Systematic review and meta-analysis of randomised, controlled trials of the timing of chest radiotherapy in patients with limited-stage, small-cell lung cancer

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Background: We undertook a systematic review and literature-based meta-analysis to determine whether the timing of chest radiotherapy may influence the survival of patients with limited-stage small-cell lung cancer (LS-SCLC).

Materials: Eligible randomised controlled clinical trials were identified according to the Cochrane Collaboration Guidelines, comparing different timing of chest radiotherapy in patients with LS-SCLC. Early chest irradiation was defined as beginning within 30 days after the start of chemotherapy.

Results: Considering all seven eligible trials, the overall survival at 2 or 5 years was not significantly different between early or late chest radiotherapy. When only trials were considered that used platinum chemotherapy concurrent with chest radiotherapy, a significantly higher 5-year survival was observed when chest radiotherapy was started within 30 days after the start of chemotherapy (2-year survival: OR: 0.73, 95% CI 0.51–1.03, \(P = 0.07\); 5-year survival: OR: 0.64, 95% CI 0.44–0.92, \(P = 0.02\)). This was even more pronounced when the overall treatment time of chest radiotherapy was less than 30 days.

Conclusions: There are indications that the 5-year survival rates of patients with LS-SCLC are in favour of early chest radiotherapy, with a significant difference if the overall treatment time of chest radiation is less than 30 days.

Key words: timing radiotherapy, small-cell lung cancer, limited-stage, meta-analysis, review

introduction

Small-cell lung cancer (SCLC) accounts for about 20% of all lung cancer cases, with only one third of the patients presenting with limited stage (LS) [1, 2]. Without treatment, tumour progression in patients with SCLC is rapid, with a median survival of 2 to 4 months. Chemotherapy has improved the median survival time substantially, but long-term survival remains below 10% [3]. Two meta-analyses [4, 5] have shown an improvement of 5.4%, in absolute survival at 2 years and 3 years, in patients who received chest irradiation and chemotherapy versus those receiving chemotherapy alone. The 5-year survival rate remains disappointingly low at 10–15% [4]. Although evidence for a significant survival benefit of chest radiotherapy was provided by the meta-analyses, no conclusions could be drawn regarding the optimal timing and sequencing of chemotherapy and radiation [6, 7].

This leaves several issues unresolved. These issues include the administration of early or late chest irradiation during chemotherapy, the optimal overall treatment time and dose of chest irradiation and the concurrent or non concurrent delivery of radiotherapy with chemotherapy.

There is evidence that chest radiotherapy given in addition to chemotherapy improves survival in patients with LS-SCLC compared with chemotherapy alone. However, the best timing of chest radiotherapy with chemotherapy has not been elucidated to date, and is the focus of this systematic review and meta-analysis.

methods

criteria for selecting studies

The protocol was peer reviewed and published in the Cochrane Database of Systematic Reviews [8]. Analyses planned in the protocol were: survival, local tumour control, toxicity and compliance. Analyses were stratified according to total treatment time of chest irradiation and to concurrent versus sequential administration of chemotherapy. Stratification for the type of chemotherapy was carried out in a post hoc analysis.
Studies eligible for inclusion were randomised controlled clinical trials fully published in journals and those identified from other sources (abstracts and proceedings of relevant scientific meetings, and contacts with investigators) for which full details are available from investigators. Patients of any age had to have histologically and cytologically proven LS-SCLC and a performance status 0–2. For this review we used the following definition of LS: cancer confined to one hemi-thorax including contralateral mediastinal and hilar lymph nodes as well as ipsilateral and/or bilateral supraclavicular involvement, but excluding malignant pleural effusion. 

Early chest radiotherapy was defined as beginning radiation within 30 days after the start of chemotherapy. This choice is made because it has become clear in recent years that accelerated proliferation of tumour clonogens during both radiotherapy and chemotherapy, starting from 30 days after the beginning of treatment onwards, affects prognosis [9–13].

