VOLUME 30 · NUMBER 22 · AUGUST 1 2012

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Hyperfractionated or Accelerated Radiotherapy in Lung Cancer: An Individual Patient Data Meta-Analysis

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Submitted January 9, 2012; accepted May 3, 2012; published online ahead of print at www.jco.org on July 2, 2012.

Written on behalf of the Meta-Analysis of Radiotherapy in Lung Cancer Collaborative Group.

Supported by unrestricted grants from French Programme Hospitalier de Recherche Clinique, Ligue Nationale Contre le Cancer, and sanofi-aventis (J.-P.P.). The funding sources had no role in study design, data collection, data analysis, data interpretation, or manuscript writing.

Presented in part at the 2nd European Lung Cancer Conference, April 28-May 1, 2010, Geneva, Switzerland; the 29th Annual Meeting of the European Society of Therapeutic Radiation and Oncology, September 12-16, 2010, Barcelona, Spain; and fully at the 14th World Conference on Lung Cancer, July 3-7, 2011, Amsterdam, the Netherlands.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/12/3022-2788/$20.00

DOI: 10.1200/JCO.2012.41.6677

ABSTRACT

Purpose
In lung cancer, randomized trials assessing hyperfractionated or accelerated radiotherapy seem to yield conflicting results regarding the effects on overall (OS) or progression-free survival (PFS). The Meta-Analysis of Radiotherapy in Lung Cancer Collaborative Group decided to address the role of modified radiotherapy fractionation.

Material and Methods
We performed an individual patient data meta-analysis in patients with nonmetastatic lung cancer, which included trials comparing modified radiotherapy with conventional radiotherapy.

Results
In non–small-cell lung cancer (NSCLC; 10 trials, 2,000 patients), modified fractionation improved OS as compared with conventional schedules (hazard ratio [HR] = 0.88, 95% CI, 0.80 to 0.97; P = .009), resulting in an absolute benefit of 2.5% (8.3% to 10.8%) at 5 years. No evidence of heterogeneity between trials was found. There was no evidence of a benefit on PFS (HR = 0.94; 95% CI, 0.86 to 1.03; P = .19). Modified radiotherapy reduced deaths resulting from lung cancer (HR = 0.89; 95% CI, 0.81 to 0.98; P = .02), and there was a nonsignificant reduction of non–lung cancer deaths (HR = 0.87; 95% CI, 0.66 to 1.15; P = .33). In small-cell lung cancer (SCLC; two trials, 685 patients), similar results were found: OS, HR = 0.87, 95% CI, 0.74 to 1.02, P = .08; PFS, HR = 0.88, 95% CI, 0.75 to 1.03, P = .11. In both NSCLC and SCLC, the use of modified radiotherapy increased the risk of acute esophageal toxicity (odds ratio [OR] = 2.44 in NSCLC and OR = 2.41 in SCLC; $P < .001$) but did not have an impact on the risk of other acute toxicities.

Conclusion
Patients with nonmetastatic NSCLC derived a significant OS benefit from accelerated or hyperfractionated radiotherapy; a similar but nonsignificant trend was observed for SCLC. As expected, there was increased acute esophageal toxicity.

J Clin Oncol 30:2788-2797. © 2012 by American Society of Clinical Oncology

INTRODUCTION

Worldwide, lung cancer accounts now for the largest number of new cancer cases, with approximately 85% non–small-cell lung cancer (NSCLC) and 15% small-cell lung cancers (SCLC); poor survival rates are common even in patients with nonmetastatic disease.[1-3] In recent years, considerable interest has been raised about modified fractionation radiotherapy (RT) regimens for head and neck and lung cancers.[4-7] Two types of altered fractionation have been studied[7]: hyperfractionation in which the dose per fraction was decreased, with two or three fractions given per day instead of one; and acceleration, consisting of reducing the overall treatment time, thus delivering to the tumor a higher dose in a shorter overall time. Accelerated radiotherapy is often combined with hyperfractionation. In head and neck cancer, an individual patient data meta-analysis on altered-fractionated RT has demonstrated a significant benefit on overall survival (OS) of hyperfractionated and/or accelerated over conventionally fractionated RT.[8] The randomized trials assessing hyperfractionated and/or accelerated RT in lung cancer seem to give conflicting results about the benefit on locoregional control and OS. The Meta-Analysis of Radiotherapy in Lung Cancer (MAR-LC) collaborative group decided to perform an individual patient data meta-analysis to accurately estimate the effect of modified RT on survival

outcomes and toxicity and to distinguish between ineffective treatment and moderate treatment effects, which may be clinically relevant.[8-13]

MATERIALS AND METHODS

This meta-analysis was performed in accordance with a prespecified protocol, available on request.

Selection Criteria and Search Strategy

To be eligible, trials were to include patients with nonmetastatic lung cancer, randomly assigned in a way that precluded prior knowledge of treatment assignment. They had to compare modified radiotherapy (accelerated, hyperfractionated, or both) with conventional radiotherapy (five daily 1.8- to 2-Gy fractions per week and a minimum total dose of 40 Gy for SCLC and 60 Gy for NSCLC). Trials must have accrued between January 1, 1970, and December 31, 2005, and not be confounded by additional therapeutic differences between the two arms. Trials combining chemotherapy (CT) with radiotherapy were included only if CT doses and schedule were the same in the two arms. The searching strategy is available (Data Supplement).

Individual Patient Data

For each eligible trial, individual patient data were requested for all randomly assigned patients and comprised characteristics of both patient and tumor, date of randomization and treatment arm allocated, and details on treatment actually received. Acute and late toxicities (hematologic, esophageal, pulmonary, and cardiac) were collected. Data on the type of pulmonary and cardiac toxicities were not collected. Follow-up information was as updated as possible.

