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review

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Impact of thoracic radiotherapy timing in limited-stage small-cell lung cancer: usefulness of the individual patient data meta-analysis†

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Background: Chemotherapy (CT) combined with radiotherapy is the standard treatment of 'limited-stage' small-cell lung cancer. However, controversy persists over the optimal timing of thoracic radiotherapy and CT.

Materials and methods: We carried out a meta-analysis of individual patient data in randomized trials comparing earlier versus later radiotherapy, or shorter versus longer radiotherapy duration, as defined in each trial. We combined the results from trials using the stratified log-rank test to calculate pooled hazard ratios (HRs). The primary outcome was overall survival.

Results: Twelve trials with 2668 patients were eligible. Data from nine trials comprising 2305 patients were available for analysis. The median follow-up was 10 years. When all trials were analysed together, 'earlier or shorter' versus 'later or longer' thoracic radiotherapy did not affect overall survival. However, the HR for overall survival was significantly in favour of 'earlier or shorter' radiotherapy among trials with a similar proportion of patients who were compliant with CT (defined as having received 100% or more of the planned CT cycles) in both arms (HR 0.79, 95% CI 0.69–0.91), and in favour of 'later or longer' radiotherapy among trials with different rates of CT compliance (HR 1.19, 1.05–1.34, interaction test, $P < 0.0001$). The absolute gain between 'earlier or shorter' versus 'later or longer' thoracic radiotherapy in 5-year overall survival for similar and for different CT compliance trials was 7.7% (95% CI 2.6–12.8%) and –2.2% (–5.8% to 1.4%), respectively. However, 'earlier or shorter' thoracic radiotherapy was associated with a higher incidence of severe acute oesophagitis than 'later or longer' radiotherapy.

Conclusion: 'Earlier or shorter' delivery of thoracic radiotherapy with planned CT significantly improves 5-year overall survival at the expense of more acute toxicity, especially oesophagitis.

Key words: individual participant data meta-analysis, randomized clinical trials, thoracic radiotherapy, radiotherapy timing, small-cell lung cancer, chemotherapy compliance

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§See Appendix.

introduction

Small-cell lung cancer (SCLC) is a rapidly disseminating cancer so that its primary treatment is chemotherapy (CT), whatever the stage [1]. Approximately 25% of patients present with localized disease, formerly known as 'limited-stage' disease, now called stage

I–IIIB [2]. It is well known that optimal survival is achieved when CT can be administered at the total intended dose and at the required intervals [1, 3]. Nevertheless, due to loco-regional failures after CT alone, the adjunction of thoracic radiotherapy was investigated. A worldwide meta-analysis showed that adding thoracic radiotherapy to CT improved long-term survival [4]. Concurrent use of CT, comprising cisplatin and etoposide, and thoracic radiotherapy has become the standard of care [1, 5, 6]. In non-progressing patients, this can be followed by prophylactic cranial irradiation, at the optimal dose of 25 Gy, as this treatment further prolongs survival [7, 8].

However, the optimal timing and sequencing of thoracic radiotherapy with CT has fuelled debate for many years. When all trials were pooled together, no survival gain was detected whether thoracic radiotherapy was delivered early with CT or later [9–12]. However, in trials where patients were treated with cisplatin-based CT at full dose, early administration of thoracic radiotherapy seemed to confer a long-term survival advantage. There is considerable variation in the definition of early or late radiotherapy: early radiotherapy was defined as starting before 9 weeks following the beginning of CT and before the third cycle of CT in two previous literature-based meta-analyses [12, 13], whereas a 30-day cut-off was used in other literature-based meta-analyses [9–11, 14] (supplementary Table S1, available at *Annals of Oncology* online for description of previous meta-analyses). One of these meta-analyses suggested that early delivery of thoracic radiotherapy yielded higher survival rates if all the intended cycles of CT could be administered [12], implying that the question of optimal radiotherapy timing and fractionation [15, 16] could only be addressed with precise information on individual patient compliance with CT administration. Such information can only be provided by an individual patient data (IPD) meta-analysis. We therefore undertook such a study, aiming at defining the best approach for combining thoracic radiotherapy with CT in stage I–IIIB SCLC.

materials and methods

The meta-analysis was carried out according to a pre-specified protocol that is available on the Gustave Roussy website (http://www.gustaveroussy.fr/sites/default/files/meta-analyses-protocol-rtt-sclc.pdf).

selection criteria and search strategy

To be eligible, trials had to compare two timing schedules of curative thoracic radiotherapy, i.e. earlier versus later within an individual trial in patients with limited-stage SCLC treated with chemo-radiotherapy. Our post hoc criterion to define early radiotherapy was similar to the one used by Fried et al. [13] and Spiro et al. [12]: radiotherapy should have been initiated before 9 weeks after randomization and before the third cycle of CT. Trials comparing two radiotherapy durations, i.e. a shorter versus a longer course within an individual trial with at least a two-week treatment difference observed between the two arms, were also eligible. In this article, we will use the term 'earlier or shorter' for arms where earlier and/or shorter radiotherapy was used and the term 'later or longer' for later and/or longer radiotherapy arms. Trials had to start after 1969 and to end before 2006 and be properly randomized. The planned CT schedule (drugs, doses, number of cycles) had to be the same in both arms, but radiotherapy modalities could be different. The total dose of radiotherapy had to be at least 30 Gy. Orthovoltage radiotherapy was an exclusion criterion. Eligible patients should have had a WHO (or equivalent) performance status of 0–2 and should not have received previous treatment of this cancer. To limit publication bias, we searched for both published and unpublished trials without language restriction (see supplementary Appendix S1, available at *Annals of Oncology* online for search strategy).

statistical analysis

We describe IPD collection and quality control in supplementary Appendix S2, available at *Annals of Oncology* online. The main end point was overall survival, and the secondary end points were progression-free survival and severe acute toxicities. Overall survival was defined as the time from randomization until death from any cause or the last follow-up for surviving patients. Progression-free survival was defined as the time from randomization until first progression or death from any cause, or the last follow-up for surviving patients without progression. We did not perform analyses on loco-regional control, cancer deaths and late toxicities due to lack of data. The median follow-up was estimated using the reverse Kaplan–Meier method [17].

