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ORIGINAL REPORT

Meta-Analysis of Concomitant Versus Sequential Radiochemotherapy in Locally Advanced Non–Small-Cell Lung Cancer

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ABSTRACT

Purpose
The previous individual patient data meta-analyses of chemotherapy in locally advanced non–small-cell lung cancer (NSCLC) showed that adding sequential or concomitant chemotherapy to radiotherapy improved survival. The NSCLC Collaborative Group performed a meta-analysis of randomized trials directly comparing concomitant versus sequential radiochemotherapy.

Methods
Systematic searches for trials were undertaken, followed by central collection, checking, and reanalysis of updated individual patient data. Results from trials were combined using the stratified log-rank test to calculate pooled hazard ratios (HRs). The primary outcome was overall survival; secondary outcomes were progression-free survival, cumulative incidences of locoregional and distant progression, and acute toxicity.

Results
Of seven eligible trials, data from six trials were received (1,205 patients, 92% of all randomly assigned patients). Median follow-up was 6 years. There was a significant benefit of concomitant radiochemotherapy on overall survival (HR, 0.84; 95% CI, 0.74 to 0.95; $P = .004$), with an absolute benefit of 5.7% (from 18.1% to 23.8%) at 3 years and 4.5% at 5 years. For progression-free survival, the HR was 0.90 (95% CI, 0.79 to 1.01; $P = .07$). Concomitant treatment decreased locoregional progression (HR, 0.77; 95% CI, 0.62 to 0.95; $P = .01$); its effect was not different from that of sequential treatment on distant progression (HR, 1.04; 95% CI, 0.86 to 1.25; $P = .69$). Concomitant radiochemotherapy increased acute esophageal toxicity (grade 3-4) from 4% to 18% with a relative risk of 4.9 (95% CI, 3.1 to 7.8; $P < .001$). There was no significant difference regarding acute pulmonary toxicity.

Conclusion
Concomitant radiochemotherapy, as compared with sequential radiochemotherapy, improved survival of patients with locally advanced NSCLC, primarily because of a better locoregional control, but at the cost of manageable increased acute esophageal toxicity.

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INTRODUCTION

Lung cancer remains a major cause of death worldwide with more than 1.1 million deaths per year.[1] Non–small-cell lung cancer (NSCLC) represents more than 80% of all lung tumors, and approximately 35% of patients with NSCLC present with locally advanced nonmetastatic disease. Since the mid-1990s, the standard treatment for these patients was thoracic radiotherapy and then combined radiochemotherapy. The NSCLC Collaborative Group meta-analysis[2] and the meta-analysis of platin-based concomitant chemotherapy in NSCLC[3] demonstrated that adding sequential or concomitant chemotherapy to radical radiotherapy improved survival in locally advanced NSCLC. The hazard ratio (HR) for survival resulting from the addition of sequential chemotherapy to radiotherapy was 0.88 (95% CI, 0.81 to 0.96).[2] The HR resulting from the addition of platin-based concomitant chemotherapy to radiotherapy was 0.89 (95% CI, 0.81 to 0.98), but this had to be interpreted cautiously owing to heterogeneity across trials and sensitivity analyses yielding inconsistent results.[3]

Several NSCLC trials have compared sequential and concomitant combinations directly; almost all of which showed a trend in favor of concomitant radiochemotherapy. The NSCLC Collaborative Group performed a systematic review and individual patient data meta-analysis of the latter trials to estimate accurately the effect on survival and acute toxicity.

METHODS

The meta-analysis was performed according to a prespecified protocol that is available on Institut de Cancérologie Gustave-Roussy web site.[4]

Selection Criteria

Trials were eligible for inclusion provided that they randomly assigned patients with unresected NSCLC without distant metastases who received thoracic radiotherapy with a curative intent either combined with sequential or with concomitant chemotherapy. Sequential chemotherapy was defined as chemotherapy given before and/or after radiotherapy. Concomitant chemotherapy was defined as chemotherapy administered during radiotherapy. Radiotherapy modalities should be similar in both arms of the trial. Patients should not have received any prior radiotherapy or chemotherapy. Trials had to be properly randomized. The meta-analysis included trials that had completed accrual by the end of 2003 in order to have long enough follow-up.

Search Methods

Published and unpublished trials were eligible. Trials published were sought by searching electronic databases (Medline, Embase, Cancerlit) without language restriction, using the Cochrane Collaboration optimal search strategy for identifying randomized controlled trials. This was supplemented by manual searches (reference lists of trial publications, review articles, relevant books, meeting proceedings of American Society of Clinical Oncology and International Association for the Study of Lung Cancer). The National Cancer Institute Physician Data Query clinical trial registry, the United Kingdom Coordinating Committee for Cancer Research trials register, the Current Controlled Trials metaRegister of trials, and the Cochrane library were also searched to identify unpublished and ongoing trials. Experts and investigators who took part in the meta-analysis were asked to help identifying other trials. When there was uncertainty about the eligibility of a trial, this was discussed and resolved by consensus within the project secretariat and the international advisory group.

