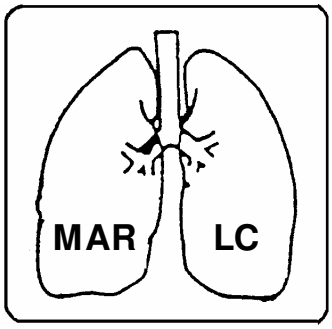

Meta-Analysis of Radiotherapy in Lung Cancer

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

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[8-13]. 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.

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).[13,14]

	Hyperfractionation	Accelerated fractionation without total dose reduction	Accelerated fractionation with total dose reduction	p*	Overall	p†
Locoregional control	0·76 (0·66–0·89)	0·79 (0·72–0·87)	0·90 (0·80–1·02)	0·15	0·82 (0·77–0·88)	<0·0001
Local control‡	0·75 (0·63–0·89)	0·74 (0·67–0·83)	0·83 (0·71–0·96)	0·50	0·77 (0·71–0·83)	<0·0001
Regional control‡	0·83 (0·66–1·03)	0·90 (0·77–1·04)	0·87 (0·72–1·06)	0·83	0·87 (0·79–0·97)	0·01
Metastatic control	1·09 (0·76–1·58)	0·93 (0·74–1·19)	0·95 (0·68–1·32)	0·77	0·97 (0·82–1·15)	0·75

*Comparison of the three hazard ratios for each type of radiotherapy. †Test of overall treatment effect. ‡Data from 14 trials; for three trials, only locoregional failure without specification if the failure was local, regional, or both, was available.

Table: Hazard ratio (95% CI) of altered fractionated radiotherapy versus conventional radiotherapy on overall population and by type of radiotherapy for locoregional, local, regional, and metastatic control (n=7073)

Variation of treatment effect with age

The effect of altered fractionated radiotherapy on overall survival decreased with increased age (see Table below)[14]. 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)

	Altered fractionated RT vs. standard RT		
Age (y)	No. of patients	Hazard ratio (95% CI)	Test for trend (*p*)
≤50	1311	0.78 (0.65–0.94)	0.007
51–60	2300	0.95 (0.83–1.09)	
61–70	2346	0.92 (0.81–1.06)	
≥71	1085	1.08 (0.89–1.30)	

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[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[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[8], the Small Cell Lung Cancer Meta-analysis[9], the Prophylactic Cranial Irradiation Overview[11], the MACH-NC[13], and the Non Small Cell Lung Cancer Overview[10]. The latter study has been recently updated and collected data from more than 100 trials on chemotherapy in lung cancer[17-19], in particular 43 trials on radio-chemotherapy combinations in locally advanced disease[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[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[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[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. **Appendixes 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.

- Cause of death.
- Date of loco-regional failure, distant failure, and second primary.
- Acute toxicity (neutropenia, thrombocytopenia, anemia, cardiac, esophageal and pulmonary)
  + Specification of toxicity grading system used
- Late toxicity (esophageal, cardiac and pulmonary) + specification of toxicity grading system used
- Whether excluded from trial analysis.
- 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 method[23].

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 model[24]. 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)[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)[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 χ^2 heterogeneity tests[10,13] will be used to test for gross statistical heterogeneity, the I^2 statistic[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[28]. They will be used to calculate absolute benefit at 3-years, and 5-years with their 95% confidence intervals[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.

Acceleration	Acc1	Acc2
0-13%	0	0
14-49%	1	0
50%+	0	1
Total dose	Tot1	Tot2
Identical	0	0
Lower	1	0
Higher	0	1
Hyperfractionation	Hyp1	Hyp2
Normal	0	0
1.25-1.75Gy	1	0
<1.25Gy	0	1

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

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

**Stage for Non Small Cell Lung Cancer

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

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 (loco-regional 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[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.

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

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

http://www.clinicaltrials.gov/ct2/show/NCT00433563?term=lung+cancer+AND+radiotherapy+AND+randomised&phase=2&rank=11

Consulted on 29 November 29, 2007.

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The reason for exclusion were:

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

Cox JD, Azarnia N, Byhardt RW, Shin KH, Emami B, Pajak TF. A Randomized Phase I/II Trial of Hyperfractionated Radiation Therapy With Total Doses of 60.0 Gy to 79.2 Gy: Possible Survival Benefit With 69.6 Gy in Favorable Patients With Radiation Therapy Oncology Group Stage III Non-Small-Cell Lung Carcinoma: Report of Radiation Therapy Oncology Group 83-11. J Clin Oncol 1990; 8:1543-1555.

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Kagami Y, Nishio M, Narimatsu N, Ogawa H, Sakurai T. Prospective randomized trials comparing hyperfractionated radiotherapy with conventional radiotherapy in stage III non-small cell lung cancer. Nippon Igaku Hoshasen Gakkai Zasshi 1992; 52:1452-1455.