We carried out all analyses on an intention-to-treat basis. Survival analyses were stratified by trial, and the log-rank expected number of deaths and variance were used to calculate individual and overall pooled hazard ratios (HRs) by the fixed-effect model [15]. A similar model was used to estimate odds ratios (ORs) for the comparison of toxicity between arms. χ^2 tests and the I^2 statistic were used to study heterogeneity between trials [18]. HRs were calculated using a DerSimonian–Laird random-effects model if heterogeneity had a P-value of <0.10 [19]. Stratified survival curves were estimated for control and experimental groups, using annual death rates and the pooled HR, and were used to estimate the absolute benefit at 3 and 5 years with their 95% CIs [20]. Five-year mean survival times, parameters commonly used in economic evaluation, were also estimated (supplementary Appendix S3, available at *Annals of Oncology* online) [21–23].

Subset analyses according to trial characteristics were preplanned. We investigated whether the treatment effect was dependent on any difference in the proportion of patients who were compliant with CT between the treatment arms within each trial. A patient was defined as compliant if he/she received 100% or more of the planned number of CT cycles, except for the CALGB8083 trial in which patients receiving six CT cycles or more were considered to be compliant. A trial was considered to be having different 'between-arm' compliance if the difference was ≥10% and to be having similar 'between-arm' compliance if it was <10% [12]. No other information on CT administration, such as the actual drug dose received or delays in CT administration, was available. χ^2 tests for interaction or trend were used to assess treatment effects across trial subsets. Overall heterogeneity was decomposed into the sum of between-subset and residual (within-subset) heterogeneity: the lower the residual heterogeneity, the greater the overall heterogeneity of the treatment effect between trials was explained by the trial characteristic [24]. χ^2 tests for interaction or trend were also used to test whether there was any evidence that a particular type of patient benefited

more or less from 'earlier or shorter' radiotherapy according to predefined subgroups. If there was substantial overall heterogeneity, then subgroup analyses were planned within treatment categories. All *P*-values were two-sided. Analyses were carried out using SAS version 9.3.

role of the funding source

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results

Twelve randomized trials [12, 16, 25–34] including 2668 patients were eligible. Data on nine trials and 2305 patients (86% of potentially eligible patients) were available for this IPD meta-analysis (supplementary Figure S1, available at *Annals of Oncology* online). Data from one trial were lost [32], and we did not succeed in contacting the investigator of two other trials [33, 34]. Table 1 depicts the nine trials included [12, 16, 25–31] and supplementary Table S2, available at *Annals of Oncology* online summarizes the trials with no available data. Four trials [16, 27, 30, 31] had different radiotherapy modalities between the two arms, including three trials [16, 30, 31] comparing shorter versus longer radiotherapy duration. Central randomization was used in all trials, except one that used sealed envelopes [25]. In total, out of the 80 patients initially excluded from the individual trial analyses, data concerning 75 patients were recovered. The median follow-up was 10 years without any difference between the treatment arms. Patient characteristics were well balanced between the two arms of the analysis (supplementary Table S3, available at *Annals of Oncology* online). Three trials [16, 26, 28] were categorized as having similar CT compliance in both arms, and they had a proportion of at least 79% of patients who were compliant with CT (i.e. receiving all their cycles) (supplementary Table S4, available at *Annals of Oncology* online). Five trials [12, 25, 27, 29, 31] had different CT compliance, with all of them exhibiting a lower compliance rate in the 'earlier or shorter' arm. For the CCWFU62286 trial, we had no data available on individual CT compliance neither in the patient-level data provided by the investigator nor in the publication [30]: the CCWFU62286 trial was thus excluded from the trial subset analysis based on CT compliance. In the 'later or longer' arm, 88% of patients started radiotherapy when compared with 93% in the 'earlier or shorter' arm (supplementary Table S5, available at *Annals of Oncology* online). Among the five trials [12, 25, 26, 27, 29] comparing earlier and later radiotherapy with individual data on radiotherapy compliance, the observed difference in median times between the two arms from randomization to the start of radiotherapy ranged from 63 to 93 days compared with 56 to 84 days for the planned difference (supplementary Table S6, available at *Annals of Oncology* online). There was also a significant association between individual RT compliance and CT compliance (Cochran–Mantel–Haenszel test stratified by trial: $P < 0.0001$). The more a patient was compliant with CT (i.e. receiving all their cycles), the more he/she was compliant with RT (i.e. receiving 90% of the total RT dose).

overall survival and progression-free survival

In our main analysis, when all trials were pooled together, 'earlier or shorter' radiotherapy did not have a significant impact on overall survival compared with 'later or longer' radiotherapy (HR 0.99, 95% CI 0.91–1.08, $P = 0.78$) (supplementary Figure S2, available at *Annals of Oncology* online). Treatment effect heterogeneity was observed ($P = 0.006$, $I^2 = 63\%$). With a random-effects model, the HR was not significant (0.99, 0.85–1.15, $P = 0.90$).