**search strategy**

A search for identification of studies on the review topic was undertaken using the following electronic databases: the Cochrane Central Register of Controlled Trials (CENTRAL, 2003 Issue 4), MEDLINE (1966 to present), EMBASE (1974 to present), CINAHL (1982 to present). Furthermore, the Cochrane Lung Cancer Groups Specialised Register was consulted. Searches were performed without a language of studies retrieved.

Reference lists from identified studies were scrutinised for any other additional studies. The electronic searches for clinical trials were complemented with manual searches from the following oncology journals: International Journal of Radiation, Oncology, Biology and Physics (1985–present); Radiotherapy and Oncology (1985–present); Journal of Clinical Oncology (1985–present); Clinical Oncology (1999–present); Lung Cancer (1985–present); and Thorax (1985–present). Abstracts were hand searched from the principal oncology conferences from 1985 onwards with a minimum follow up of 3 years. Colleagues, collaborators, and other experts in the field were asked to identify missing and unreported trials.

**data extraction**

Randomised trials identified by the search were assessed to determine if they met the inclusion criteria. They were assessed by three independent reviewers (D.D.R., M.P.I., J.V.) both for the quality of the methods against pre-determined criteria (see below) and for the results of key outcomes, which were identified and tabulated.

Two reviewers (D.D.R., J.V.) extracted the data independently to ensure validity. Discrepancies were resolved by a third referee (M.P.I.). All data extracted from randomised trials were included in these analyses. The following data were collected from the manuscript: identifiers, gender, age, performance status at the time of randomisation, initial disease stage, definition of chemotherapy regimen, induction treatment that led to a complete response, start date of induction treatment, randomisation timing, treatment allocated, overall treatment time of chest irradiation according to the protocol and updated information on survival, brain metastasis, other metastases and loco-regional recurrence.

**quality assessment**

Methodological quality was assessed according to the following criteria: Was the randomisation process adequate? Was there adequate allocation concealment? Were the analyses performed according to intention to treat? Were the groups similar at baseline for the most important prognostic indicators? Were eligibility criteria specified? Were losses to follow up fully accounted for and was the withdrawal/drop-out rate unlikely to cause bias? Were co-interventions which may have influenced the results controlled for? Were co-interventions which may have influenced the results controlled for? and was the withdrawal/drop-out rate unlikely to cause bias?

The overall quality of the included studies is depicted in the table of included studies (Table 1).

For local tumour control, there was no uniform definition of local tumour control or of the methods of how it was to be assessed. Analyses were only performed on an intention to treat basis in four of seven studies [14–17]. The co-interventions that may have influenced the results were not co-controlled for. We therefore chose the cumulative incidence of local tumour control, which was, if extractable from the paper, derived from the actuarial chest recurrences at 5 years according to randomisation. Only the 5-year rates were included because these will probably not be influenced by second line chemotherapy given for recurrence after primary treatment. However, as the proportion of the surviving patients after 5 years was small, the numbers of patients with long-term local control are obviously low as well thus making these results more difficult to interpret.

**statistical analysis**

We performed a literature-based meta-analysis. A weighted estimate of the typical treatment effect across studies was computed for 2-year survival data as well as the 5-year survival data, the cumulative local tumour control at 5 years and toxicities (incidence of haematological, lung- and oesophageal grade 3–4 toxicity, if available or extractable from the manuscript).

The odds ratio (OR) was used as the effect measure. Chi-square heterogeneity tests were used to test for statistical heterogeneity among trials. As we anticipated that the trial results would be heterogeneous, all analyses were performed using a random effects model. For the study of James [18], only 3-year survival data were available. For the clarity of the tables and text, these were set under the denominators ‘2-year survival’. A post hoc analysis was carried out according to whether platinum-based chemotherapy had been used or not during chest radiotherapy.

