989 A</td>
<td>101</td>
<td>1989-1995</td>
<td>NSCLC</td>
<td>Standard: 60 Gy / 30 fr / 6 w Experimental: 60 Gy / 30 fr / 3 w bid</td>
<td>None</td>
<td>PS 0-1 Stage I-III</td>
</tr>
<tr>
<td>Ball 1989 B</td>
<td>107</td>
<td>1989-1995</td>
<td>NSCLC</td>
<td>Standard: 60 Gy / 30 fr / 6 w Experimental: 60 Gy / 30 fr / 3 w bid</td>
<td>Carboplatin 70 mg/m² d₁,₅ + Carboplatin 70 mg/m² d₂₉-₃₃ in standard arm</td>
<td>PS 0-1 Stage I-III</td>
</tr>
<tr>
<td>Fu 1990</td>
<td>109</td>
<td>1990-1991</td>
<td>NSCLC</td>
<td>Standard: 63.9 Gy / 35 fr / 7 w Experimental: 69.6 Gy / 60 fr / 6 w bid</td>
<td>None</td>
<td>Stage I-III</td>
</tr>
<tr>
<td>CHART</td>
<td>563</td>
<td>1990-1995</td>
<td>NSCLC</td>
<td>Standard: 60 Gy / 30 fr / 6 w Experimental: 54 Gy / 36 fr / 1.5 tid</td>
<td>None</td>
<td>PS 0-1 Stage I-III</td>
</tr>
<tr>
<td>Bonner 1992 NCCTG</td>
<td>67§§</td>
<td>1992-1993</td>
<td>NSCLC</td>
<td>Standard: 60 Gy / 30 fr / 6 w Experimental: 60 Gy / 40 fr / 6 w sc bid</td>
<td>None</td>
<td>PS 0-2 Stage III</td>
</tr>
<tr>
<td>Sun 1994</td>
<td>106§§</td>
<td>1994-1998</td>
<td>NSCLC</td>
<td>Standard: 70.8 Gy / 38 fr / 7.5 w Experimental: 65 Gy / 26 fr / 5.5 w</td>
<td>None</td>
<td>KPS &gt;=60 Stage IB-III</td>
</tr>
<tr>
<td>Reference</td>
<td>Number of patients randomized</td>
<td>Inclusion period</td>
<td>Histology</td>
<td>RT dose (Gray)/ fraction/ duration (weeks) compared*</td>
<td>CT dose**</td>
<td>Patients characteristics***</td>
</tr>
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<td>-------------------------------</td>
<td>------------------</td>
<td>-----------</td>
<td>-----------------------------------------------------</td>
<td>-----------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>Schild 1994 NCCTG</td>
<td>246</td>
<td>1994-1999</td>
<td>NSCLC</td>
<td>Standard: 60 Gy / 30 fr / 6 w Experimental: 60 Gy / 40 fr / 6 w sc bid</td>
<td>Cisplatin 30 mg/m² d1-3,28-30 Etoposide 100 mg/m² d1-3,28-30</td>
<td>PS 0-1 Stage III</td>
</tr>
<tr>
<td>Belani ECOG 2597</td>
<td>119</td>
<td>1998-2001</td>
<td>NSCLC</td>
<td>Standard: 64 Gy / 32 fr / 6.5 w Experimental: 57.6 Gy / 36 fr / 2.5 w tid</td>
<td>Carboplatin AUC 6 d1 Paclitaxel 225 mg/m² d1 2 cycles† (3 w)</td>
<td>PS 0-1 Stage III</td>
</tr>
<tr>
<td>Zajusz 2001</td>
<td>58</td>
<td>2001-2006</td>
<td>NSCLC</td>
<td>Standard: 72 Gy / 40 fr / 8 w Experimental: 72 Gy / 40 fr / 5.5 w</td>
<td>None</td>
<td>NA</td>
</tr>
</tbody>
</table>

* RT: Radiotherapy; **CT: chemotherapy; if not specified, the chemotherapy is concomitant to the radiotherapy *** (K) PS: (Karnofsky) Performance Status; $ + 32 patients ineligible, but proportion in the 2 arms unknown, 3-arm trial; $$ + 11 patients ineligible, but proportion in the 2 arms unknown, 3-arm trial; $$§§ whom 9 patients with incomplete data (lost to follow-up); £ 2 series of 8 days with a break of 2.5 weeks; ££ 2 series of 2 weeks with a break of 2 weeks; † 3 cycles induction, 2 cycles concomitant and 1 after RT; Etoposide dose was reduced to 100 mg/m² for cycles 4 to 6; ‡ Induction chemotherapy; ;