Each trial database was checked according to a standard procedure for missing data, inconsistencies, and for ensuring a suitable quality of follow-up in the two treatment arms. Randomization integrity was assessed through search of unusual patterns in the sequencing of allocation or imbalances between treatment arms. Queries were solved and final database validated by the responsible trial investigator or statistician.

Statistical Considerations

Definition of outcomes measures. The primary outcome was OS, defined as the time from randomization until death resulting from any cause. Living patients were censored at their date of last follow-up. Progression-free survival (PFS) was defined as time from randomization to first event among locoregional or distant progression and death. Living patients without progression were censored at their date of last follow-up. Locoregional and distant failures were studied within the framework of competing risks as follows. Time to locoregional failure was defined as time from randomization until date of locoregional failure as first event. Patients having distant failure before locoregional failure were censored at the time of distant failure, and patients dying without recurrence were censored at date of death. Time to distant failure was similarly defined. Patients having both locoregional and distant failures occurring at the same time were considered as event for distant failure analysis only.

Non–lung cancer deaths were defined as deaths resulting from causes other than cancer and not occurring after disease progression. All other deaths, including deaths resulting from unknown cause, were considered as lung cancer deaths.[9]

Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC), WHO criteria, or Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer (RTOG/EORTC) criteria depending on the trials. Severe toxicity was defined as grade 3 to 4 toxicity.

Analysis

Analysis was done according to the intent-to-treat principle, including patients excluded from previous trials analyses. Two separate analyses were performed for SCLC and NSCLC. Median follow-up was estimated using the reverse Kaplan-Meier method.[14] Analyses were stratified on trial. Individual and pooled hazard ratios (HRs) and 95% CIs were estimated through a fixed-effects model using log-rank expected number of events and its variance.[15] A similar model was used to estimate odds ratios (OR) for comparison of toxicity between arms. Heterogeneity among trials was investigated through χ^2 heterogeneity tests[11] and was quantified through calculation of I^2 index.[16] Lung cancer and non–lung cancer mortality were analyzed according to Peto's method to take into account the competing risk framework.[9,13] Peto's curves for survival and absolute benefits were calculated using OS rate in the control group and estimated HR at each time of interest. Rates of toxicity in the experimental arm were calculated using rate in the control arm and the OR.[17] In the NSCLC trials, four prespecified and mutually exclusive subsets of trials were constituted according to number of daily fractions, total dose, and total duration: very accelerated RT, defined as shortening of the total duration of 50% or more compared with that of the control arm; moderately accelerated RT, defined as shortening of the total duration of more than 15%, but less than 50% as compared with the control arm; hyperfractionated RT with identical total dose; and hyperfractionated RT with increased total dose. HRs were computed by subset, and interaction with treatment effect was investigated through χ^2 tests.[11] As prespecified, influence of administration of CT on patient outcomes was also analyzed. Interaction between treatment effect and patients subgroups was also examined through χ^2 test comparing effect between subgroups to study whether subgroups of patients benefit more or less from modified radiotherapy. Studied characteristics were age, sex, and performance status, and, in NSCLC trials only, histologic subtype and stage. If significant interaction was found, the result was to be confirmed with a second method that pools interactions between treatment effect and subgroups computed in each trial, minimizing the risk of bias related to indirect comparison.[18] As exploratory analyses, survival and toxicity analyses adjusted on covariates were done through multivariate Cox models for survival end points and logistic models for toxicity end points. Results were similar with the nonadjusted analyses, thus only log-rank or χ^2 ones are presented.

Individual patient data on treatment actually received were used to study the biologic effective dose (BED) corrected for the overall treatment time, [19,20] which allows the comparison of various dose-fractionation regimens. The BED was here defined as follows:

$$BED = (nd)(1 + d/[\alpha/\beta]) - 0.693.t/\alpha.Tpot$$

where n is the total number of fractions delivered, d is the dose per fraction (Gy), and t is the total duration of radiotherapy (days). The following assumptions were made on radiobiologic parameters for tumors: $\alpha/\beta = 10$ Gy (for tumor and most acute effects); $\alpha = 0.3$ Gy; and *Tpot* (the potential doubling time) equals 5.6 days. Exploratory analyses studied the impact on OS of the value of the equivalent BED received by patients through Cox model as well as the impact on the risk of acute esophageal toxicity through logistic model, stratified on trial and adjusted for age, sex, performance status, histologic type, and disease stage. The BED was initially studied in four categories defined by the quartiles, containing one fourth of the patients each. However, results of three categories were very similar, and as this was an exploratory analysis, these categories were aggregated to simplify the results. Consequently, the BED is presented in two categories, first quartile versus other quartiles. The equivalent dose using a fraction size of 2 Gy corrected for time, EQD2t, was similarly studied.[21]

All P values were two-sided. Analyses were performed using SAS software, version 9.1 (SAS Institute, Cary, NC).

