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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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ABSTRACT

Background Chemotherapy 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 chemotherapy.

Material and methods We performed a meta-analysis of individual patient data in randomised trials comparing earlier versus later radiotherapy, or shorter vs. 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 2,668 patients were eligible. Data from nine trials comprising 2,305 patients were available for analysis. The median follow-up was 10 years. When all trials were analysed together, "earlier or shorter" vs. "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 chemotherapy (defined as having received 100% or more of the planned chemotherapy 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 chemotherapy compliance (HR 1.19, 1.05–1.34, interaction test $p<0.0001$). The absolute gain between "earlier or shorter" vs. "later or longer" thoracic radiotherapy in 5-year overall survival for similar and for different chemotherapy compliance trials was 7.7% (95% CI 2.6–12.8 %) and -2.2% (-5.8–1.4 %), 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 chemotherapy significantly improves 5-year overall survival at the expense of more acute toxicity, especially oesophagitis.

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

Key message:

The optimal timing and sequencing of thoracic radiotherapy and chemotherapy, which is the standard treatment of "limited-stage" small-cell lung cancer, has fuelled debate for many years. This individual patient data meta-analysis provides the best evidence of the beneficial effect of "earlier or shorter" radiotherapy when chemotherapy is administered with good compliance.

INTRODUCTION

Small-cell lung cancer (SCLC) is a rapidly disseminating cancer so that its primary treatment is chemotherapy, whatever the stage [1]. Approximately 25% of patients present with localised disease, formerly known as “limited-stage” disease, now called stage I-IIIB [2]. It is well known that optimal survival is achieved when chemotherapy can be administered at the total intended dose and at the required intervals [1,3]. Nevertheless, due to loco-regional failures after chemotherapy alone, the adjunction of thoracic radiotherapy was investigated. A worldwide meta-analysis showed that adding thoracic radiotherapy to chemotherapy improved long-term survival [4]. Concurrent chemotherapy 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 chemotherapy has fuelled debate for many years. When all trials were pooled together, no survival gain was detected whether thoracic radiotherapy was delivered early with chemotherapy or later [9-12]. However, in trials where patients were treated with cisplatin-based chemotherapy 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 chemotherapy and before the third cycle of chemotherapy in two previous literature-based meta-analyses [12,13], whilst a 30-day cut-off was used in other literature-based meta-analyses [9-11,14] (Table S1 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 chemotherapy 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 chemotherapy administration. Such information can only be provided by an individual patient data (IPD) meta-analysis. We therefore undertook such a study, aiming to define the best approach for combining thoracic radiotherapy with chemotherapy in stage I-IIIB SCLC.

METHODS-MATERIAL

The meta-analysis was performed 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 randomisation and before the third cycle of chemotherapy. Trials comparing two radiotherapy durations, i.e. a shorter vs. 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 paper, 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 randomised. The planned chemotherapy 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 for this cancer. To limit publication bias, we searched for both published and unpublished trials without language restriction (see Web-Appendix 1 for search strategy).

Statistical Analysis

We describe IPD collection and quality control in Web-Appendix 2. The main endpoint was overall survival and the secondary endpoints were progression-free survival and severe acute toxicities. Overall survival was defined as the time from randomisation until death from any cause or the last follow-up for surviving patients. Progression-free survival was defined as the time from randomisation 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 (HR) by the fixed effect model [15]. A similar model was used to estimate odds ratios (OR) for the comparison of toxicity between arms. χ^2 tests and the I^2 statistic were used to study heterogeneity between trials [18]. Hazard ratios were calculated using a DerSimonian-Laird random effects model if heterogeneity had a p-value <0.10 [19]. Stratified survival curves were estimated for control and experimental groups, using annual death rates and the pooled hazard ratio, and were used to estimate the absolute benefit at 3 and 5 years with their 95% confidence intervals [20]. Five-year mean survival times, parameters commonly used in economic evaluation, were also estimated (Web-Appendix 3) [21-23].

Subsets analyses according to trial characteristics were pre-planned. We investigated whether the treatment effect was dependent on any difference in the proportion of patients who were compliant with chemotherapy 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 6 CT cycles or more were considered as compliant. A trial was considered as having different "between-arm" compliance if the difference was ≥10% and as having similar "between-arm" compliance if it was <10% [12]. No other information on chemotherapy administration, such as the actual drug dose received or delays in chemotherapy 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 performed using SAS version 9.3.

Role of the funding source

The funding sources had no role in the study design, data collection, data analysis, data interpretation, or manuscript writing. BL and J-PP had full access to all the raw data. The corresponding author had the final responsibility for the decision to submit for publication.