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

Nalca Andrieu M, Eraslan A, Hicsonmez A, Guney Y. Concomitant boost technique versus conventional radiotherapy in locally advanced non-small cell lung cancer. Radiother Oncol 2006; 81(Suppl 1):S385. [Poster]

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

Coy P, Hodson I, Payne DG, Evans WK, Feld R, MacDonald AS, Osoba D, Pater JL. The effect of dose of thoracic irradiation on recurrence in patients with limited stage small cell lung cancer. Initial results of a Canadian Multicenter Randomized Trial. Int J Radiat Oncol Biol Phys 1988; 14:219-226.

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

Perez CA, Stanley K, Rubin P et a/. A prospective randomized study of various irradiation doses and fractionation schedules in the treatment of inoperable non-oat cell carcinoma of the lung: Preliminary report by the Radiation Therapy Oncology Group. Cancer 1980 45: 2744-27 5 3,

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Randomized phase I

Tsuchiya S, Ohe Y, Sugiura T, Fuwa N, Kitamoto Y, Mori K, Kobayashi H, Nakata K, Sawa T, Hirai K, Etoh T, Saka H, Saito A, Fukuda H, Ishizuka N, Saijo N. Randomized phase I study of standard-fractionated or accelerated-hyperfractionated radiotherapy with concurrent cisplatin and vindesine for unresectable non-small cell lung cancer: A report of Japan Clinical Oncology Group Study (JCOG 9601). Jpn J Clin Oncol 2001; 31:488-494.

Intra-arterial associated chemotherapy

Wang G, Song M, Xu H, Fang Y. prospective trial of combined hyperfractionated radiotherapy and bronchial arterial infusion of chemotherapy for locally advanced non-small cell lung cancer. Int J Radiat Oncol Biol Phys1996;34:309-313.

Appendix A: trial search strategy

Base	Search strategy	Limites	References	Date
PubMed MEDLINE	(("Lung Neoplasms/radiotherapy"[MeSH] AND Randomized Controlled Trial[ptyp]) OR ("Lung Neoplasms/radiotherapy"[MAJR] AND "Randomized Controlled Trials"[MeSH Terms]) OR ("Lung Neoplasms"[MAJR] AND (radiother*[Title] OR radiat*[Title]) AND random*[Title]) OR (lung[Title] AND (radiother*[Title] OR radiat*[Title]) AND random*[Title])) AND ("1980"[PDAT] : "3000"[PDAT])	2007-1980	575 Fichier joint pubmed-resultcancer poumon radither random 11 01 07.txt	11-janv.-07
EMBASE via Datastar Dialog	(LUNG-CANCER-RT.MJ. OR LUNG.TI. AND CANCER.TI. AND radiother$.TI.) AND (random$.TI. OR RANDOMIZED-CONTROLLED-TRIAL.DE.) AND CLINICAL-TRIAL#	2007-1980	125 Fichier joint	11-janv.-07
Cochrane Central Register of Controlled Trials	There are 5 results out of 479462 records for: "lung cancer radiotherapy and randomized in Publication Type not PubMed, from 1980 to 2007 in The Cochrane Central Register of Controlled Trials"	2007-1980	1 Fichier joint	11-janv.-07
ASTRO Annual Meeting	http://www.redjournal.org/content/astro_abstracts	2006-2005	8	12-Jan-07
ASCO's comprehensive database of abstracts http://www.asco.org/	search for lung in Title and randomized in Title and radiotherapy in Title within selected meetings returned 14 items.	2006-1995	14	12-Jan-07

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

Reference	Number of patients randomized	Inclusion period	Histology	RT dose (Gray)/ fraction/ duration (weeks) compared*	CT dose**	Patients characteristics***
Turrisi 1989	417	1989-1992	SCLC	Standard: 45 Gy / 25 fr / 5 w Experimental: 45 Gy / 30 fr / 3 w bid	Cisplatin 60 mg/m² d_1 Etoposid 120 mg/m² $d_{1,2,3}$ 4 cycles (3 w)	PS 0-2
Schild 1990 NCCTG	261	1990-1996	SCLC	Standard: 50.4 Gy / 28 fr / 5.5 w Experimental: 48 Gy / 32 fr / 5.5 w sc[£] bid	Cisplatin 30 mg/m² $d_{1,2,3}$ Etoposide 130 mg/m² $d_{1,2,3}$ 6 cycles[†] (4 w)	PS 0-2
Sause RTOG 88-08 ECOG 4588	306[$]	1989-1992	NSCLC	Standard: 60 Gy / 30 fr / 6 w Experimental: 69.6 Gy / 58 fr / 6 w bid	None	KPS >=70 II-III
Ball 1989 A	101	1989-1995	NSCLC	Standard: 60 Gy / 30 fr / 6 w Experimental: 60 Gy / 30 fr / 3 w bid	None	PS 0-1 Stage I-III
Ball 1989 B	107	1989-1995	NSCLC	Standard: 60 Gy / 30 fr / 6 w Experimental: 60 Gy / 30 fr / 3 w bid	Carboplatin 70 mg/m² d_{1-5} + Carboplatin 70 mg/m² d_{29-33} in standard arm	PS 0-1 Stage I-III
Fu 1990	109	1990-1991	NSCLC	Standard: 63.9 Gy / 35 fr / 7 w Experimental: 69.6 Gy / 60 fr / 6 w bid	None	Stage I-III
CHART	563	1990-1995	NSCLC	Standard: 60 Gy / 30 fr / 6 w Experimental: 54 Gy / 36 fr / 1.5 tid	None	PS 0-1 Stage I-III
Bonner 1992 NCCTG	67[$$]	1992-1993	NSCLC	Standard: 60 Gy / 30 fr / 6 w Experimental: 60 Gy / 40 fr / 6 w sc[£$] bid	None	PS 0-2 Stage III
Sun 1994	106[$$$]	1994-1998	NSCLC	Standard: 70.8 Gy / 38 fr / 7.5 w Experimental: 65 Gy / 26 fr / 5.5 w	None	KPS >=60 Stage IB-III