**Other abbreviations**
- bid = CT given twice a day; fr = fraction; sc = Split course; tid = CT given three times a day; w = week
- NSCLC = Non-Small Cell Lung Cancer; SCLC = Small Cell Lung Cancer
- CHART = Continuous Hyperfractionated Accelerated Radiation Therapy; ECOG = Eastern Cooperative Oncology Group; NCCTG = North Central Cancer Treatment Group; RTOG = Radiation Therapy Oncology Group
TABLE A-2: Randomized trials of hyperfractionated versus conventional radiotherapy in lung cancer: **Ongoing trials**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Accrual period</th>
<th>Planned sample size</th>
<th>Inclusion period</th>
<th>Histology</th>
<th>RT dose (Gray)/ fraction/ duration (weeks) compared</th>
<th>CT dose</th>
<th>Characteristics patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Christie Hospital</td>
<td>Not yet accruing 532</td>
<td>January 2008-</td>
<td>SCLC</td>
<td>Standard: 33 fr / 6.5 w Experimental: 30 fr / 3w Doses non specified</td>
<td>Cisplatin d1-3 Etoposide d1-3 Concurrent CT - 6 courses</td>
<td>PS 0-1 Limited stage</td>
<td></td>
</tr>
</tbody>
</table>

See previous table for abbreviations
Appendix C: Classification of trials
comparing conventional radiotherapy with altered fractionation radiotherapy

1) Definition

A suggestion was made by JC Horiot to provide more accurate definition of acceleration and hyperfractionation. This was done according to the publication of Horiot et al Radiother Oncol, 1997;44:111.

Conventional radiotherapy for definitive radiotherapy in lung cancer = 60 Gy (mainly in US) to 70 Gy (mainly in Europe) for NSCLC and more than 40 Gy for SCLC, 1.8-2 Gy / fraction, 5 fractions per week during 6 to 7 weeks for NSCLC and 5 to 5.5 weeks for SCLC.

There are two main possibilities for increasing the dose intensity of radiotherapy, with the goal of improving the tumor control, through modifications of the fractionation:

a) Accelerated radiotherapy = a significant reduction of the overall treatment time, compared to conventional radiotherapy

b) Hyperfractionation (pure) = a higher number of fraction with a smaller dose per fraction, in the same overall time than conventional radiotherapy.

Acceleration is often combined with hyperfractionation

2) Description of the trials according to total dose, dose/fraction and degree of acceleration

The Ball et al. trial had a 2x2 factorial design: conventional versus altered fractionated radiotherapy; concomitant chemotherapy versus no chemotherapy. The two arms with chemotherapy were considered as a distinct “trial” from the group with the two arms without chemotherapy.

a) Total dose

· In the reference arm, the total dose was 60 Gy in 6 trials, 64-65 in two and 71-72 in two trials for NSCLC, and 45 to 50 Gy in the two SCLC trials (11 trials, table B-1). In conclusion, most of the trials used conventional radiotherapy as the reference arm, and it was not proposed to exclude trials according to the total radiation dose.

· In the experimental arm, the distribution of the trials according to the total dose showed 3 categories of trials (table B-2):
  1) Total dose lower (5 to 10%) than the reference arm = 3 trials, all but one were very accelerated,
  2) Total dose identical (+/- 5%) to the reference arm = 6 trials,
  3) Total dose higher (5 to 15%) than the reference arm = 2 trials that were hyperfractionated.
b) Dose / fraction in the experimental arm

The distribution of the trials according to the dose per fraction is presented in table B-3, showing that the dose per fraction ranged from 0.7 Gy to 2 Gy. Trials with doses per fraction of 1.8 Gy to 2 Gy were considered as normofractionated (3 trials), as opposed to those with lower doses that were hyperfractionated (9 trials). Two of these trials used very small dose per fraction (< 1.25 Gy) and five trials, a dose per fraction of 1.5. One trial combined fraction with different doses: 1.5 + 1.8 +1.5 (ECOG 22597), and another used 1.8 Gy and a concomitant boost of 0.7 Gy (Sun).

c) Degree of acceleration in the experimental arm

The distribution of the trials according to the degree of acceleration is presented in table B-4. Trials were classified as a function of the percentage of acceleration of the experimental arm, as compared to the control arm. Three categories of trials were found:
1) No acceleration (less than 15%) compared to the control arm (5 trials)
2) Moderate acceleration (3 trials)
3) Strong acceleration with a shortening of the overall time of 50% or more, as compared to the control arm. (4 trials).