Sources of heterogeneity in the assessment of the primary outcome measure were explored by random effects meta-regression. These analyses assessed the effect of the overall treatment time of chest irradiation and of the concurrent administration of chemotherapy. This procedure gives an indication of the robustness of the results.

All statistical analysis were performed with RevMan (Review Manager (RevMan) [Computer program], Version 4.2 for Windows. Oxford, England: The Cochrane Collaboration, 2003) and STATA version 8.0 for Windows.

**results**

The search strategy identified eleven studies. From these 11 studies, seven were suitable for survival analysis [14–20]. Four trials were excluded. [21–24] Two were excluded because chest radiotherapy started on the same day, thus making comparison between early and late radiation impossible. [22–24] The study of the EORTC [21] was not suitable for this analysis because in one arm chest radiotherapy started on day 49 and in the other arm on day 91, implying that according to our inclusion criteria in both arms late radiotherapy was delivered. Likewise, the trial of Lebeau [23] was excluded because the start of chest radiotherapy varied between day 30–64 in one arm and day 36–47 or day 64–75 in the other arm.

From the seven studies suitable for survival analysis, five gave enough information for local toxicity analysis, i.e. severe pneumonitis and severe oesophagitis [15–19] and six studies for haematological toxicity evaluation.[14–18, 20] Local tumour control data were available from five of these seven studies [14–16, 19, 20]. However, in the study from Japan [20], only the site of first recurrence was available, whereas in the other trials,
<table>
<thead>
<tr>
<th>Trials</th>
<th>Patients randomised (excluded)</th>
<th>Performance Status included patients E/L</th>
<th>Median age patients: (range E/L)</th>
<th>Timing RT E/L (day)</th>
<th>Concurrent CT</th>
<th>PCI E/L</th>
<th>RT schedule: compliance rates</th>
<th>Allocation concealment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Platinum–etoposide based CT</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>James 2003 [18]</td>
<td>325 (NR)</td>
<td>ECOG 0–1: 91%/89%</td>
<td>62 (34–74/33–74)</td>
<td>21/105</td>
<td>E: Yes</td>
<td>Yes, only if CR &lt;br&gt;40 Gy/15 f/ 21d &lt;br&gt;no data available for compliance rates</td>
<td>Not clear</td>
<td></td>
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<tr>
<td>Jeremic 1997 [15]</td>
<td>107 (4)</td>
<td>KPS 90–100: 52%/47%</td>
<td>59 (40–67/ 44–66)</td>
<td>1/42</td>
<td>E: Yes</td>
<td>Yes, only if CR or &lt;br&gt;PR: 98%/84%</td>
<td>Not clear</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>KPS 50–80: 48%/53%</td>
<td></td>
<td></td>
<td>L: Yes</td>
<td></td>
<td>RT: &gt; 96% /96%  &lt;br&gt;CT: NS</td>
<td></td>
</tr>
<tr>
<td>Murray 1993 [19]</td>
<td>332 (24)</td>
<td>ECOG 0–1: 87%/90%</td>
<td>62 (NS)</td>
<td>21/105</td>
<td>E: Yes</td>
<td>Yes, only if CR: &lt;br&gt;40 Gy/15 f/ 4%/13%  &lt;br&gt;98%/84%</td>
<td>Not clear</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>ECOG 2–3: 3%/10%</td>
<td></td>
<td></td>
<td>L: Yes</td>
<td></td>
<td></td>
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<tr>
<td>Work 1997 [14]</td>
<td>199 (?)</td>
<td>KPS: 80–100: 82%/80%</td>
<td>60 (36–70/36–69)</td>
<td>1/126</td>
<td>E: No</td>
<td>Yes, only if CR: &lt;br&gt;100%/58%</td>
<td>Not clear</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>KPS: 40–70: 18%/20%</td>
<td></td>
<td></td>
<td>L: No</td>
<td></td>
<td>RT: 40 Gy: 78% received 40 Gy, whereas 19% received less and 3% more than 40 Gy: RT: 45 Gy: 74% received 45 Gy, whereas 21% received less and 5% more than 45 Gy</td>
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<td></td>
<td>Cyclophosphamide: 87%/87%,  &lt;br&gt;Doxorubicin: 86%/87%,  &lt;br&gt;Vincristine: 89%/86%  &lt;br&gt;Etoposide: 86%/86%,  &lt;br&gt;Cisplatin: 84%/83%</td>
<td></td>
</tr>
<tr>
<td>Skarlos 2001 [17]</td>
<td>86 (5)</td>
<td>ECOG 0–1: 76%/ 85%</td>
<td>61 (40–76/ 38–79)</td>
<td>1/56</td>
<td>E: Yes</td>
<td>Yes, only if CR: &lt;br&gt;41%/57%</td>
<td>Adequate</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>ECOG 2: 24%/15%</td>
<td></td>
<td></td>
<td>L: Yes</td>
<td></td>
<td>RT: 45 Gy/ 30f/ 19d</td>
<td></td>
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<tr>
<td>Takada 2002 [20]</td>
<td>231 (3)</td>
<td>ECOG 0–1: 95%/95%</td>
<td>65 (39–74/30–74)</td>
<td>2/85</td>
<td>E: Yes</td>
<td>Yes, only if CR or near CR: 27%</td>
<td>Adequate</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>ECOG 2: 5%/5%</td>
<td></td>
<td></td>
<td>L: No</td>
<td></td>
<td>RT: 90%/90%  &lt;br&gt;Cisplatin: 94%/91%,  &lt;br&gt;Etoposide: 93%/90%</td>
<td></td>
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<tr>
<td><strong>Non-platinum based CT</strong></td>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td>Perry 1998 [16]</td>
<td>426 (27)*</td>
<td>ECOG 0–1: 86%/87%</td>
<td>60 (32–79)</td>
<td>1/64</td>
<td>E: Yes</td>
<td>Yes</td>
<td>50 Gy/ 25f/ 33d</td>
<td>Not clear</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ECOG 2: 13%/9%</td>
<td></td>
<td></td>
<td>L: Yes</td>
<td></td>
<td>RT: NS  &lt;br&gt;CT: NS</td>
<td></td>
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</tbody>
</table>