Table 1. Trial Characteristics

Trial	Accrual Period	No. of Randomly Assigned Patients	Patients Alive	Median Follow-Up (years)	Concomitant Chemoradiotherapy		Sequential Chemoradiotherapy	
					Chemotherapy	Radiotherapy	Chemotherapy	Radiotherapy
CALGB 8831[14]*	1988-1989	91	7	9.2	Cb 100 mg/m²/wk × 6 wk	Start on day 50 after induction CT: 60 Gy, 30 f, 6 wk, RT started in 80% of patients	Consolidation CT (start 3 wk after RT end): cisplatin 100 mg/m² day 1, Vb 5 mg/m² days 1, 15 for 4 cycles	Start on day 50 after induction CT: 60 Gy, 30 f, 6 wk, RT started in 78% of patients
WJLCG[15]	1992-1994	314	41	4.9	Cisplatin 80 mg/m² days 1, 29, Vd 3 mg/m² days 1, 8, 29, 36, Mi 8 mg/m² days 1,29	Start on day 2: 28 Gy 14 f, 10 days of rest, 28 Gy, 14 f, RT started in 100% of patients	Induction CT: cisplatin 80 mg/m² days 1, 29, Vd 3 mg/m² days 1, 8, 29, 36, Mi 8 mg/m² days 1,29	Start after CT completion: 56 Gy, 28 f, RT started in 98% of patients
RTOG 9410[16]	1994-1998	407	38	6.4	Cisplatin 100 mg/m² days 1, 29, Vb 5 mg/m² weekly × 5 wk	Start on day 1, 60 Gy, RT started in 99% of patients	Induction CT: cisplatin 100 mg/m² days 1, 29, Vb 5 mg/m² weekly × 5 wk	Start on day 50: 60 Gy, RT started in 90% of patients
GMMA Ankara 1995[17]	1995-1996	30	0		Cisplatin 6 mg/m² daily	Start on day 1: 36 Gy 12 f, 7 days of rest, 12.5 Gy 5 f, RT started in 100% of patients	Induction CT: cisplatin 40 mg/m², Et 200 mg/m², If 200 mg/m² days 1, 3, 5, 29, 31, 33	Start 3 wk after CT completion: 36 Gy 12 f, 7 d rest, 12.5 Gy 5 f, RT started in 100% of patients
GLOT-GFPC NPC 95-01[18]	1996-2000	205	22	8.0	Cisplatin 20 mg/m² days 1-5, 29-33, Et 50 mg/m² days 1-5, 29-33; consolidation CT: cisplatin 80 mg/m² days 78, 106, Vn 30 mg/m²/wk days 78-127	Start on day 1: 66 Gy, 33 f, 6.5 wk, RT started in 94% of patients	Induction CT: cisplatin 120 mg/m² days 1, 29, 57, Vn 30 mg/m²/wk days 1-78	Start after CT completion: 66 Gy, 33 f, 6.5 wk, RT started 64% of patients
EORTC 08972[20]	1999-2003	158	29	4.2	Cisplatin 6 mg/m² daily	Start on day 1: 66 Gy, 24 f, 32 days, RT started in 85% of patients	Induction CT: cisplatin 75 mg/m² days 2, 23, gemcitabine 1,250 mg/m² days 1, 8, 22, 29	Start on day 50: 66 Gy, 24 f, 32 days, RT started in 97% of patients

Abbreviations: CALGB, Cancer and Leukemia Group B; Cb, carboplatin; wk, week; CT, chemotherapy; f, fraction; RT, radiotherapy; Vb, vinblastine; WJLCG, West Japan Lung Cancer Group; Vd, vindesine; Mi, mitomycin; RTOG, Radiotherapy Oncology Group; GMMA, Gülhane Military Medicine Academy; Et, etoposide; If, ifosfamide; GLOT-GFPC NPC, Groupe Lyon-Saint-Etienne d'Oncologie Thoracique–Groupe Français Non Petites Cellules; Vn, vinorelbine; EORTC, European Organisation for Research and Treatment of Cancer.

*Induction chemotherapy in both arms: cisplatin 100 mg/m² days 1 and 29, Vb 5 mg/m² days 1, 8, 15, 22, and 29.

Individual Patient Data

The following individual patient data were requested for all randomly assigned patients; sex, age, performance status at the time of random assignment, stage, histopathology, random assignment date, allocated treatment, and updated information on survival, local, and distant recurrence, cause of death, and acute toxicity (hematologic, esophageal, and pulmonary) graded using WHO and Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer criteria.[5,6]

Data were checked for missing values and for data validity and consistency across variables, and were also compared with published results if there were any. To assess randomization integrity, we looked for unusual patterns in the sequencing of allocation or imbalances in baseline characteristics between treatment arms. Follow-up of patients was also assessed to ensure that it was well balanced between treatment arms and as updated as possible. Any queries were resolved with the responsible trial investigator or statisticians.

Statistical Analysis

The main end point was overall survival, which was evaluated from the time of random assignment until death due to any cause. Living patients were censored at the date of last follow-up. Secondary end points were acute toxicity rates (hematologic, esophageal, and pulmonary), and progression-free survival which was defined as the time from randomization until first event (local or distant progression or death from any cause). As data concerning complete response to treatment were not requested, local control rates were not studied. To estimate the respective contribution of local progression and of distant progression in the progression-free survival, the cumulative incidences of these two types of events were calculated within a competing risk framework.[7,8]

All randomly assigned patients were included in the analyses according to the allocated treatment. Median follow-up was estimated with the use of the reverse Kaplan-Meier method.[9]

The statistical method for compiling the results and comparing the treatments of interest has been previously described.[10] Analyses were stratified by trials. The log-rank observed and expected number of events and associated variances were used to calculate individual trial and overall combined HRs and their 95% CI by the fixed-effects model. χ^2 heterogeneity tests were used to test for statistical heterogeneity among trials. We also calculated the I^2 statistic expressing the proportion of variability in the results attributable to heterogeneity rather than to the sampling error[11] with an I^2 value below 30% considered indicative of low heterogeneity. Survival curves were estimated for both treatment groups using annual death rates and HR.[12] These were used to calculate absolute differences in the survival rates at annual intervals.