RESULTS

Trials and Patients Description

The different steps of the trial selection are presented in Figure 1. Twelve eligible trials were identified, two in SCLC and 10 in NSCLC. Excluded trials are listed (Data Supplement). Data were no longer available for two NSCLC trials,[22,23] so that 10 trials were analyzed, two SCLC trials[24,25] and eight NSCLC trials.[26-33] One trial had a factorial

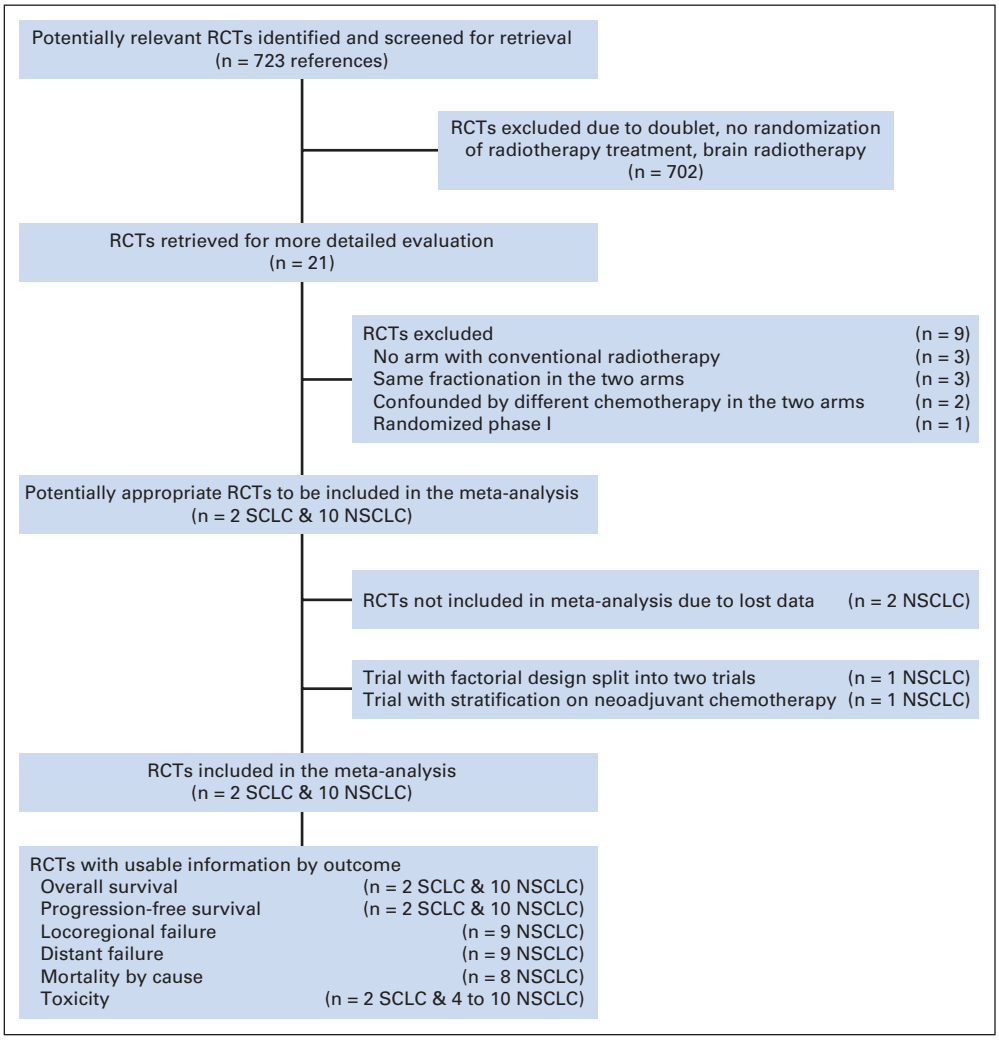


Fig 1. Flowchart of the trial selection and contribution to analyses. NSCLC, non–small-cell lung cancer; RCTs, randomized controlled trials; SCLC, small-cell lung cancer.

design: patients were also randomly assigned to receive or not concomitant CT[27]; one trial had a randomization stratified on administration of induction chemotherapy.[31] Each of these two trials were split into two separate trials, with and without chemotherapy (PMCI 88C091 and PMCI 88C091 CT; CHARTWEL and CHARTWEL CT). Therefore, 12 trials and 2,685 patients were analyzed (Table 1). In the two SCLC trials, patients received cisplatin and etoposide concomitantly with RT, plus induction and consolidation in one. In the 10 NSCLC trials, CT was administered concomitantly with RT in two trials[27,30] (carboplatin alone or cisplatin plus etoposide) and as induction chemotherapy in two trials[31,32] (according to the center practice or based on carboplatin plus paclitaxel). The NSCLC trials were divided into four categories as follows: six trials in the very accelerated RT subset,[27,28,31,32] one trial in the moderately accelerated RT subset,[33] two trials in the hyperfractionated RT with identical dose subset,[29,30] and one trial in the hyperfractionated RT with increased total dose[26] (Data Supplement).

Patients with NSCLC were mainly men (75%) and younger than 70 years (71%), with a performance status (PS) of 0 to 1 (> 99%); more than 60% had squamous cell cancer, and more than 80% had stage III cancer. All patients with SCLC had a limited stage, 58% were men, 6% had PS of 2, and 83% were younger than 70 years (Data Supplement). As compared with published trials, 63 additional patients were analyzed (+3%), allowing us to analyze all patients known to be randomly assigned in the included trials. Characteristics of patients were well balanced between the two randomization arms (Data Supplement).

NSCLC Trials

OS. Overall survival results are based on 2,000 patients with a median follow-up of 6.9 years and 1,849 deaths. Across trials the risk of death was significantly reduced by 12% with the use of modified RT (HR = 0.88; 95% CI, 0.80 to 0.97; P = .009; Fig 2). The absolute benefit was 3.8% at 3 years and 2.5% at 5 years, increasing the survival rate from 15.9% to 19.7% at 3 years and from 8.3% to 10.8% at 5 years (Fig 3A). As shown in Figure 2, there was no evidence of heterogeneity in treatment effect between the trials (heterogeneity test, P = .37, I^2 = 8%), and the effect of modified RT did not seem to differ between the trials subsets (interaction test, P = .98). Impact on overall survival seemed similar according to CT: HR = 0.92 (95% CI, 0.77 to 1.10) and HR = 0.87 (95% CI, 0.78 to 0.97) in trials with and without CT, respectively (interaction test, P = .57). There was no evidence that any subgroup of patients benefited more or less from modified RT, as shown on Figure 4.