*All three arms considered (the third arm (n = 129) in which patients only received chemotherapy was not taken up in this review).
ECOG, Eastern Cooperative Oncology Group; KPS, Karnofsky Performance Status; RT, radiotherapy; CT, chemotherapy; E, early RT; L, late RT; Gy, Gray; f, fraction; d, day; C/E, carboplatin/etoposide; ys, years; CR, complete response; NR, not reported.
the cumulative rate of local tumour failure at 2 and 5 years was available. Compliance, defined as the percentage of intended total radiation dose completed, was registered in five of these seven studies [14, 15, 17, 19, 20]. In only one of the six studies, chemotherapy was not delivered concomitantly with chest radiotherapy [14]. In another trial [20], the early chest radiotherapy group received concurrent radiation and chemotherapy, whereas the late radiation group only had their radiotherapy after chemotherapy. As a consequence, there are not enough trials available to investigate the effect of the sequencing of chemotherapy and thoracic radiotherapy on survival.

As in all studies, prophylactic cranial irradiation (PCI) was given to at least a group of patients in each research arm, it was not possible to stratify for this parameter.

**survival**

Taking all seven studies into account, the overall survival at 2 years or at 5 years was not significantly different between early or late chest radiotherapy (Figure 1a). When the one trial that delivered non-platinum chemotherapy concurrently with chest radiation [16] was excluded, the OR was not significantly different at 2 years, but was significantly in favour of early
A

Review: Early versus Late Chest Radiotherapy in patients with limited stage small cell lung cancer (Version 250105)
Comparison: 01 Early versus Late Chest RT
Outcome: OS 2–3 yrs Survival (death within 2 or 3 years) only studies with overall treatment time of chest RT less than 30 days