Analyses by trial characteristics were performed to study whether the difference between concomitant and sequential radiochemotherapy could vary according to the type and dose of chemotherapy, and to whether induction or consolidation chemotherapy was used. Analyses by patient characteristics were performed studying the interaction between the treatment effect and the following characteristics: sex, age, performance status, stage, and histopathology. These analyses between groups of trials or subgroups of patients were determined a priori as described in the meta-analysis protocol, except for the number of administered drugs as a subsequent publication showed an effect of this factor.[13] All *P* values were two sided. All analyses have been performed using SAS software, version 9.1 (SAS Institute, Cary, NC).

RESULTS

Description of Trials

Eleven trials were identified,[14-22](two unpublished: Netherlands Cancer Institute M03IVC and Sequential or Concurrent Chemotherapy and Radiotherapy in NSCLC [SOCCAR]). Four trials were not eligible because of accrual time: three small trials[21,22](M03IVC), which randomized a total of 132 patients completed accrual in 2004 or 2005 and one completed accrual in 2009 (SOCCAR). The other seven trials[14-20] which randomly assigned 1,307 patients were eligible. However, as data from one trial[19] were not available, the analyses were based on 1,205 patients randomly assigned in six trials (92% of all randomly assigned patients).

Table 1 presents the trial characteristics. The median follow-up was 6 years and did not differ between the two arms.

Two trials[15,16] used the same chemotherapy regimen in both arms. In the sequential radiochemotherapy arm, induction chemotherapy was used in five trials and consolidation chemotherapy in one.[14] In this trial, patients in both arms received induction chemotherapy. All sequential regimens used cisplatin combined with one other drug in four trials, or with two drugs in two trials. Vinorelbine or gemcitabine were used in two trials. In the concomitant radiochemotherapy arm, cisplatin was used in five trials, either on a daily basis as single agent (two trials) or combined with other drugs every 4 weeks (three trials). Carboplatin administered weekly was used in only one trial.[14] One trial[18] used consolidation chemotherapy after concomitant chemoradiotherapy.

Most trials used a two-dimensional radiotherapy technique and total dose was 60 and 66 Gy in two trials each, and 56 and 48.5 Gy in one trial each. The European Organisation for the Research and Treatment of Cancer (EORTC) trial[20] used a dose of 66 Gy delivered with a three-dimensional conformal technique. In one trial,[15] the radiotherapy protocol was slightly different in the two arms—there was a 10 days split in the concomitant arm. In another trial,[16] radiotherapy was delivered in split course in both arms. In the five trials[15-20] using induction chemotherapy in the sequential arm, patients randomly

Table 2. Patient Characteristics

Characteristic	Concomitant Arm (n = 603) No.	%	Sequential Arm (n = 602) No.	%
Male sex	457	76	464	77
Median age, years	61.0		62.4	
Range	33-79		33-82	
< 60	273	45	246	41
60-64	114	19	111	18
65-69	140	23	130	22
≥ 70	76	13	113	19
Unknown	0		2	
Performance status				
0	309	52	297	50
1	278	46	293	49
2	13	2	9	1
Unknown	3		3	
Histology				
Squamous carcinoma	282	47	267	44
Adenocarcinoma	198	33	197	33
Other	121	20	135	23
Unknown	2		3	
Stage				
I	3	0.5	3	0.5
II	5	0.8	7	1
IIIA	221	37	220	37
IIIB	369	61.5	366	61
IV	1	0.2	2	0.5
Unknown	4		4	

NOTE. Percentages were calculated on known values.