Data on tumour progression were not available for two trials [27, 31], thus the progression-free survival analysis concerned only seven trials comprising 1764 patients and 1596 events. There was no significant impact of radiotherapy timing on progression-free survival (HR 0.93, 95% CI 0.84–1.02, $P = 0.13$) (supplementary Figure S3, available at *Annals of Oncology* online).

trial subsets

Table 2 shows the HRs for overall survival according to the different preplanned subsets analyses, described in supplementary Table S7, available at *Annals of Oncology* online, with overall between-trial heterogeneity decomposed into the sum of between-subset and residual (within-subset) heterogeneity. Trial subsets were in decreasing order of residual heterogeneity: the lower the residual heterogeneity for one trial subset, the greater the studied characteristic (CT compliance, RT dose per fraction, etc.) explained overall heterogeneity. In Table 2, between-subset heterogeneity was associated with an interaction test between the treatment received ('earlier or shorter' RT versus 'later or longer' RT) and the studied characteristic of the subset, and also with a trend test when the studied subset categories were ordinal (RT dose per fraction and RT overall treatment time). Five trial characteristics were found to be associated with an improvement in overall survival with 'earlier or shorter' radiotherapy (Table 2): similar CT compliance in both arms, a dose per fraction lower than 1.8 Gy, hyperfractionated radiotherapy, overall treatment time of less than 30 days and platin-based CT. It should be emphasized that trials using hyperfractionated radiotherapy delivered fractions of less than 1.8 Gy, and the overall treatment time was less than 30 days.

The 'between-arm' CT compliance (number of cycles actually given) is the factor that best explained between-trial heterogeneity, i.e. with the lowest residual heterogeneity (Table 2).

CT compliance and overall survival

The HR for overall survival was significantly in favour of 'earlier or shorter' radiotherapy among trials in which the defined CT compliance was similar in both arms (Figure 1; HR 0.79, 95% CI 0.69–0.91) and in favour of 'later or longer' radiotherapy among trials with different CT compliance: (1.19, 1.05–1.34). There was a significant interaction between CT compliance and the treatment effect (interaction test, $P < 0.0001$). In trials with similar CT compliance in both arms, 'earlier or shorter' radiotherapy compared with 'later or longer' radiotherapy increased the absolute 3-year and 5-year overall survival rate by 5.7% (from 24.4% to 30.1%) and by 7.7% (from 16.5% to 24.2%), respectively (Figure 2). In trials with different CT compliance, 'earlier or shorter' radiotherapy decreased the absolute 3-year and 5-year overall survival rate, respectively, by 3.8% (from 16.1% to 12.3%) and 2.2% (from 10.5% to 8.3%) (Figure 2). In other words, 'earlier or shorter' radiotherapy extended the 5-year mean survival time by 4.2 months (95% CI 1.8–6.7) from 24.7 to

Table 1. Description of trials

Trials	Inclusion period	Start of thoracic radiation (day)	RT dose (Gy)/fraction/ duration (weeks)	CT (mg/m^2)	Number of CT cycles (before RT, during RT, after RT)	Number of patients randomized[$a]	Median follow-up (years)
Earlier versus later radiotherapy							
CALGB8083 [25]	1981–84	EoS: Day 1 LoL: Day 64	50 Gy/24 fr/5 weeks	C: 1000 mg/m^2, every 3 weeks V: 1.4 mg/m^2, every 3 weeks E: 80 × 3 mg/m^2 every 3 weeks Starting at cycle 7 for odd-numbered cycles: C: 1000 mg/m^2, every 3 weeks V: 1.4 mg/m^2, every 3 weeks A: 50 mg/m^2, every 3 weeks	About 26 cycles EoS: 2 cycles during RT, up to 24 cycles after RT LoL: 3 cycles before RT, 2 cycles during RT, up to 21 cycles after RT	292	17.2
BR.6 [26]	1985–88	EoS: Day 22 LoL: Day 106	40 Gy/15 fr/3 weeks	EoS: P: 25 mg/m^2 × 3 days, $weeks_{4,11,17}$ E: 100 mg/m^2 × 3 days, $weeks_{4,11,17}$ alternating with C: 1000 mg/m^2, $weeks_{1,8,14}$ A: 50 mg/m^2, $weeks_{1,8,14}$ V: 2 mg, $weeks_{1,8,14}$ LoL: P: 25 mg/m^2 × 3 days, $weeks_{4,10,16}$ E: 100 mg/m^2 × 3 days, $weeks_{4,10,16}$ alternating with C: 1000 mg/m^2, $weeks_{1,7,13}$ A: 50 mg/m^2, $weeks_{1,7,13}$ V: 2 mg, $weeks_{1,7,13}$	EoS: 6 cycles (1 before RT, 1 during RT, 4 after RT) LoL: 6 cycles (5 before RT, 1 during RT)	332	11.2
EORTC08877 [27]	1989–95	EoS: Day 43 LoL: Day 99	EoS: 12.5 Gy/5 fr/1 week + break 3 weeks + 12.5 Gy/5 fr/1 week + break 3 weeks + 12.5 Gy/5 fr/1 week + break 3 weeks + 12.5 Gy/5 fr/1 week LoL: 50 Gy/20 fr/4 weeks	EoS: C: 1000 mg/m^2, $weeks_{1,5,9,13,17}$ A: 45 mg/m^2 $weeks_{1,5,9,13,17}$ E: 100 × 3 mg/m^2 $weeks_{1,5,9,13,17}$ LoL: C: 1000 mg/m^2 $weeks_{1,4,7,10,13}$ A: 45 mg/m^2 $weeks_{1,4,7,10,13}$ E: 100 × 3 mg/m^2, $weeks_{1,4,7,10,13}$	EoS: 5 cycles (1 before RT, 4 alternating with RT[b]) LoL: 5 cycles (5 before RT)	349	7.2
JCOG9104 [28]	1991–95	EoS: Day 2 LoL: Day 85	45 Gy/30 fr/3 weeks bid	EoS: P: 80 mg/m^2, $weeks_{1,5,9,13}$ E: 100 × 3 mg/m^2, $weeks_{1,5,9,13}$ LoL: P: 80 mg/m^2, $weeks_{1,4,7,10}$ E: 100 × 3 mg/m^2, $weeks_{1,4,7,10}$	EoS: 4 cycles (1 during RT, 3 after RT) LoL: 4 cycles (4 before RT)	231	6.8
LLCG93 [12]	1993–99	EoS: Day 22 LoL: Day 106	40 Gy/15 fr/3 weeks	P: 25 × 3 mg:m^2, $weeks_{4,10,16}$ E: 100 × 3 mg/m^2, $weeks_{4,10,16}$ alternating with C: 1000 mg/m^2, $weeks_{1,7,13}$ A: 50 mg/m^2, $weeks_{1,7,13}$ V: 2 mg, $weeks_{1,7,13}$	EoS: 6 cycles (1 before RT, 1 during RT, 4 after RT) LoL: 6 cycles (5 before RT, 1 during RT)	325	5.3
HeCOG93 [29]	1993–99	EoS: Day 1 LoL: Day 57	45 Gy/30 fr/3 weeks bid	Cb: 6 AUC, $weeks_{1,4,7,10,13,16}$ E: 100 × 3 mg/m^2, $weeks_{1,4,7,10,13,16}$	EoS: 6 cycles (1 during RT, 5 after RT) LoL: 6 cycles (3 before RT, 1 during RT, 2 after RT)	81	11.8