Table 1. Description of Included Trials

Trial	No. of Patients Randomly Assigned	Inclusion Period	Median Follow-Up (years)	Histology	RT Total Dose (Gy)	No. of Fractions	Duration (weeks)	BED St/EXP	CT Dose	Patient Characteristic
ECOG 3588[24]	417	1989-1992	13.0	SCLC	Standard: 45	25	5	39.5	Cisplatin 60 mg/m^2 day 1	PS 0-2
					Experimental: 45	30	3 BID	43.9	Etoposide 120 mg/m^2 days 1-3	
									4 cycles (3 weeks)	
NCCTG 892052[25]	268	1990-1996	9.3	SCLC	Standard: 50.4	28	5.5	43.8	Cisplatin 30 mg/m^2 days 1-3	PS 0-2
					Experimental: 48	32	5.5 SC* BID	39.5	Etoposide 130 mg/m^2 days 1-3	
									6 cycles† (4 weeks)	
RTOG 8808-ECOG 4588[26]	326	1989-1992	6.8	NSCLC	Standard: 60 Gy	30	6	55.5	None	KPS ≥ 70
					Experimental: 69.6	58	6 BID	61.9		Stage II-III
PMCI 88C091[27]	101	1989-1995	Not reached	NSCLC	Standard: 60	30	6	55.5	None	PS 0-1
					Experimental: 60	30	3 BID	64.2		Stage I-III
PMCI 88C091 CT[27]	107	1989-1995	Not reached	NSCLC	Standard: 60	30	6	55.5	Carboplatin 70 mg/m^2 days 1-5	PS 0-1
					Experimental: 60	30	3 BID	64.2	+ Carboplatin 70 mg/m^2 days 29-33 in standard arm	Stage I-III
CHART[28]	563‡	1990-1995	6.9	NSCLC	Standard: 60	30	6	55.5	None	PS 0-1
					Experimental: 54	36	1.5TID	57.2		Stage I-III
NCCTG 902451[29]	74	1992-1993	8.1	NSCLC	Standard: 60	30	6	55.5	None	PS 0-2
					Experimental: 60	40	6 SC§ BID	52.5		Stage III
NCCTG 942452[30]	246	1994-1999	7.3	NSCLC	Standard: 60	30	6	55.5	Cisplatin 30 mg/m^2 days 1-3, 28-30	PS 0-1
					Experimental: 60	40	6 SC§ BID	52.5	Etoposide 100 mg/m^2 days 1-3, 28-30	Stage III
CHARTWEL[31]	300	1997-2005	4.9	NSCLC	Standard: 66	33	6.5	60.6	None	PS 0-1
					Experimental: 60	40	2.5TID	61.6		Stage I-III
CHARTWEL CT[31]	106	1997-2005	3.5	NSCLC	Standard: 66	33	6.5	60.6	Induction CT—dependent on institution's choice	PS 0-1
					Experimental: 60	40	2.5TID	61.6		Stage I-III
ECOG 2597[32]	119	1998-2001	6.7	NSCLC	Standard: 64	32	6.5	58.7	Carboplatin AUC 6 day 1	PS 0-1
					Experimental: 57.6	36	2.5TID	60.2	Paclitaxel 225 mg/m^2 day 1	Stage III
									2 cycles‖ (3 weeks)	
Gliwice 2001[33]	58	2001-2006	5.3	NSCLC	Standard: 72	40	8	62.7	None	PS 0-1
					Experimental: 72	40	5.5	68.5		Stage II-III

Abbreviations: BED, biologic effective dose; BID, RT given twice a day; CT, chemotherapy; if not specified, the chemotherapy is concomitant to the radiotherapy; CHART, Continuous Hyperfractionated Accelerated Radiation Therapy; CHARTWEL, CHART Week-End Less; ECOG, Eastern Cooperative Oncology Group; Exp, experimental; (K) PS, (Karnofsky) performance status; NCCTG, North Central Cancer Treatment Group; NSCLC, non–small-cell lung cancer; PCMI, Peter MacCallum Institute; RT, Radiotherapy; RTOG, Radiation Therapy Oncology Group; SC, split course; SCLC, small-cell lung cancer; St, standard; TID, RT given three times a day.

*Two series of 8 days with a break of 2.5 weeks.

†Three cycles induction, two cycles concomitant, and one after RT; etoposide dose was reduced to 100 mg/m^2 for cycles 4 to 6.

‡Patients were randomly allocated in a 3:2 ratio to CHART or conventional radiotherapy.

§Two series of 2 weeks with a break of 2 weeks.

‖Induction chemotherapy.