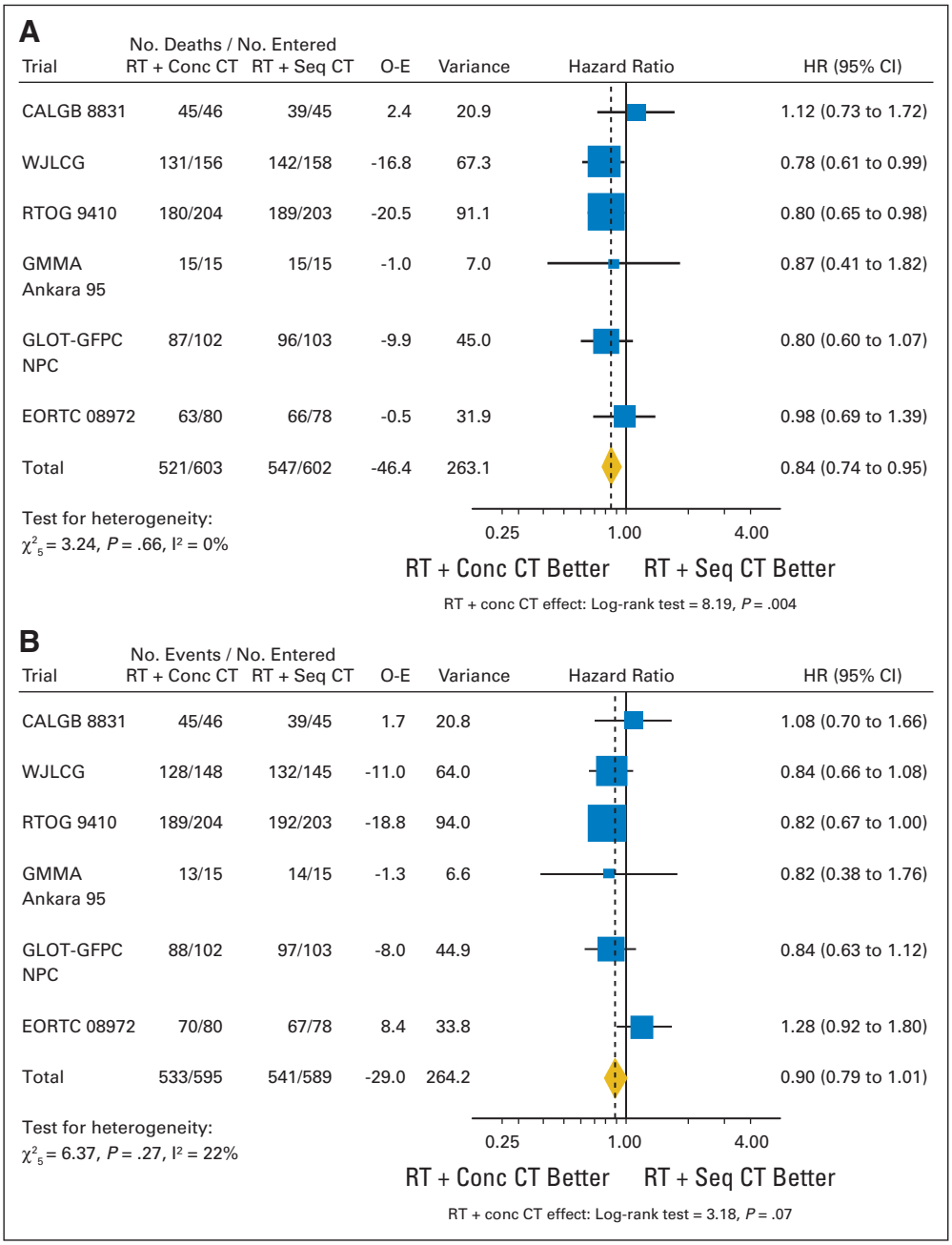

Fig 1. (A) Hazard ratio (HR) plots for survival, (B) progression-free survival, (C) local progression and (D) distant progression. The center of each square represents the HR for individual trial and each horizontal line its 95% CI; the area of the square is proportional to the amount of information from the trial. The center of the diamond represents the pooled HR and its extremities its 95% CI. RT, radiation therapy; Conc, concurrent; CT, chemotherapy; Seq, sequential; O-E, observed-expected; CALGB, Cancer and Leukemia Group B; WJLCG, West Japan Lung Cancer Group; RTOG, Radiation Therapy Oncology Group; GMMA, Gülhane Military Medicine Academy; GLOT-GFPC NPC, Groupe Lyon-Saint-Etienne d'Oncologie Thoracique–Groupe Français de Pneumo-Cancérologie NPC; EORTC, European Organisation for the Research and Treatment of Cancer.

assigned to concomitant arm received radiotherapy more frequently than those randomly assigned to the sequential arm, except in the EORTC trial.[20]

There were no significant differences between the two treatment arms concerning patient characteristics (Table 2).

Survival

The survival analysis was based on six trials, 1,205 patients, and 1,068 deaths. There was a significant benefit of concomitant radiochemotherapy as compared with sequential radiochemotherapy (HR, 0.84; 95% CI, 0.74 to 0.95; $P = .004$; Fig 1A), with an absolute survival benefit of 5.7% at 3 years, increasing survival from 18.1% in the sequential arm to 23.8% in the concomitant arm and an absolute benefit of 4.5% at 5 years, from 10.6% to 15.1% (Fig 2A). There was no evidence of important statistical heterogeneity with an I^2 value of 0% (χ^2 test for heterogeneity $P = .66$).

Progression-Free Survival

The progression-free survival analysis was based on six trials, 1,184 patients, and 1,074 events. The HR was 0.90 (95% CI, 0.79 to 1.01; $P = .07$; Fig 1B), with an absolute benefit of 2.9% at 3 years, increasing progression-free survival from 13.1% with sequential radiochemotherapy to 16.0% with concomitant radiochemotherapy and an absolute benefit of 2.2% at 5 years, from 9.4% to 11.6% (Fig 2B). There was no evidence of important statistical heterogeneity with an I^2 value of 22% (χ^2 test for heterogeneity $P = .27$).