Reference	Number of patients randomized	Inclusion period	Histology	RT dose (Gray)/ fraction/ duration (weeks) compared*	CT dose**	Patients characteristics***
Schild 1994 NCCTG	246	1994-1999	NSCLC	Standard: 60 Gy / 30 fr / 6 w Experimental: 60 Gy / 40 fr / 6 w sc££ bid	Cisplatin 30 mg/m² $d_{1\text{-}3;28\text{-}30}$ Etoposide 100 mg/m² $d_{1\text{-}3;28\text{-}30}$	PS 0-1 Stage III
Belani ECOG 2597	119	1998-2001	NSCLC	Standard: 64 Gy / 32 fr / 6.5 w Experimental: 57.6 Gy / 36 fr / 2.5 w tid	Carboplatin AUC 6 d_1 Paclitaxel 225 mg/m² d_1 2 cycles‡ (3 w)	PS 0-1 Stage III
Zajusz 2001	58	2001-2006	NSCLC	Standard: 72 Gy / 40 fr / 8 w Experimental: 72 Gy / 40 fr / 5.5 w	None	NA

*** 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**

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

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:

50 Gy	60 Gy	65 Gy	70 Gy
Turrisi SCLC	**RTOG 88-08**		**Sun**
Schild 1990 SCLC	**Ball A**		**Zajusz**
	Ball B		
	CHART		
	Bonner		
	Schild 1994		
	Fu		
	ECOG 2597		

TABLE B2: TOTAL DOSE IN THE EXPERIMENTAL ARM (% / reference arm)

-10%	-5%	0	+10%	+15%
	Schild 1990 SCLC	Turrisi SCLC		
CHART		Ball A		RTOG 88-08
		Ball B	Fu	
ECOG 2597		Bonner		
	Sun	Schild 1994		
		Zajusz		

TABLE B3: DOSE per FRACTION IN THE EXPERIMENTAL ARM (Gy)

1.2	1.3	1.4	1.5	1.6	1.7	1.8	1.9	2	2.5Gy
RTOG 88-08			**Turrisi SCLC**			**Zajusz**			
Fu			**Schild 1990 SCLC**			**ECOG 2597***		**Ball A**	
			CHART					**Ball B**	
			Bonner			**Sun****			
			Schild 1994						

* 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

0%	10%	20%	30%	40%	50%	60%	70%	80%
Schild 1990 SCLC				Turrisi SCLC				
			Zajusz					CHART
RTOG 88-08								
Bonner					Ball A			
Schild 1994					Ball B			
		Fu	Sun			ECOG 2597		

TABLE B5:
TOTAL DOSE IN THE EXPERIMENTAL ARM

ACCELERATION	LOWER	IDENTICAL (+/- 5%)	HIGHER
0-13%		Schild 1990 SCLC Bonner Schild 1994	RTOG 88-08
14-49%	Sun	Turrisi SCLC Zajusz	Fu
≥ 50%	CHART ECOG 2597	Ball A Ball B	

	Hyperfractionated		Normal	Hyperfractionated		Normal	Hyperfractionated		Normal
	< 1.25 Gy	**1.25-1.75 Gy**	**1.8-2 Gy**	**< 1.25 Gy**	**1.25-1.75 Gy**	**1.8-2 Gy**	**< 1.25 Gy**	**1.25-1.75 Gy**	**1.8-2 Gy**

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.

Variable	Format/Coding
Patient Identifier	Type character **(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
Or Age at randomization	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 (SCLC), 2=AJCC, 3=1986 ISS, 4=1997 UICC (for SCLC, limited versus extensive staging is recommended)
Limited vs. extensive disease (SCLC)	0=limited disease, 1=extensive disease
Nodes extension (SCLC)	Type numeric - Width 1 0=no, 1=yes, 9=unknown
Mediastinal nodes extension (SCLC)	Type numeric - Width 1 0=no, 1=yes, 9=unknown
Sus-clavicular nodes extension (SCLC)	Type numeric - Width 1 0=no, 1=yes, 9=unknown
If possible, provide complete TNM, if not possible provide stage	
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 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

	Code 1-4, 9=unknown
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	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