Trials	Inclusion period	Start of thoracic radiation (day)	RT dose (Gy)/ fraction/ duration (weeks)	CT (mg/m^2)	Number of CT cycles (before RT, during RT, after RT)	Number of patients randomized[a]	Median follow-up (years)
Shorter versus longer radiotherapy duration							
CCCWFU62286 [30]	1987–92	EoS: Day 1 LoL: Day 8	EoS: 50 Gy/25 fr/5 weeks LoL: 20 Gy/8 fr/2 weeks + break 1 week + 20 Gy/8 fr/2 weeks + break 1 week + 10 Gy/4 fr/1 week	C: 750 mg/m^2, weeks$_{7,10,16}$ A: 60 mg/m^2, weeks$_{7,10,16}$ V: 2 mg, weeks$_{7,10,16}$ alternating with P: 60 mg/m^2, weeks$_{1,4,13}$ E: 120 × 3 mg/m^2, weeks$_{1,4,13}$	EoS: 6 cycles (2 during RT, 4 after RT) LoL: 6 cycles (3 alternating with RT, 3 after RT)	114	17.3
03PCL88 [31]	1988–94	EoS: Day 30 LoL: Day 36	EoS: 50 Gy/20 fr/5 weeks LoL: 20 Gy/8 fr/2 weeks + break 2 weeks + 20 Gy/8 fr/2 weeks + break 2 weeks + 15 Gy/6 fr/1.5 weeks	C: 1000 mg/m^2, weeks$_{1,13,17,21}$ A: 45 mg/m^2, weeks$_{1,13,17,21}$ E: 150 × 2 mg/m^2, weeks$_{1,13,17,21}$ Alternating with C: 1000 mg/m^2, weeks$_{5,9}$ Vd: 3 mg/m^2, weeks$_{5,9}$ E: 150 × 2 mg/m^2, weeks$_{5,9}$	EoS: 6 cycles (2 before RT, 1 during RT, 3 after RT) LoL: 6 cycles (2 before RT, 2 alternating with RT, 2 after RT)	164	6.5
ECOG3588 [16]	1989–92	Both arms: Day 1	EoS: 45 Gy/30 fr/3 weeks bid LoL: 45 Gy/ 25 fr/5 weeks	P: 60 mg/m^2, weeks$_{1,4,7,10}$ E: 120 × 3 mg/m^2, weeks$_{1,4,7,10}$	4 cycles (2 during RT, 2 after RT)	417	13.0

Trials are chronologically ordered within each category of trials (earlier versus later RT, and shorter versus longer RT).

bid, RT given twice a day; CT, chemotherapy; EoS, 'earlier or shorter' radiotherapy; fr, fraction; Gy, Gray; LoL, 'later or longer' radiotherapy; RT, radiotherapy; A, adriamycin; C, cyclophosphamide; Cb, carboplatin; E, etoposide; P, cisplatin; V, vincristine; Vd, vindesine; BR, bronchus; CALGB, Cancer and Leukaemia Group B; CCCWFU, Comprehensive Cancer Centre of Wake Forest University; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organisation for Research and Treatment of Cancer; HeCOG, Hellenic Cooperative Oncology Group; JCOG, Japan Clinical Oncology Group; LLCG, London Lung Cancer Group; PCL, Petites Cellules Limitées.

[a]Number of patients analysed equals the number of patients randomized, except for the HeCOG trial for which data on 81 patients were available out of the 86 randomized patients.

[b]Publication [27] stated that 'RT started […] on the 14th day of the second and subsequent courses of chemotherapy in arm Earlier RT'.