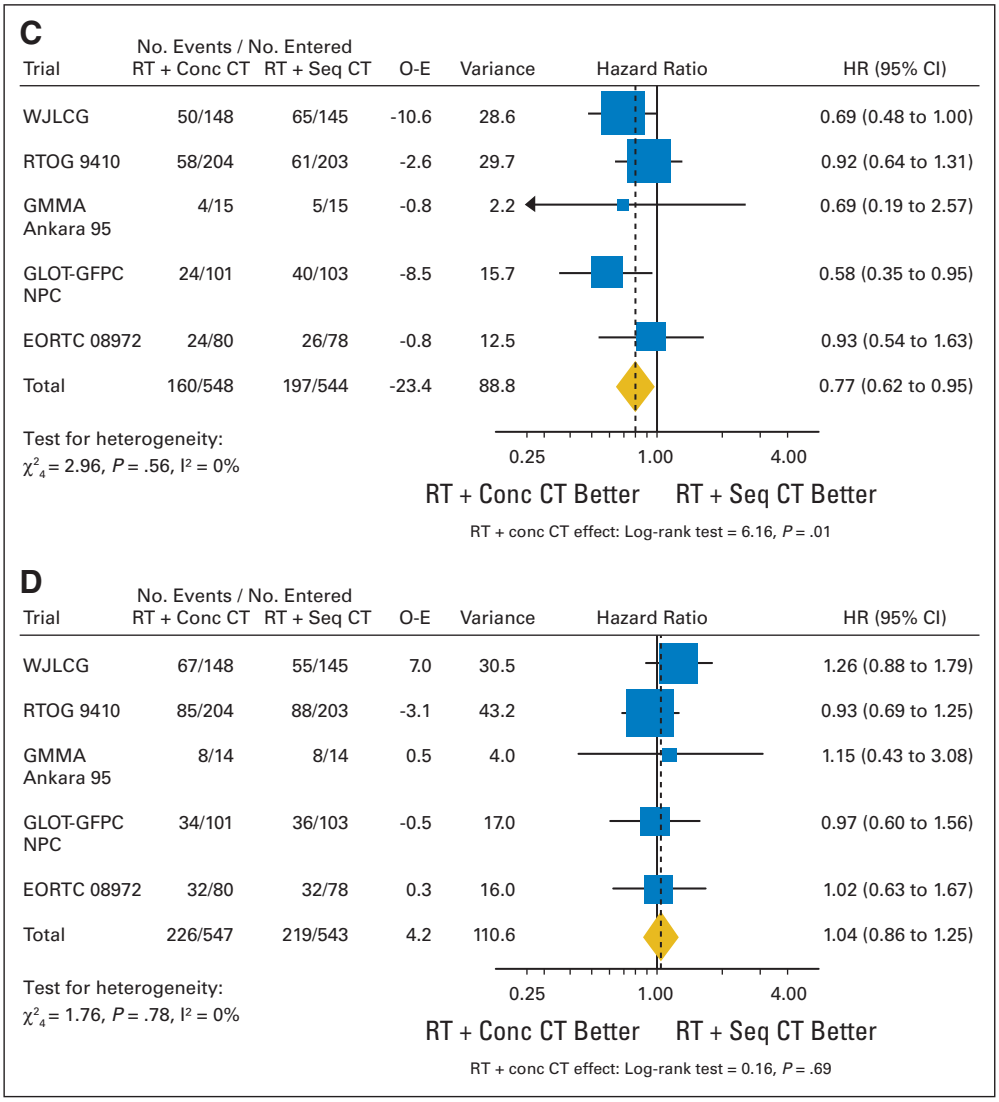

Fig 1. Continued.

Locoregional and Distant Progressions

Locoregional and distant progression analyses were based on five trials, and 1,092 and 1,090 patients, respectively. Concomitant radiochemotherapy had a significant effect on locoregional progression as shown in Figure 1C (HR, 0.77; 95% CI, 0.62 to 0.95; $P = .01$), with an absolute decrease of 6.0% at 3 years, decreasing locoregional progression rate from 34.1% with sequential radiochemotherapy to 28.1% with concomitant radiochemotherapy and an absolute decrease of 6.1% at 5 years, from 35.0% to 28.9%. There was no difference between the two treatments concerning distant progression (HR, 1.04; 95% CI, 0.86 to 1.25; $P = .69$) with 3-year rates of 39.5 and 39.1% and 5-year rates of 40.6% and 39.5% in concomitant and sequential combinations respectively (Fig 1D).

Analyses by Trial and Patient Characteristics

There was no difference in either overall survival or progression-free survival according to whether the same chemotherapy was used in both arms, or if different chemotherapies were used (Figs 3A, 3B). There was also no evidence of a difference in effect according to whether induction or consolidation chemotherapy was used in the sequential arm. However, the number of patients with consolidation chemotherapy was very low. Concomitant polychemotherapy (doublet or triplet) appeared to improve progression-free survival more than concomitant single-agent chemotherapy (HR, 0.83 [95% CI, 0.72 to 0.95] *v* 1.15 [95% CI, 0.90 to 1.48] $P = .02$). However, this result was not found for overall survival nor for locoregional progression and therefore should be interpreted cautiously.

There was no clear evidence that any subgroup of patients defined by age, sex, performance status, histology, or stage benefited more or less from concomitant radiochemotherapy in terms of overall or progression-free survival (Figs 3C, 3D). Thus, the advantage of concomitant chemotherapy was observed also in patients older than 70 years.

Toxicity

Data were available for 1,077 patients (89%) for acute esophageal toxicity, 1,088 patients (90%) for acute pulmonary toxicity, and 1,098 patients (91%) for hematologic toxicity. Concomitant radiochemotherapy significantly increased acute grade 3 to 4 esophageal toxicity as compared with sequential radiochemotherapy, from 4% to 18% with