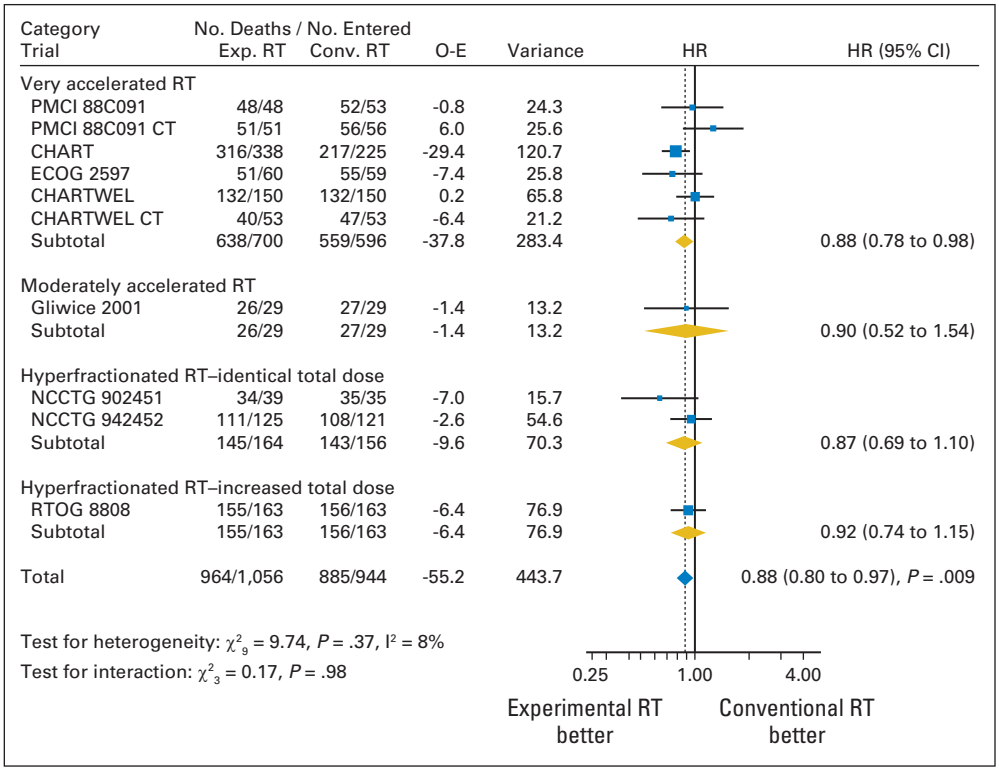
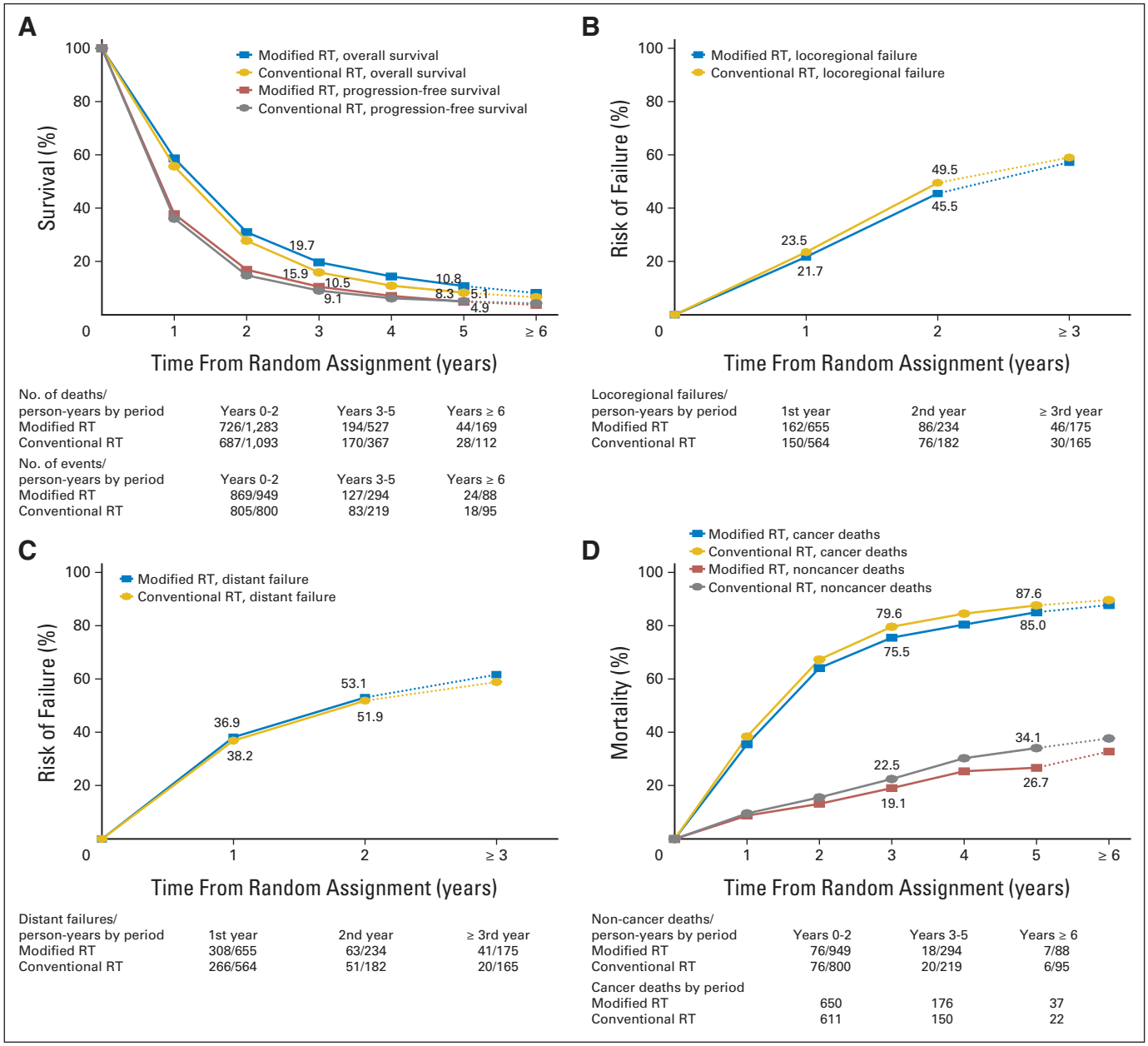


Fig 2. Effect of modified radiotherapy (RT) versus conventional RT on overall survival, by RT types in non–small-cell lung cancer trials. Each trial is represented by a blue square, the center of which denotes the hazard ratio (HR) for that trial comparison, with the horizontal lines showing the 95% CIs. The size of the square is directly proportional to the amount of information contributed by the trial. The gold diamonds represent pooled HRs for the trial groups and the blue diamond the overall HRs, with the center denoting the HR and the extremities the 95% CI. The fixed effect model was used. CHART, Continuous Hyperfractionated Accelerated Radiation Therapy; CHARTWEL, CHART Week-End Less; CT, chemotherapy; Conv., conventional; ECOG, Eastern Cooperative Oncology Group; Exp., experimental; NCCTG, North Central Cancer Treatment Group; O-E, observed-expected; PCMI, Peter MacCallum Institute; RTOG, Radiation Therapy Oncology Group.