3) Classification of the trials according to the 3 parameters: dose/fraction, degree of acceleration and total dose (NSCLC trials only)

To classify this heterogeneous group of trials, they are grouped in a single table according to the 3 parameters: the dose / fraction, the total dose and the overall time. This distribution is presented in table B-5.

Based on this table, the trials are classified according to five groups:

- The trials with very accelerated RT using identical or lower dose = 4 trials (Ball A, Ball B*, CHART, ECOG 2597; 890 patients),

- The trials with moderately accelerated RT using identical or higher total dose = 2 trials (Fu, Zajusz; 167 patients),

- The trials with no acceleration of RT (hyperfractionated RT with split course), and using identical total dose = 2 trials (Bonner, Schild 1994*; 313 patients),

- The fourth group includes one trial (n=106), difficult to classify: a trial in which the experimental arm used simultaneous boost (Sun), resulting in an arm with a moderate acceleration and a lower total dose.

* trial with chemotherapy
### TABLE B1: TOTAL DOSE IN THE STANDARD ARM:

<table>
<thead>
<tr>
<th>50 Gy</th>
<th>60 Gy</th>
<th>65 Gy</th>
<th>70 Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Turrisi SCLC</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Schild 1990 SCLC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60 Gy</td>
<td>RTOG 88-08</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sun</td>
<td></td>
<td></td>
</tr>
<tr>
<td>65 Gy</td>
<td>Ball A</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Zajusz</td>
<td></td>
<td></td>
</tr>
<tr>
<td>70 Gy</td>
<td>Ball B</td>
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<tr>
<td></td>
<td>CHART</td>
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<tr>
<td></td>
<td>Bonner</td>
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<tr>
<td></td>
<td>Schild 1994</td>
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<tr>
<td></td>
<td>Fu</td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ECOG 2597</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
TABLE B2: TOTAL DOSE IN THE EXPERIMENTAL ARM (% / reference arm)

<table>
<thead>
<tr>
<th></th>
<th>-10%</th>
<th>-5%</th>
<th>0</th>
<th>+10%</th>
<th>+15%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schild 1990 SCLC</td>
<td>Turrisi SCLC</td>
<td>Ball A</td>
<td>RTOG 88-08</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHART</td>
<td>Turrisi SCLC</td>
<td>Ball B</td>
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<td>ECOG 2597</td>
<td>Ball A</td>
<td>Bonner</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sun</td>
<td>Ball B</td>
<td>Schild 1994</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Zajusz</td>
<td></td>
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<td></td>
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</tbody>
</table>
### TABLE B3: DOSE per FRACTION IN THE EXPERIMENTAL ARM (Gy)

<table>
<thead>
<tr>
<th>1.2</th>
<th>1.3</th>
<th>1.4</th>
<th>1.5</th>
<th>1.6</th>
<th>1.7</th>
<th>1.8</th>
<th>1.9</th>
<th>2</th>
<th>2.5Gy</th>
</tr>
</thead>
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<td>Turrisi SCLC</td>
<td>Zajusz</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Fu</td>
<td>Schild 1990 SCLC</td>
<td>ECOG 2597*</td>
<td>Ball A</td>
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<tr>
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<td>Ball B</td>
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<tr>
<td></td>
<td>Bonner</td>
<td>Sun**</td>
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<tr>
<td></td>
<td>Schild 1994</td>
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</tbody>
</table>

* three fractions a day: 1.5+1.8.1.8  
** 1.8 Gy + simultaneous boost of 0.7 Gy on a reduced volume
**TABLE B4: DEGREE OF ACCELERATION AS A FUNCTION OF REFERENCE ARM**