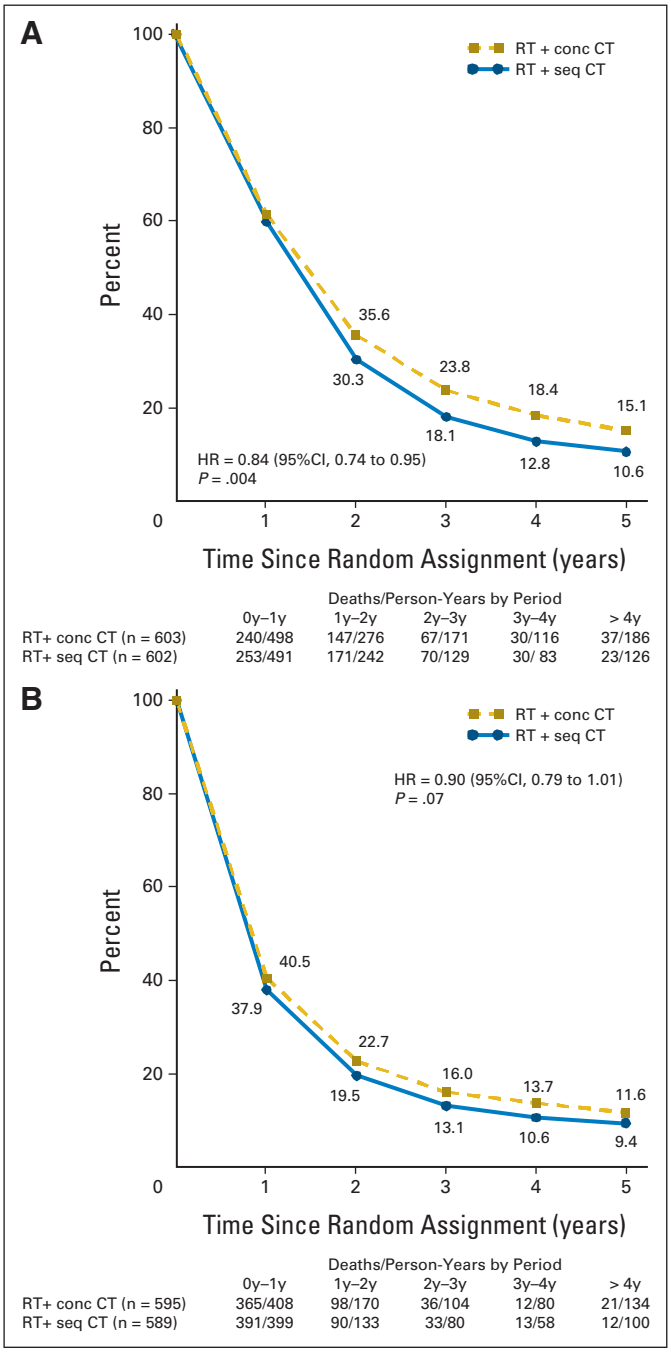

Fig 2. (A) Survival curves and (B) progression-free survival curves. The numbers of person-years and of deaths observed each year during the first 4 years and after are given. RT, radiation therapy; HR, hazard ratio; conc, concurrent; CT, chemotherapy; seq, sequential.

a relative risk of 4.9 (95% CI, 3.1 to 7.8; $P < .001$). There was no significant difference between concomitant and sequential combination for acute grade 3 to 4 pulmonary toxicity (relative risk, 0.69; 95% CI, 0.42 to 1.12; $P = .13$). The reported grade 3 to 4 hematologic toxicity rates were highly variable across trials, from fewer than 20% to more than 90%, as the type of chemotherapy and the timing of control blood counts were different among trials. Thus, it was impossible to pool the data.

We were unable to analyze esophageal and pulmonary late toxicity owing to sparse data because these data were rarely available in the trials.

DISCUSSION

This meta-analysis based on individual patient data provided by six randomized trials comparing concomitant and sequential radiochemotherapy in 1,205 patients with locally advanced NSCLC showed that concomitant combination resulted in a significant 16% relative reduction in mortality, corresponding to a 5.7% absolute benefit in overall survival at 3 years and a 4.5% absolute benefit at 5 years, and to survival rate of 18.4% at 3 years and of 15.1% at 5 years. The survival improvement is likely to be due to a decrease of locoregional failures as there was no difference between the two treatment options in distant failure rates. Similar results were found in head and neck cancers.[23] We found no difference in the effect of concomitant radiochemotherapy according to patients' characteristics or to the type of chemotherapy used. Although doublet or triplet concomitant chemotherapy regimen had significantly more impact on progression-free survival than single agents, this difference was not observed for overall survival nor locoregional failures.

These results clearly support the use of concomitant radiochemotherapy, and represent much more robust data than conclusions drawn from an indirect comparison of two previous meta-analyses, comparing sequential radiochemotherapy[2] and platin-based concomitant radiochemotherapy[3] to radiotherapy alone. These meta-analyses showed both types of combinations to have a very similar relative benefit on survival as compared to radiotherapy alone with HRs of 0.88 and 0.89 respectively. Most trials included in the meta-analysis of concomitant radiochemotherapy versus radiotherapy alone[3] used single agents, carboplatin or cisplatin, at radiosensitizing doses, whereas the current meta-analysis included several trials using full-dose platin-based concomitant chemotherapy.[24-26]

It is important to note that this type of treatment is generally proposed for selected, fit patients with minimal comorbidities. The percentage of patients with good performance status (WHO 0) increased from 40% in the meta-analysis of sequential radiochemotherapy to 45% in the meta-analysis of concomitant radiochemotherapy and to 50% in the current meta-analysis. Concomitant radiochemotherapy with daily low-dose cisplatin could be an option for more frail patients, as the profile for hematologic and cardiac toxicity appeared to be favorable in the EORTC trial.[20] Sequential radiochemotherapy may also remain a good alternative treatment.

It is commonly thought that sequential combinations would improve survival because of a decrease of distant metastases rate[27] whereas concomitant combinations with chemotherapy given at radiosensitizing doses would improve survival because of an increased local control rate. Thus, the decrease of locoregional failure observed with concomitant combinations in the current meta-analysis could be related to the well known radiosensitizing effect of cisplatin-based chemotherapy and the absence of difference in the distant progression could be due to the use of full-dose chemotherapy in both treatment arms.