Other survival outcomes. Analysis of PFS was based on 2,000 patients and 1,926 events. Patterns of failure as first event were as follows: distant failure (30%), locoregional failure (29%), deaths (26%), locoregional and distant failure (8%), and unspecified (6%). No evidence of a benefit of modified RT was observed on PFS (HR = 0.94; 95% CI, 0.86 to 1.03; P = .19 [Data Supplement]). Absolute benefit was 1.4% at 3 years and −0.2% at 5 years (Fig 3A). There was no evidence of heterogeneity between trials (P = .28, I^2 = 18%) and no evidence of interaction between trials subsets (P = .85). No evidence of interaction of treatment effect with subgroup of patients was found (Data Supplement). Similarly, on the basis of nine trials and 1,862 patients, there was no evidence that modified RT had an impact on locoregional failure (550 events, HR = 0.92; 95% CI, 0.77 to 1.09; P = .32) or distant failure (749 events, HR = 1.07; 95% CI, 0.92 to 1.24; P = .37, Figs 3B and 3C). For these two end points, no evidence of heterogeneity was observed. The benefit observed on OS was similar in size when considering lung cancer-related deaths only (2,000 patients and 1,646 events; HR = 0.89; 95% CI, 0.81 to 0.98, P = .02 [Data Supplement]) and non–lung cancer mortality only (1,942 patients and 203 events, HR = 0.87; 95% CI, 0.66 to 1.15; P = .33 [Data Supplement]). Absolute decrease in mortality rates was 4.1% and 3.4% at 3 years and 2.6% and 7.4% at 5 years, respectively, for lung cancer and non–lung cancer deaths (Fig 3D).

Toxicity assessment. As shown in Table 2, modified RT increased the risk of acute severe esophageal toxicity from 9% to 19% (OR = 2.44; 95% CI, 1.90 to 3.14; P < .001). There was a significant interaction between RT modality and acute severe esophageal toxicity (P = .001), with the very accelerated RT being the most toxic (OR = 3.21; 95% CI, 2.41 to 4.28 [Data Supplement]). Overall, modified RT significantly reduced the risk of platelet toxicity (OR = 0.55; 95% CI, 0.32 to 0.96; P = .03), but no severe platelet toxicity was reported in the trials without CT. Severe hematologic toxicity was mainly reported in trials with CT, which principally influenced overall results. Consequently, no differences between trials with CT and trials without CT could be observed (interaction test, P = .72). Modified RT had no impact on other acute hematologic toxicities as well as long-term toxicity (Table 2).

Compliance and exploratory analyses. Some individual patient data on RT parameters were available for seven trials. As shown (Data Supplement), compliance to RT was good, with 90% or more patients receiving the treatment as planned in terms of total dose and fractionation, and superior to 80% for the overall treatment time. Compliance in the experimental arm was similar to the one in the control arm. The delivered BED could be calculated for 1,471 patients in six trials (Data Supplement). The BED ranged from 3.7 Gy to 74.9 Gy. The first quartile was 54.7 Gy (53.9 Gy in the conventional arm and 57.2 Gy in the experimental arm). The BED corresponding to the radiotherapy actually delivered to patients was significantly associated with OS: the 1,076 patients receiving a BED ≥ 55 Gy had a decreased risk of death as compared with the 395 patients with BED less than 55 Gy (HR = 0.75; 95% CI, 0.65 to 0.85; P < .001). This resulted in an absolute benefit of 5.1% at 3 years and 3.4% at 5 years (Data Supplement). However, this was at the price of a higher risk of acute esophageal toxicity (OR = 2.9; 95% CI, 1.9 to 4.4; P < .001). Similar results were found when studying the EQD2t (data not shown). Because incomplete treatment could be related to early progression and death, a sensitivity analysis was done to test this effect after exclusion of 306 patients with follow-up less than 6 months. Results were robust and supported the outcome (HR = 0.86; 95% CI, 0.74 to 1.00; P = .04) for OS.



No. of deaths/ person-years by period

	Years 0-2	Years 3-5	Years ≥ 6
Modified RT	726/1,283	194/527	44/169
Conventional RT	687/1,093	170/367	28/112

No. of events/ person-years by period

	Years 0-2	Years 3-5	Years ≥ 6
Modified RT	869/949	127/294	24/88
Conventional RT	805/800	83/219	18/95

Locoregional failures/ person-years by period

	1st year	2nd year	≥ 3rd year
Modified RT	162/655	86/234	46/175
Conventional RT	150/564	76/182	30/165

Distant failures/ person-years by period

	1st year	2nd year	≥ 3rd year
Modified RT	308/655	63/234	41/175
Conventional RT	266/564	51/182	20/165

Non-cancer deaths/ person-years by period

	Years 0-2	Years 3-5	Years ≥ 6
Modified RT	76/949	18/294	7/88
Conventional RT	76/800	20/219	6/95

Cancer deaths by period

Modified RT	650	176	37
Conventional RT	611	150	22

Fig 3. Survival curves for the non–small-cell lung cancer trials: (A) overall and progression-free survival; (B) locoregional failure; (C) distant failure; (D) lung and non–lung cancer mortality. RT, radiotherapy.