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Early nN</th>
<th>Late nN</th>
<th>OR (random) 95% CI</th>
<th>Weight %</th>
<th>OR (random) 95% CI</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skates et al. 2001</td>
<td>27/42</td>
<td>28/39</td>
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</tr>
<tr>
<td>Tedeski 2002</td>
<td>32/114</td>
<td>74/114</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>James 2003</td>
<td>134/159</td>
<td>133/166</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Jeremie 1997</td>
<td>18/52</td>
<td>24/51</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Murray 1993</td>
<td>93/155</td>
<td>103/153</td>
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</tbody>
</table>

Total (95% CI) 522
Total events: 321 (Early), 522 (Late)
Test for heterogeneity: CH² = 6.56, df = 4 (P = 0.07), P = 53.5%
Test for overall effect: Z = 1.19 (P = 0.09)

B

Review: Early versus Late Chest Radiotherapy in patients with limited stage small cell lung cancer (Version 250105)
Comparison: 01 Early versus Late Chest RT
Outcome: OS 5–6 yrs Survival (death within 5 years) only studies with overall treatment time of chest RT less than 30 days

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Early nN</th>
<th>Late nN</th>
<th>OR (random) 95% CI</th>
<th>Weight %</th>
<th>OR (random) 95% CI</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tedeski 2002</td>
<td>87/114</td>
<td>93/114</td>
<td></td>
<td></td>
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<tr>
<td>Jeremie 1997</td>
<td>32/52</td>
<td>43/61</td>
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<td></td>
</tr>
<tr>
<td>Murray 1993</td>
<td>124/153</td>
<td>136/153</td>
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</tbody>
</table>

Total (95% CI) 321
Total events: 987 (Early), 272 (Late)
Test for heterogeneity: CH² = 1.12, df = 2 (P = 0.07), P = 90.3%
Test for overall effect: Z = 2.74 (P = 0.006)

Figure 2. Meta-analysis of survival as a function of the timing of chest radiotherapy: Overall treatment time of thoracic radiation less than 30 days.

(A) 2–3 year survival*; (B) 5-year survival.

Figure 3. Meta-analysis of local tumour recurrence as a function of the timing of chest radiotherapy.

Chest radiotherapy at 5 years (2-year survival: OR: 0.73, 95% CI 0.51–1.03, P = 0.07; 5-year survival: OR: 0.64, 95% CI 0.44–0.92, P = 0.02) (Figure 1b). Considering studies with an overall treatment time of chest radiation of less than 30 days [15, 17–20], the 5-year survival (OR: 0.56, 95% CI: 0.37–0.85; P = 0.006), but not the 2-year survival, was significantly higher for early chest radiotherapy (Figures 2a and 2b).

Local tumour control

All included studies determined the local tumour control by chest X-rays or CT-scans.

No significant effect of delivering chest radiotherapy early or late on local tumour control was observed (Figure 3). The same held true when the study combining non-platinum based chemotherapy with thoracic radiotherapy [16] was omitted.
Only a trend for a higher incidence for severe pneumonitis was observed for early chest radiotherapy compared with late irradiation when all four studies [15–17, 19] were considered (OR: 1.95; 95% CI: 0.96–3.94; P = 0.06) (Figure 4a). A higher incidence of severe oesophagitis was observed for early chest radiotherapy when all five studies [15–19] were taken into account (OR: 1.50; 95% CI: 1.03–2.20; P = 0.04) (Figure 4a).

The same observation was found when only platinum concurrent with chest radiotherapy was investigated (Figure 4b), or only studies with an overall treatment time of chest radiation of less than 30 days were taken into account (Figure 4c). Taking all studies into account [14–20], severe leukopenia was significantly more frequent in patients receiving early chest radiotherapy (OR: 2.45; 95% CI: 1.49–4.04; P = 0.0004) (Figure 4a). Taking all studies into account, severe thrombocytopenia was not significantly different between early or late chest radiotherapy (Figure 4a).