In the trials included in this meta-analysis, the staging work-up was not up to current standards. Most of patients were not staged with positron emission tomography scan and brain magnetic resonance

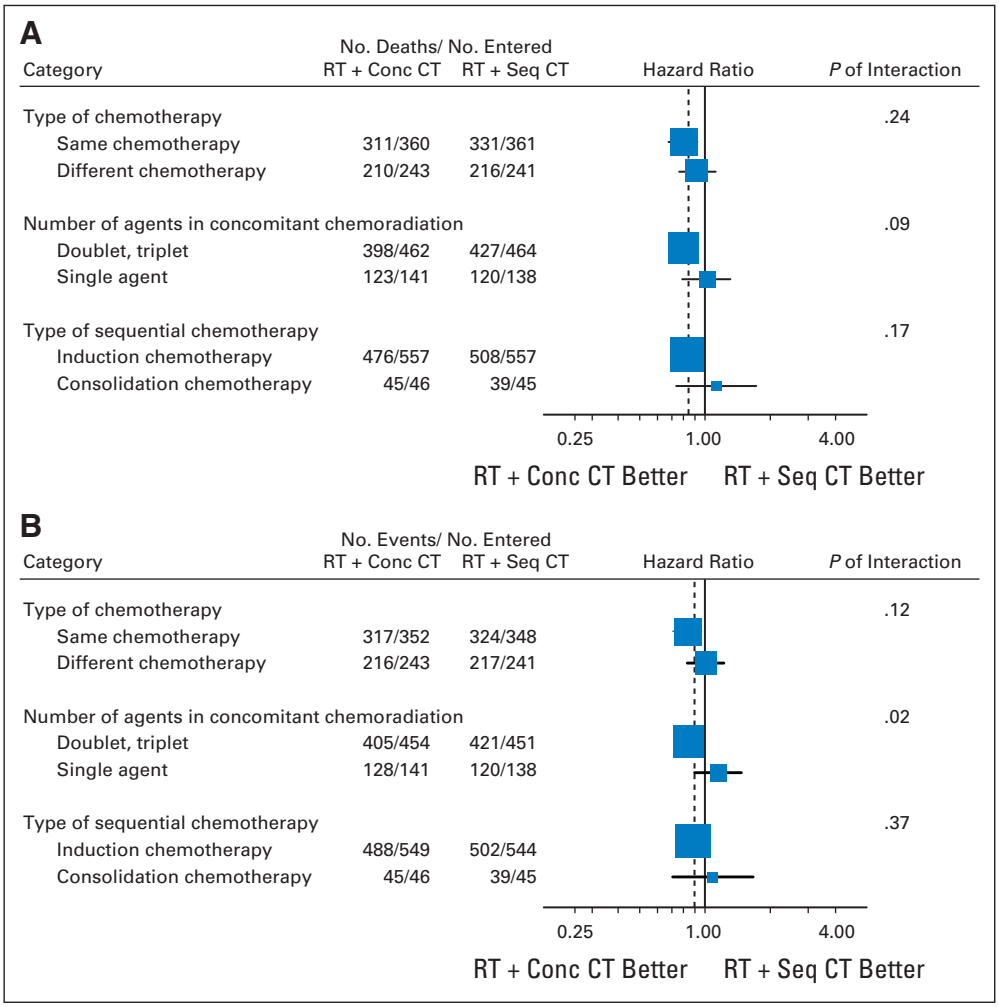

Fig 3. Hazard ratio plots according to (A) the type of chemotherapy for survival and (B) progression-free survival and according to (C) the patient characteristics for survival and (D) progression-free survival. RT, radiation therapy; Conc, concurrent; CT, chemotherapy; Seq, sequential. (*) Trend test.

imaging. In these patients the improved survival can be attributed to decreased local failures. As approximately 10% to 30% of patients with nonmetastatic NSCLC as determined by conventional imaging may be found to have distant metastases with more modern diagnostic tools,[28,29] we can hypothesize that in the future, in better staged patients with no detected metastasis, local control may have even more impact on survival. In contrast, in case of suspected mediastinal involvement on imaging exams, pathologic confirmation was not required routinely in these trials, so that some patients may have been upstaged in these trials. In these patients, local control may have a greater impact in determining prognosis.

If we consider sequential radiochemotherapy, five[15-18,20] of the six trials used induction chemotherapy. El Sharouni et al[30] showed that the interval between the end of induction chemotherapy and the start of radiotherapy may allow rapid tumor progression. This time interval was not available in the meta-analysis, but it should be emphasized that the percentage of patients who did not receive any radiation treatment after induction chemotherapy was higher than in the concomitant arm (10% *v* 4%), which is detrimental for tumor control.

As expected, there was an increase of acute esophageal toxicity in the concomitant as compared with the sequential combination arm. However, this rate was relatively low (lower than 20%) and clinically manageable. There was no significant difference in terms of acute pulmonary toxicity.