Table 2. Effect of 'earlier or shorter' radiotherapy versus 'later or longer' radiotherapy on overall survival according to different trial subsets

Trials characteristics	HR [95% CI][a]	Heterogeneity[b]	
		Between-subset	Residual (or within-subset)
CT compliance between arms			
Similar	0.79 [0.69–0.91]	19.5***	1.9
Different	1.19 [1.05–1.34]		
RT dose per fraction			
<1.8 Gy	0.82 [0.71–0.96]	7.5* (P_{trend} = 0.02)[c]	14.1*
1.8–2.4 Gy	1.11 [0.90–1.35]		
>2.4 Gy	1.06 [0.94–1.20]		
Type of RT			
Hyperfractionated	0.82 [0.71–0.96]	7.4**	14.2*
Standard	1.07 [0.96–1.19]		
RT overall treatment time			
≤30 days in both arms	0.89 [0.78–1.02]	5.6 (P_{trend} = 0.02)[c]	16.0*
One arm ≤30 days, one >30 days	0.99 [0.85–1.15]		
>30 days in both arms	1.16 [0.98–1.38]		
Platin-based CT during RT in both arms			
Yes	0.89 [0.79–1.01]	5.5**	16.1*
No	1.09 [0.97–1.24]		
Concurrent CT in both arms			
Yes	0.95 [0.85–1.06]	1.5	20.1**
No	1.06 [0.92–1.22]		
Same RT in the two arms			
Yes	0.96 [0.85–1.08]	0.5	21.1**
No	1.02 [0.90–1.16]		

CI, confidence interval; CT, chemotherapy; HR, hazard ratio; RT, radiotherapy.

[a]Hazard ratio of death following 'earlier or shorter' versus 'later or longer' radiotherapy.

[b]Total heterogeneity is the sum of between-subset and residual (within-subset) heterogeneity and is equal to 21.6 (analysis based on nine trials) except for CT compliance 21.4 (eight trials). The test associated with between-subset heterogeneity corresponds to the interaction test. The lower the residual heterogeneity, the greater was the overall heterogeneity of the treatment effect between trials explained by the trial characteristic.

[c]Test for trend.

*P < 0.05; **P < 0.01; ***P < 0.001.

28.9 months in trials with similar CT compliance. In trials with different CT compliance, 'earlier or shorter' radiotherapy shortened the 5-year mean survival time by 3.1 months (95% CI 1.3–4.9) from 20.6 to 17.5 months.

compliance with CT and progression-free survival

The HR for progression-free survival favours trials in which 'earlier or shorter' radiotherapy was delivered with similar CT compliance in both arms (HR for similar CT compliance: 0.81, 95% CI 0.71–0.92; for different CT compliance: 1.12, 0.95–1.31) (Figure 3). In trials in which CT compliance was similar, 'earlier or shorter' radiotherapy increased the 3-year progression-free survival rate by 6.3% (95% CI 1.0%–11.6%) and the 5-year progression-free survival rate by 5.6% (0.7%–10.5%) (supplementary Figure S4, available at *Annals of Oncology* online).

compliance with CT and landmark analysis

As the observed effect of CT compliance may be due to early treatment interruption because of progression or death, a post hoc landmark analysis on the impact of individual CT compliance on overall survival and progression-free survival was carried out among patients who survived (or had no disease progression) for at least 120 days. This landmark was chosen because most of the patients finished their chemoradiation treatment at 120 days. Patients with good CT compliance, i.e. those receiving the planned total number of CT cycles, had higher overall survival and progression-free survival than those with poor CT compliance (HR 0.56, 95% CI 0.49–0.64 and 0.70, 0.59–0.83, respectively; supplementary Table S8, available at *Annals of Oncology* online).

subgroup analyses

When the two subsets of trials with similar and different CT compliance were considered separately, no variation in the treatment effect was seen according to age, sex or the performance status (supplementary Figure S5, available at *Annals of Oncology* online).

sensitivity analyses

Supplementary Table S9, available at *Annals of Oncology* online shows the results of preplanned sensitivity analyses after excluding some trials. The results were similar to those of the main analysis, in particular to those related to CT compliance.