SCLC Trials

OS. Analyses were based on 685 patients with a median follow-up of 12.1 years and 622 deaths. Effect of modified RT on OS was similar to that of NSCLC, but nonsignificant (HR = 0.87; 95% CI, 0.74 to 1.02; $P = .08$ [Data Supplement]). No heterogeneity was seen between the two trials ($P = .49$, $I^2 = 0\%$). The absolute benefit was 1.7% at 3 years (from 29.6% to 31.3%) and 5.1% at 5 years (from 18.7% to 23.8% [Data Supplement]). An interaction was seen and confirmed between modified RT effect and PS: patients with poor PS seemed to benefit less from modified RT than patients with good PS (HR = 2.22 in PS 2 *v* 0.81 and 0.86 in PS = 0 and PS = 1 respectively; $P = .03$). No interaction was observed between effect of modified RT and age or sex (Data Supplement).

Other outcomes. There was no evidence that the use of modified RT had an impact on PFS (HR = 0.88; 95% CI, 0.75 to 1.03; $P = .11$ [Data Supplement]). There was no evidence of heterogeneity between the two trials ($P = .45$, $I^2 = 0\%$). The absolute benefit at 3 years and 5 years was 5.7% and 4.5%, respectively (Data Supplement). As for OS, patients with poor PS seemed to benefit less from modified RT than others ($P = .03$). Locoregional and distant failures, as well as lung cancer and non–lung cancer mortality, were not studied because of the lack of available data in these trials.

Toxicity assessment. In SCLC trials, only acute toxicities were assessed (Table 2). As in NSCLC, there was an excess of acute esophageal toxicity in the modified RT arm (OR = 2.41; 95% CI, 1.62 to 3.59; $P < .001$), without heterogeneity between the two trials, and a

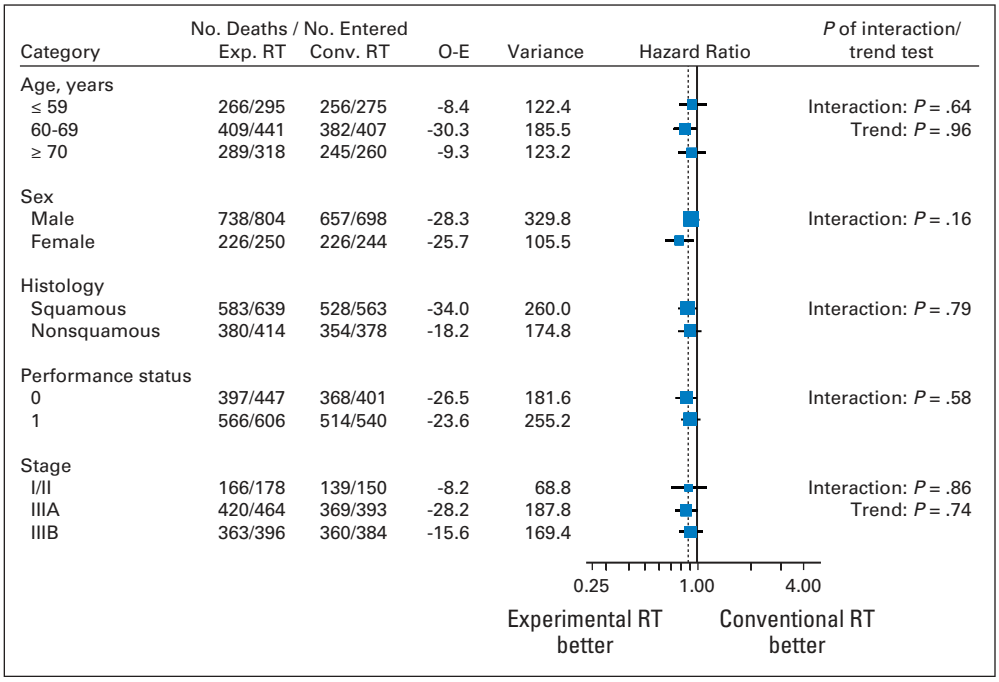


Fig 4. Effect of modified radiotherapy (RT) versus conventional RT on overall survival by patient characteristics. Conv., conventional; Exp., experimental; O-E, observed-expected.

reduction of risk of platelet toxicity (OR = 0.70; 95% CI, 0.50 to 0.98; $P = .04$). Risk of cardiac toxicity was higher with modified RT (OR = 2.96; 95% CI, 1.13 to 7.73; $P = .03$), but the toxicity rate in the control arm was only 1%. No evidence of impact of modified RT on acute hemoglobin, neutrophils, or pulmonary toxicity was found.

Exploratory Analysis

Individual patient data on RT parameters were only available for one trial, and no exploratory analysis was done.

DISCUSSION

On the basis of this meta-analysis, the use of modified RT has led to a significant 12% to 13% relative reduction of mortality in patients with lung cancer, resulting in a 5-year survival absolute benefit of 2.5% in NSCLC and 5.1% in SCLC. Because there were fewer patients with SCLC, this difference was nonsignificant except for in patients with good PS. Results are based on a minimum follow-up of 5 years in each trial. In exploratory analyses, we could not identify any subgroup (age, sex, performance status, stage, histology) for whom modified RT was any more or less effective, except a detrimental effect was observed in patients with SCLC and poor PS. However, detailed data in histology were not available in several trials, and the effect of the modified RT in adenocarcinoma could not be studied.