Considering the survival benefit of more than 5% at 3 years, concomitant radiochemotherapy should now be the reference treatment for locally advanced NSCLC. Systematic integration of three-dimensional conformal radiotherapy in concomitant combinations will probably contribute to improve results. Elective nodal irradiation (ie, delivering radiotherapy to involved nodes but also to uninvolved elective regional lymph nodes [ipsilateral hilar, mediastinal and occasionally, supraclavicular or contralateral hilar areas]) was systematic in most of the trials included in this meta-analysis. As failure in the nodal elective areas does not exceed 10%, elective nodal irradiation is not routine clinical practice and depends on the staging examinations performed.[31,32] Because of the use of conformal radiotherapy covering only tumor and involved nodes, esophageal toxicity has decreased considerably in recent trials.[33] The implementation of better nodal staging techniques such as functional imaging ([18F]fluorodeoxyglucose positron emission tomography) in radiotherapy treatment planning now allows us to deliver higher doses to anatomically and biologically defined target volumes, while better sparing normal tissues. Increased radiation doses administered concomitantly to chemotherapy may result in better local control and survival, and this is being explored in ongoing trials such as the randomized trial led by the

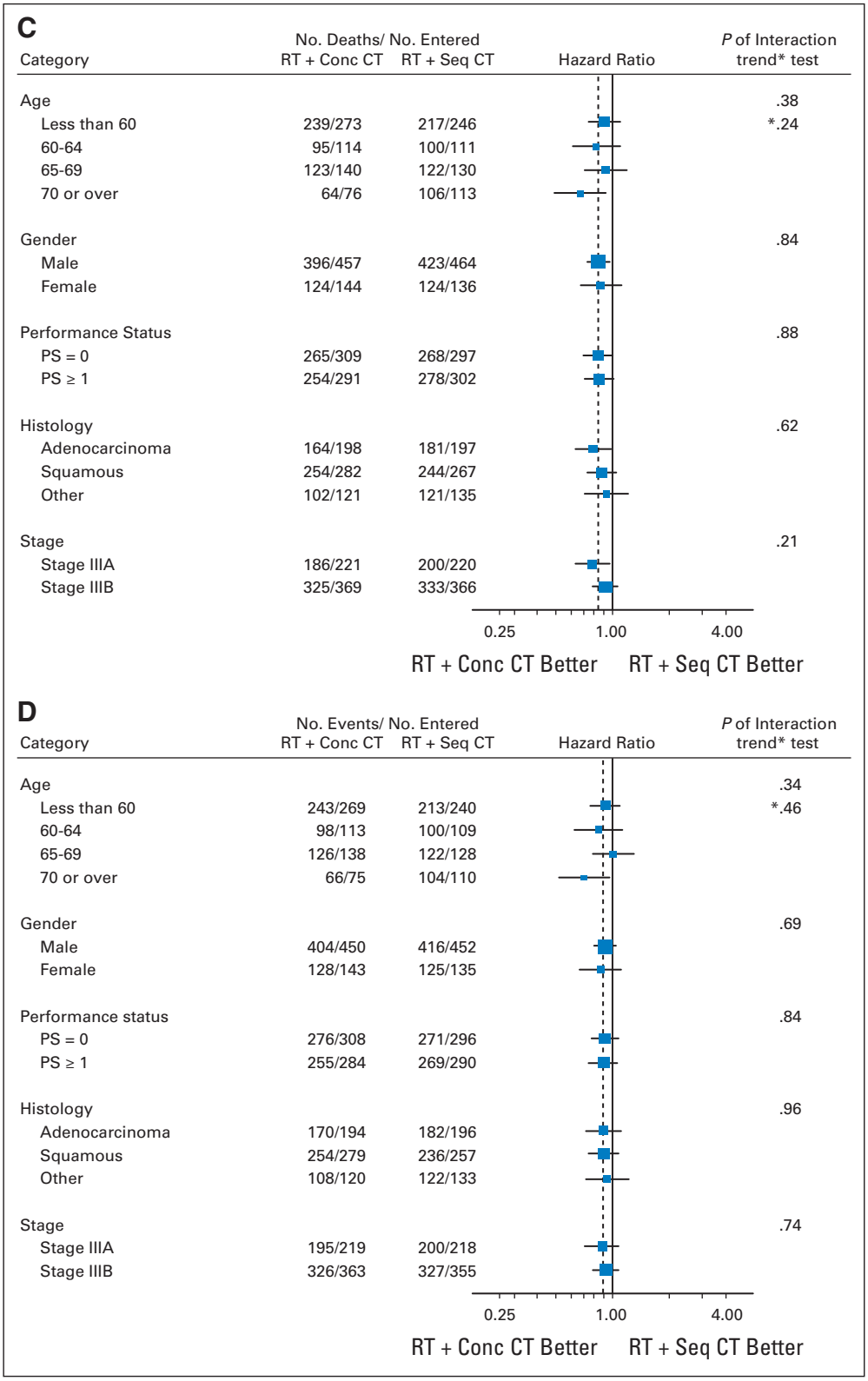

Fig 3. Continued.

Radiation Therapy Oncology Group (RTOG 0617). Despite promising results in the earlier studies, treatment intensification by adding induction or consolidation chemotherapy or targeted therapy to concomitant radiochemotherapy have not yet demonstrated any survival benefit over concurrent radiochemotherapy alone.[26,34-36] Identification of new cytotoxic or targeted agents that can be combined concomitantly to radiotherapy with more efficacy and less toxicity is warranted.[37-39] However, intensification of both radiotherapy

and concurrent chemotherapy may result also into excessive toxicity or incomplete treatment.[40,41] One of the future challenges is to tailor combination treatments, taking into consideration the tumor and toxicity profile, as well as functional imaging and image-guided radiotherapy.

In conclusion, concomitant radiochemotherapy, as compared with sequential radiochemotherapy, improved the overall survival of patients with locally advanced NSCLC, primarily because of decreased locoregional progression, at the cost of manageable increased acute esophageal toxicity. Concomitant radiochemotherapy should be considered as the reference treatment for future trials testing new combined treatment approaches integrating the recent developments in three-dimensional conformal radiotherapy.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(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.

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AUTHOR CONTRIBUTIONS

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