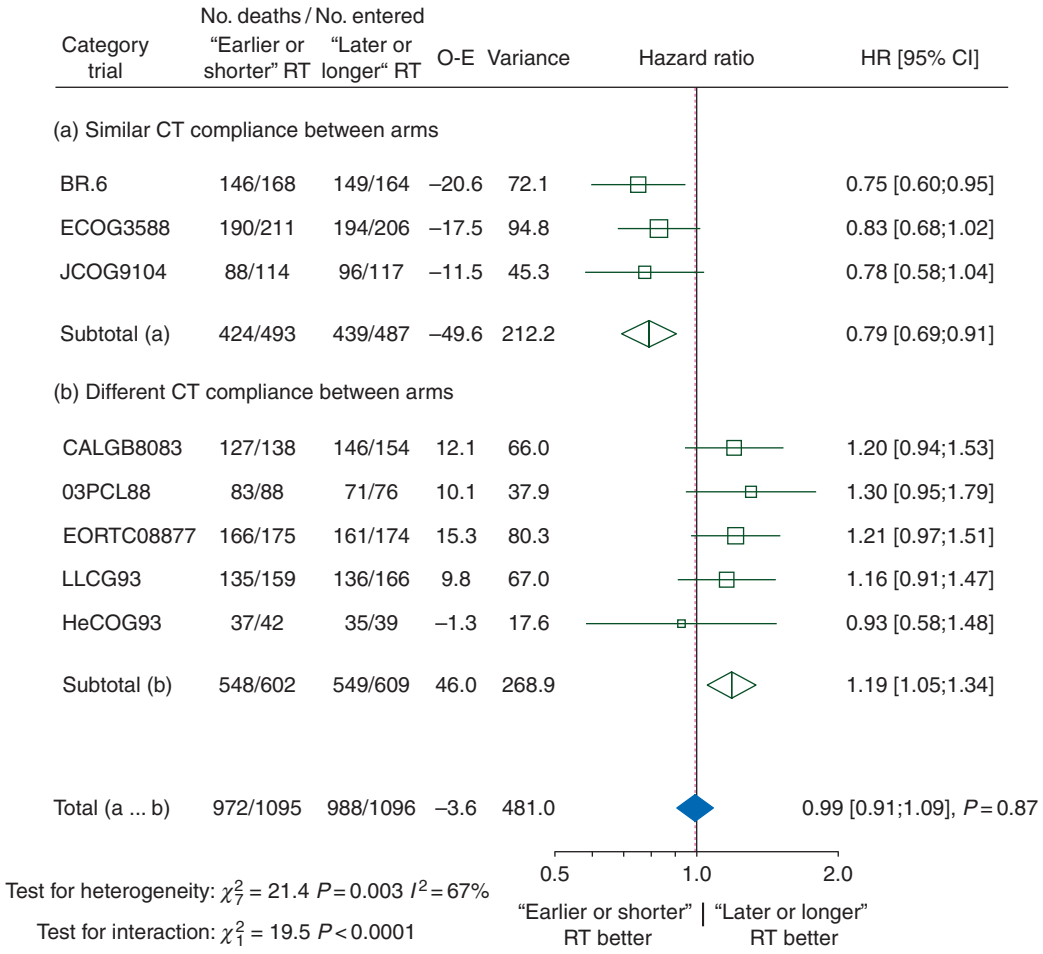


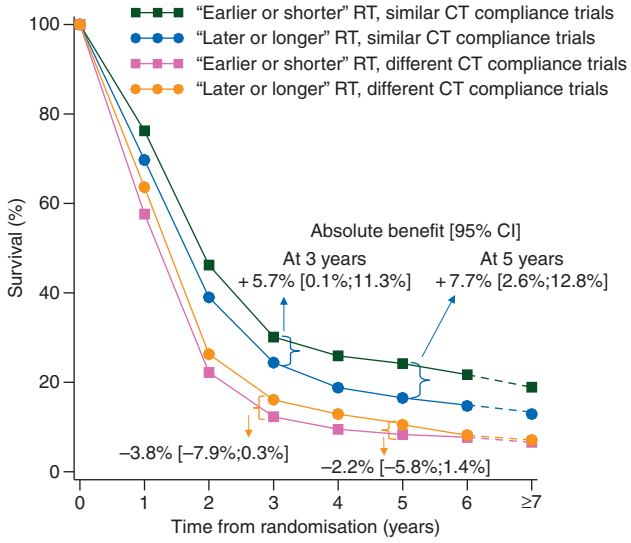
Figure 1. Effect of 'earlier or shorter' radiotherapy versus 'later or longer' radiotherapy on overall survival according to CT compliance. Each trial is represented by a square, the centre of which denotes the HR of death for that trial comparison, with the horizontal lines showing the 95% CIs. The size of the square is directly proportional to the amount of information contributed by the trial. The clear diamonds represent pooled HRs for the trial groups and the black diamond the overall HR, with the centre denoting the HR and the extremities the 95% CI. The fixed-effect model was used. Trials were chronologically ordered within each category of trials. Of note, data on CT compliance were not available for the CCCWFU62286 trial, which is thus not included in this analysis. CI, confidence interval; CT, chemotherapy; HR, hazard ratio; O-E, observed-expected; RT, radiotherapy.

toxicity

Three types of severe acute toxicities were significantly more frequent in patients receiving 'earlier or shorter' thoracic radiotherapy: neutrophil, oesophageal and cardiac toxicity (Table 3) [35]. The toxicity ORs according to trial subsets based on CT compliance are shown in supplementary Table S10, available at *Annals of Oncology* online. We did not perform analyses on late toxicities as IPD were available only for two trials [26, 27].

discussion

On the basis of this IPD meta-analysis of nine trials evaluating the optimal timing of thoracic radiotherapy in SCLC, overall there was no survival difference between 'earlier or shorter' and 'later or longer' thoracic radiotherapy (HR 0.99; $P = 0.78$). As individual trials favoured either 'earlier or shorter' or 'later or longer' thoracic radiotherapy, it seemed relevant to further analyse these data and perform a subset analysis focusing on CT compliance. For trials with different CT compliance, in which lower compliance was always observed in the 'earlier or shorter' arm, 'earlier or shorter' delivery had a deleterious effect on survival compared with 'later or longer' radiotherapy (HR 1.19, 95% CI 1.05–1.34). For trials that had similar (and good, i.e. at least 79% of compliant patients per arm) CT compliance, 'earlier or shorter' delivery of thoracic radiotherapy improved overall survival (HR 0.79, 95% CI 0.69–0.91). 'Earlier or shorter' thoracic radiotherapy, when delivered with similar and good CT compliance, yielded an absolute survival gain of 5.7% at 3 years and 7.7% at 5 years compared with 'later or longer' thoracic radiotherapy. Similar results were found for progression-free survival. We carried out sensitivity analyses by only taking into account trials in which patients received concomitant chemoradiation and trials that exclusively addressed the timing of thoracic radiotherapy in their design. In these sensitivity analyses, the survival gain of delivering 'earlier or shorter' thoracic radiotherapy with similar CT compliance remained significant (supplementary Table S9, available at *Annals of Oncology* online). Using a landmark analysis, it was possible to confirm with IPD that good CT compliance was associated with longer survival. Of note, there was a significant association at the patient level