Because uncontrolled locoregional disease continues to be a major challenge in lung cancer, there is a conceptual rationale in support of more aggressive RT, as explored in the investigational arm of the various trials included in the meta-analysis. The survival results support this hypothesis. In a previous meta-analysis comparing concomitant and sequential radiochemotherapy in patients with locally advanced NSCLC, the absolute benefit of 4.5% in 5-year overall survival was mainly due to a decrease of locoregional failures,[34] but not in the present meta-analysis. There may be several explanations: the relatively low statistical power (only 550 events), the extreme difficulty of local control evaluation in trials mostly performed in the early 1990s, the difficulties to define the patterns of failure, the burden of distant failures that may have outweighed local recurrences, and lastly, an improvement in non–lung cancer mortality. It is possible that better control of distant disease obtained with improved integration of newer systemic therapy agents could uncover improved local control in future trials. Furthermore, the biologic advantage may have been undermined by the use of suboptimal RT techniques (use of split course radiotherapy, no computed tomography–based planning) contributing to an insufficient local outcome.

Even if some toxicity results should be interpreted with caution, data are robust in terms of acute esophageal toxicity, which was increased by a factor of 2.4. It was, however, reversible for most patients. Aggressive types of RT fractionation are not only associated with severity of esophagitis, but also its duration.[27,28,35] Interestingly, compliance with modified RT was good, especially in terms of overall treatment duration in very accelerated regimens, as esophageal maximal toxicity occurred after the end of the RT schedule.[27,28,31] More modern RT techniques may contribute to diminish esophageal toxicity, which can be severe and disabling. However, reversible toxicity in fit patients may be considered subsidiary to improving survival.

Preclinical and clinical research studies suggest that most cancer cells have a doubling time of less than 1 week.[36,37] Prolonging total duration of treatment may be detrimental because it results in accelerated tumor repopulation.[38,39] Thus in SCLC, the results, even if not significant, support such accelerated regimens with concomitant CT. In NSCLC, where there is less biologic background to support hyperfractionated regimens, we could also observe a similar HR favoring modified RT regimens, with 64% of individual data issued from very accelerated trials and with good compliance regarding radiation dose and duration. This seemed related to a decrease in non–cancer-related deaths.

Table 2. Effect of Modified Radiotherapy Compared With Conventional Radiotherapy on Toxicity Events

Severe Toxicity	Availability		Toxicity Rate in Control Arm (%)	Toxicity Rate in Experimental Arm (%)*	Result		*P* Efficacy	I^2 (%)	*P* Heterogeneity
	No. of Trials	No. of Patients			OR	95% CI			
Non–small-cell lung cancer									
Acute toxicity									
Esophageal	10	1,968	9	19	2.44	1.90 to 3.14	< .001	57	.01†
Pulmonary	9	1,390	7	5	0.67	0.42 to 1.05	.08	0	.65
Cardiac	6	940	1	1	1.33	0.46 to 3.83	.59	0	.92
Hematologic‡	5	607	34	29	0.79	0.48 to 1.32	.38	0	.54
Neutrophils	5	600	33	28	0.80	0.46 to 1.40	.44	3	.39
Platelets	5	595	13	8	0.55	0.32 to 0.96	.03	0	.98
Hemoglobin	6	677	1	1	1.36	0.46 to 4.08	.58	0	.86
Late toxicity									
Pulmonary	7	866	15	16	1.07	0.73 to 1.56	.73	0	.56
Esophageal	7	861	3	4	1.24	0.61 to 2.56	.55	0	.89
Cardiac	4	515	1	1	1.49	0.40 to 5.60	.55	0	.96
Any of above	4	533	13	16	1.27	0.79 to 2.06	.33	0	.97
Small-cell lung cancer									
Acute esophageal	2	667	12	25	2.41	1.62 to 3.59	< .001	0	.99
Acute pulmonary	2	675	5	6	1.32	0.69 to 2.51	.40	0	.33
Acute cardiac	2	670	1	3	2.96	1.13 to 7.73	.03	0	.76
Hematologic§	2	674	83	86	1.22	0.81 to 1.86	.34	0	.36
Neutrophils	2	643	84	87	1.31	0.84 to 2.04	.23	0	.70
Platelets	2	666	38	30	0.70	0.50 to 0.98	.04	36	.21
Hemoglobin	2	673	18	19	1.06	0.71 to 1.59	.76	0	.35

Abbreviation: OR, odds ratio.
*See Statistical Considerations section in the text for the methods used to compute the rate in the experimental arm.
†Significant interaction: very accelerated radiotherapy is more toxic than other radiotherapy types (interaction test, $P = .001$, Data Supplement).
‡Including three trials (456 patients) with chemotherapy.
§Chemotherapy treatment was administered in the two small-cell lung cancer trials.

To better compare the different regimens, we calculated the BED for each RT schedule. We observed an absolute benefit in terms of 3-year survival of 5.1% in patients who had a BED $\geq$ 55 Gy (corresponding to 60 Gy over 6 weeks). Similar results were found when studying the EQD2t. Repopulation is hypothesized to be one of the major factors that limit the success of conventional dose-escalation approaches, so that accelerated regimen should be reconsidered in the light of these results, and hyperfractionated regimens may better protect normal tissues and enable concomitant approaches.

Concomitant chemoradiotherapy is at present considered the standard regimen for locally advanced lung cancer. The integration of optimized conformal RT to improve local control as well as the combination with systemic agents to reduce systemic failures using modified RT regimens should be reconsidered. The search for biologic predictive factors that could enable us to better individualize the optimal treatment for patients with lung cancer is also warranted, as this meta-analysis seems to show that there are different possibilities to improve curability of lung cancer. Further research is needed to identify the optimal schedule of modified fraction RT, including new techniques in target volume definition, treatment techniques, and delivery, such as positron emission tomography scans, intensity-modulated RT, and dose-guided RT.[40]

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.
Employment or Leadership Position: None **Consultant or Advisory Role:** None **Stock Ownership:** None **Honoraria:** None **Research Funding:** Jean-Pierre Pignon, sanofi-aventis **Expert Testimony:** None **Other Remuneration:** None

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