<table>
<thead>
<tr>
<th></th>
<th>0%</th>
<th>10%</th>
<th>20%</th>
<th>30%</th>
<th>40%</th>
<th>50%</th>
<th>60%</th>
<th>70%</th>
<th>80%</th>
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<tbody>
<tr>
<td>Schild 1990 SCLC</td>
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<td>Schild 1994</td>
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<td>Ball A</td>
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<tr>
<td>ECOG 2597</td>
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<td></td>
</tr>
</tbody>
</table>
**TABLE B5:**
TOTAL DOSE IN THE EXPERIMENTAL ARM

<table>
<thead>
<tr>
<th>LOWER</th>
<th>IDENTICAL (+/- 5%)</th>
<th>HIGHER</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-13%</td>
<td>Schild 1990</td>
<td>RTOG 88-08</td>
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<td>SCLC</td>
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</tr>
<tr>
<td></td>
<td>Bonner</td>
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</tr>
<tr>
<td></td>
<td>Schild 1994</td>
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</tr>
<tr>
<td>14-49%</td>
<td>Sun</td>
<td>Turrisi</td>
</tr>
<tr>
<td></td>
<td>Zajusz Fu</td>
<td>SCLC</td>
</tr>
<tr>
<td>≥ 50%</td>
<td>CHART ECOG 2597</td>
<td>Ball A</td>
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<tr>
<td></td>
<td></td>
<td>Ball B</td>
</tr>
<tr>
<td></td>
<td>Hyperfractionated</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>&lt; 1.25 Gy</td>
<td>&lt; 1.25 Gy</td>
</tr>
<tr>
<td></td>
<td>1.25-1.75 Gy</td>
<td>1.25-1.75 Gy</td>
</tr>
<tr>
<td></td>
<td>1.8-2 Gy</td>
<td>1.8-2 Gy</td>
</tr>
</tbody>
</table>

DOSE / FRACTION IN THE EXPERIMENTAL ARM
Appendix D: 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.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Format/Coding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Identifier</td>
<td>Type character <em>(Preferably not name)</em> - Width 15</td>
</tr>
<tr>
<td>Date of Birth</td>
<td>Type date - Width 8 or 6 Code date in dd/mm/yyyy (recommended) or dd/mm/yy format</td>
</tr>
<tr>
<td>Or Age at randomization</td>
<td>Type numeric - Width 3 Code age in years, unknown = 999</td>
</tr>
<tr>
<td>Sex</td>
<td>Type numeric - Width 1 1=male, 2=female, 9=unknown</td>
</tr>
<tr>
<td>Tumour stage used</td>
<td>Type numeric - Width 1 1=limited vs. extensive (SCLC), 2=AJCC, 3=1986 ISS, 4=1997 UICC (for SCLC, limited versus extensive staging is recommended)</td>
</tr>
<tr>
<td>Limited vs. extensive disease (SCLC)</td>
<td>0=limited disease, 1=extensive disease</td>
</tr>
<tr>
<td>Nodes extension (SCLC)</td>
<td>Type numeric - Width 1 0=no, 1=yes, 9=unknown</td>
</tr>
<tr>
<td>Mediastinal nodes extension (SCLC)</td>
<td>Type numeric - Width 1 0=no, 1=yes, 9=unknown</td>
</tr>
<tr>
<td>Sus-clavicular nodes extension (SCLC)</td>
<td>Type numeric - Width 1 0=no, 1=yes, 9=unknown</td>
</tr>
</tbody>
</table>

If possible, provide complete TNM, if not possible provide stage

\[
T : 0 \text{ to 4, 5=X, 6=in situ, 9=unknown} \\
N : 0 \text{ to 3, 4=X, 9=unknown} \\
M : 0, 1, 2=X, 9=unknown
\]

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 |

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 |

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 IIIB, 5=stage IIIA, 6=stage IIIC, 7=stage IV, 9=unknown |

Histology

| Type numeric - Width 1 1=small cell, 2=adenocarcinoma, 3=squamous cell, 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 |
**Treatment Allocated**  
Type numeric - Width 1  
Code = 1= conventional radiotherapy, 2 = hyperfractionated and/or accelerated 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

**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 fraction of radiotherapy**  
Type numeric - Width 2

**Number of daily fraction**  
Type numeric – Width 1

**If multiple daily fraction, time between fractions (hours)**  
Type numeric – Width 1

**PCI**  
Type numeric – Width 1  
0= No, 1=yes, 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

**Survival Status**  
Type numeric – Width 1  
0=alive, 1=dead

**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 hemoglobin 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 esophageal 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 esophageal 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 pulmonary 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 character - Width 25 |