Number of deaths/ PY by period	Years 0 – 2	Years 3 – 5	Years ≥ 6
Similar CT compliance			
'Earlier or shorter' RT	262/735	107/437	55/425
'Later or longer' RT	302/575	104/319	33/263
Different CT compliance			
'Earlier or shorter' RT	462/675	69/175	17/133
'Later or longer' RT	441/760	82/239	26/152

Figure 2. Survival curves for overall survival according to chemotherapy compliance. CI, confidence interval; CT, chemotherapy; HR, hazard ratio; PY, person-year; RT, radiotherapy.

between RT compliance and CT compliance, which could explain our results.

Hyperfractionated accelerated radiotherapy also improved survival when delivered 'earlier or shorter', but this finding was driven by two large trials, JCOG9104 [28] and ECOG3588 [16], with good CT compliance. In the ECOG3588 trial [16], no dose adjustment was allowed for the first two cycles. Cisplatin-based CT seems to be more beneficial when combined with 'earlier or shorter' thoracic radiotherapy. Issues such as the total radiotherapy dose and the dose per fraction are more difficult to interpret, because they are tightly correlated (Tables 1 and 2).

'Earlier or shorter' thoracic radiotherapy was associated with a higher incidence of acute severe oesophagitis than 'later or longer' radiotherapy (OR 1.93 [1.45–2.56]), but had no consequence on compliance with either CT or radiotherapy. Mauguen et al. [15] also showed that hyperfractionated accelerated radiotherapy increased oesophageal toxicity. In this IPD meta-analysis, neutropenia was more frequent with 'earlier or shorter' radiotherapy (OR 1.54, 95% CI 1.19–2.00), and this effect was observed exclusively in trials with similar CT compliance (supplementary Table S10, available at *Annals of Oncology* online). Acute severe pulmonary toxicity was similar in 'earlier or shorter' or 'later or longer' thoracic radiotherapy groups, whereas acute severe cardiac toxicity was higher when 'earlier or shorter' radiotherapy was delivered (OR 3.12, 1.46–6.68). The latter finding should be interpreted with caution because it is based on only 26 cardiac events occurring in 1648 patients among whom this toxicity was documented.

The results of this IPD meta-analysis primarily reinforce the evidence that CT should be delivered as intended whenever possible [1, 36]. Cisplatin-based CT administered with good CT compliance appeared to be the best treatment when combined with 'earlier or shorter' thoracic radiotherapy, as all the three trials [16, 26, 28] with similar CT compliance used this regimen. This is in line with previous literature-based meta-analyses, [9–14] in particular that reported by Spiro et al. [12], which focused on CT compliance (supplementary Table S1, available at *Annals of Oncology* online). Interestingly, a recently published randomized trial [37], where all patients had early hyperfractionated radiotherapy given concomitantly with the first cycle of etoposide, showed a 5-year survival rate of 34.3%, which the authors attributed to better patient selection and radiotherapy quality control. It will be interesting to observe the results of the ongoing CALGB 30610 (NCT00632853) and the completed CONVERT (NCT00433563) randomized trials comparing early hyperfractionated radiotherapy to early standard radiotherapy with a higher total dose and concomitant cisplatin plus etoposide in both arms.

The present IPD meta-analysis has some shortcomings. First, the trials were conducted at a time when imaging was not as advanced as it is today. However, the observed 5-year survival rate of about 25%, when 'earlier or shorter' thoracic radiotherapy was combined with good CT compliance, remains among the best published results. These results continue to support their applicability today, as there has been no major change in the standard of care of SCLC (NCCN and ESMO guidelines) [6]. A recently published Korean phase III trial [38], which was not included in this meta-analysis as it was closed to accrual in 2010 (supplementary Table S2, available at *Annals of Oncology* online), showed a similar 5-year survival rate of approximately 24%. This trial did not show a significant difference in terms of overall survival between the two arms (HR 0.93, 0.67–1.29), but the study included only 222 patients. Second, data were not available for two other trials [32, 34] (supplementary Table S2, available at *Annals of Oncology* online). However, when we included these three trials for which we have only published data (two in the similar CT compliance group [34, 38] and one in a different CT compliance group [32]) in a post hoc analysis, we found similar effects on overall survival (HR 0.81, 95% CI 0.72–0.90 versus 1.18, 1.06–1.32 for similar and different CT compliance subsets, respectively). Third, only the number of CT cycles administered were available, but not doses or delays in treatment. However, consistency across end points and between the main analysis and sensitivity analyses underscore the robustness of our results. Another limitation is that data on long-term toxicity were not available, but less toxicity would be expected with the newer radiotherapy techniques. Lastly, the quality of radiotherapy could not be addressed in this meta-analysis as it was not explored in the studies included.

To improve the still dismal prognosis of patients with stage I–IIIB SCLC, we postulate that the optimal treatment should be full dose but acceptable CT combined with 'earlier or shorter' thoracic radiotherapy (i.e. before 9 weeks), preferably within a short overall treatment time. Our IPD meta-analysis provides the best evidence of the beneficial effect of 'earlier or shorter' radiotherapy when CT is administered with good compliance.