RESULTS

Twelve randomised trials [12,16,25-34] including 2,668 patients were eligible. Data on nine trials and 2,305 patients (86% of potentially eligible patients) were available for this IPD meta-analysis (Figure S1). 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 Table S2 summarises 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 vs. longer radiotherapy duration. Central randomisation 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 (Table S3). Three trials [16,26,28] were categorised as having similar chemotherapy compliance in both arms, and they had a proportion of at least 79% of patients who were compliant with chemotherapy (i.e. receiving all their cycles) (Table S4). Five trials [12,25,27,29,31] had different chemotherapy (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 as compared to 93% in the "earlier or shorter" arm (Table S5). 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 randomisation to the start of radiotherapy ranged from 63 to 93 days compared with 56 to 84 days for the planned difference (Table S6). 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 to "later or longer" radiotherapy (HR 0.99, 95% CI 0.91–1.08, p=0.78) (Figure S2). 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 1,764 patients and 1,596 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) (Figure S3).

Trial subsets

Table 2 shows the HRs for overall survival according to the different pre-planned subsets analyses, described in Table S7, 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 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 vs "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 chemotherapy. It should be emphasised that trials using hyperfractionated radiotherapy delivered fractions of less than 1.8 Gy, and 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).

Chemotherapy compliance and overall survival

The HR for overall survival was significantly in favour of "earlier or shorter" radiotherapy among trials in which the defined chemotherapy 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 chemotherapy compliance and the treatment effect (interaction test, $p<0.0001$). In trials with similar CT compliance in both arms, "earlier or shorter" radiotherapy compared to "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 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 chemotherapy 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%) (Figure S4).

Compliance with chemotherapy 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 performed 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 chemo-radiation treatment at 120 days. Patients with good CT compliance, i.e. those receiving the planned total number of chemotherapy 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; Table S8).

Sub-group 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 (Figure S5).

Sensitivity analyses

Table S9 shows the results of pre-planned sensitivity analyses after excluding some trials. The results were similar to those of the main analysis, in particular to those related to chemotherapy compliance.

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 odds ratios according to trial subsets based on CT compliance are shown in Table S10. We did not perform analyses on late toxicities as IPD were available only for two trials [26,27].

DISCUSSION

Based on 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 to "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, 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 performed 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 (Table S9). 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 patient-level 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 chemotherapy 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 chemotherapy 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 (Table S10). Acute severe pulmonary toxicity was similar in "earlier or shorter" or "later or longer" thoracic radiotherapy groups, while 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, for it is based on only 26 cardiac events occurring in 1,648 patients among whom this toxicity was documented.

The results of this IPD meta-analysis primarily reinforce the evidence that chemotherapy should be delivered as intended whenever possible [1,36]. Cisplatin-based chemotherapy 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 (Table S1). Interestingly, a recently published randomised 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% that the authors attributed to better patient selection and radiotherapy quality control. It will be interesting to observe the results of the on-going CALGB 30610 (NCT00632853) and the completed CONVERT (NCT00433563) randomised 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 chemotherapy 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 (Table S2), 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. Secondly, data were not available for two other trials [32,34] (Table S2). 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 vs. 1.18, 1.06–1.32 for similar and different CT compliance subsets respectively). Third, only the number of chemotherapy cycles administered were available, but not doses or delays in treatment. However, consistency across endpoints 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 chemotherapy 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 chemotherapy is administered with good compliance.

FIGURE LEGENDS

Figure 1. Effect of "earlier or shorter" radiotherapy versus "later or longer" radiotherapy on overall survival according to chemotherapy compliance

Each trial is represented by a square, the centre of which denotes the hazard ratio of death for that trial comparison with the horizontal lines showing the 95% confidence intervals (CIs). The size of the square is directly proportional to the amount of information contributed by the trial. The clear diamonds represent pooled hazard ratios for the trial groups and the black diamond the overall hazard ratio, with the centre denoting the hazard ratio 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.

Abbreviations: CI = Confidence Interval; **CT** = Chemotherapy; **HR** = Hazard ratio; **O-E** = Observed-Expected; **RT** = Radiotherapy

Figure 2. Survival curves for overall survival according to chemotherapy compliance

Abbreviations: CI = Confidence Interval; **CT** = Chemotherapy; **HR** = Hazard ratio; **PY** = Person-Year; **RT** = Radiotherapy

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 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 hazard ratio of death or tumour progression for that trial comparison with the horizontal lines showing the 95% confidence intervals (CIs). The size of the square is directly proportional to the amount of information contributed by the trial. The clear diamonds represent pooled hazard ratios for the trial groups and the black diamond the overall hazard ratios, with the centre denoting the hazard ratio and the extremities the 95% CI. The fixed effect model was used.

Abbreviations: CI = Confidence Interval; **CT =** Chemotherapy; **HR =** Hazard ratio; **O-E =** Observed-Expected; **RT =** Radiotherapy

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