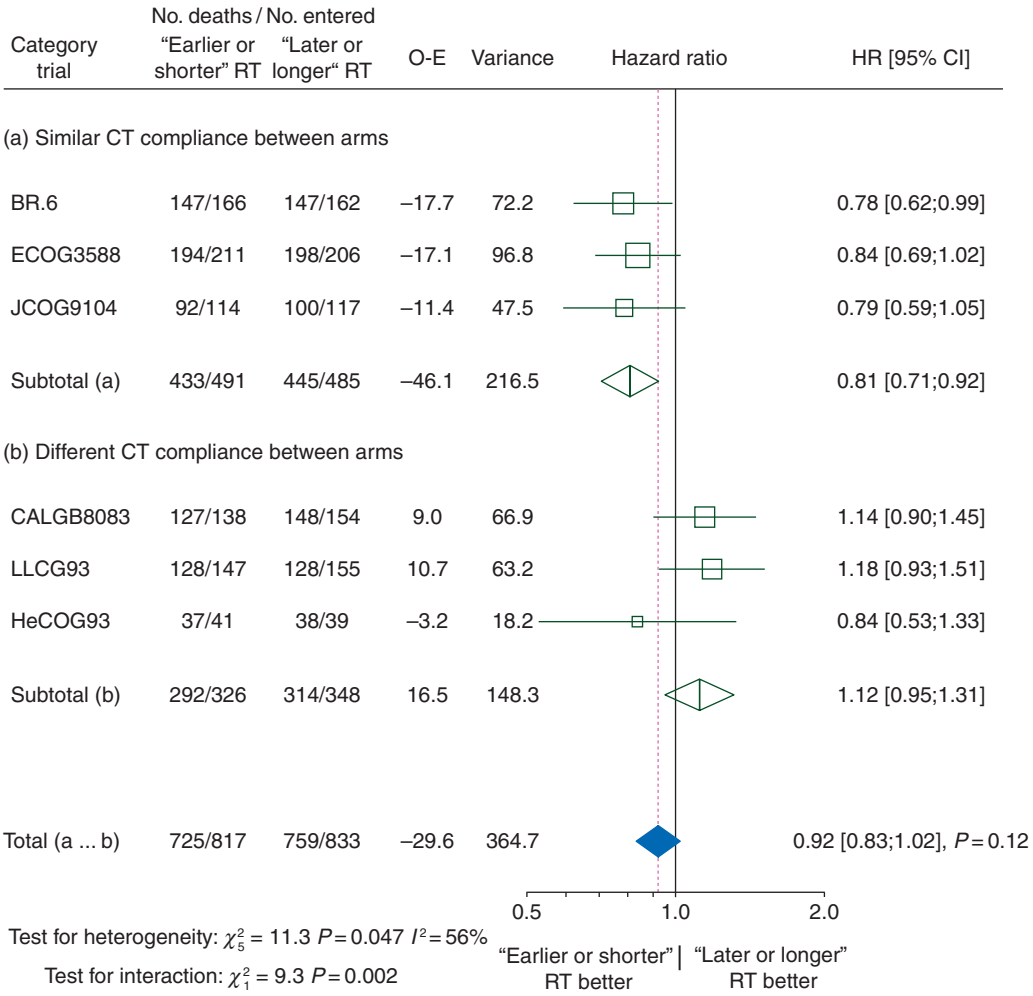


Figure 3. Effect of 'earlier or shorter' radiotherapy versus 'later or longer' radiotherapy on progression-free survival according to chemotherapy compliance. Each trial is represented by a square, the centre of which denotes the HR of death or tumour progression for that trial comparison, with the horizontal lines showing the 95% CIs. The size of the square is directly proportional to the amount of information contributed by the trial. The clear diamonds represent pooled HRs for the trial groups and the black diamond the overall HRs, with the centre denoting the HR and the extremities the 95% CI. The fixed-effect model was used. CI, confidence interval; CT, chemotherapy; HR, hazard ratio; O-E, observed-expected; RT, radiotherapy.

Table 3. Acute toxicity according to radiotherapy arm

Severe toxicity (grades 3–5)	Availability Number of trials (patients)	Toxicity rate 'Later or longer' RT	Toxicity rate 'Earlier or shorter' RT[a]	Results OR [95% CI]	*P*-value efficacy	I^2 (%)	*P*-value heterogeneity
Neutrophil	6 (1,453)	59	69	1.54 [1.19–2.00]	0.001	79	<0.001
Haemoglobin	6 (1,476)	21	24	1.17 [0.91–1.52]	0.22	31	0.21
Platelets	7 (1,817)	18	21	1.22 [0.96–1.55]	0.11	45	0.09
Oesophageal	8 (1,950)	8	14	1.93 [1.45–2.56]	<0.001	45	0.08
Pulmonary	5 (1,207)	4	6	1.50 [0.86–2.62]	0.16	0	0.68
Cardiac	6 (1,648)	1	3	3.12 [1.46–6.68]	0.003	0	0.95

Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria, World Health Organization criteria or Eastern Cooperative Oncology Group Common Toxicity Criteria, depending on the trials. Severe toxicity was defined as grades 3–5 toxicity. Grade 5 was present only for pulmonary toxicity ($n = 4$) and cardiac toxicity ($n = 1$).

CI, confidence interval; OR, odds ratio of the 'earlier or shorter' RT arm compared with 'later or longer' RT arm; RT, radiotherapy.

[a]The difference in the rate of toxicity between the two treatment arms was computed based on the rate in the 'later or longer' radiotherapy arm and the OR [35].

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disclosure

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appendix

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