Sources of heterogeneity in the assessment of the primary outcome measure were explored by random effects meta-regression. The effects of the overall treatment-time of chest radiotherapy was investigated (Figure 4b), or when taking into account studies with an overall treatment time of chest radiation of less than 30 days were taken into account (Figure 4c).
irradiation and the administration, or not, of concurrent chemotherapy were assessed. Since there was only one study that delivered non-platinum based chemotherapy concurrently with chest radiation [16], no meta-regression analyses could be performed to determine the association between delivering non-platinum based or platinum based chemotherapy concurrently with chest radiation on overall survival, local control, local toxicities and haematological toxicities. However, we identified this factor as a potential source of the observed heterogeneity.

Regarding the effect of the overall treatment time on survival, five studies delivered the radiation with an overall treatment time less than 30 days [15, 17–20] and in two studies the overall treatment time was more than 30 days [14, 16]. We found a significant association between overall treatment time and overall survival in favour of an overall treatment time less than 30 days, though only at 5-year survival, not at 2 years (5-year survival: regression coefficient \( \beta = 1.02 \); SE 0.38; \( P = 0.007 \); 95% CI: \( 1.75, 0.28 \)). We found no association between overall treatment time of chest radiotherapy on local tumour control, local toxicity and haematological toxicity.

**Discussion**

From two meta-analyses, it has become clear that adding chest radiotherapy to chemotherapy in patients suffering from LS-SCLC improves rates of survival [4, 5]. However, several issues regarding administration of thoracic radiotherapy in LS-SCLC are still unresolved, including timing with chemotherapy [5, 7]. We therefore focussed this review on the best timing of chest radiotherapy with chemotherapy. In recent years it has become clear that the overall treatment time of radiation plays an important role in the outcome of radiotherapy [9, 10]. Therefore, in addition to the timing of chest radiotherapy the overall treatment time of chest irradiation was also examined. No firm kinetic data are available on tumour cell clonogen proliferation of SCLC during and after chemotherapy and radiotherapy. However, in many common solid tumours, accelerated tumour cell clonogen proliferation occurs approximately 30 days after the start of effective cytotoxic therapy [9–13]. We therefore defined early chest radiotherapy as starting chest irradiation before 30 days after the start of chemotherapy. Late radiotherapy was defined as starting chest irradiation 30 days or more after the start of chemotherapy.
The type of chest radiotherapy was analysed according to an overall treatment time of less or more than 30 days, again taking into account accelerated tumour cell proliferation. Since the type of chemotherapy (platinum-based or not) delivered together with radiotherapy may also affect outcomes, we stratified post hoc for this factor [6, 25].

Chemotherapy was not delivered concomitantly with chest radiotherapy in only one of the seven studies [14]. In another trial [20], the early chest radiotherapy group received concurrent radiation and chemotherapy, whereas the late radiation group only had their radiotherapy after chemotherapy. As a consequence, there are not enough trials available to investigate the effect of the sequencing of chemotherapy and thoracic radiotherapy on survival. This has to be taken into account, as sequencing of radio-chemotherapy may be a cause confounding and subsequently affect the results.

Seven studies enabling the investigation of the best timing of chest radiotherapy for survival were identified [14–20]. In all but one trial [16], a combination of a platinum analogue (cisplatin or carboplatin) together with etoposide (EP), given alone or alternated with cyclophosphamide, adriamycin and vincristine (CAV) was used. In the study of Perry et al. [16], the non-platinum-based combination of cyclophosphamide, etoposide and vincristine was used during chest radiotherapy.

The effect of the timing of chest radiotherapy on survival is not clear. For all studies together, no significant differences in either the 2-year or the 5-year survival were observed. When the only trial in which non-platinum chemotherapy was delivered concurrently with chest radiotherapy was excluded [16], a trend was observed for the survival at 2 years in favour of beginning thoracic radiation within 30 days after the start of chemotherapy. However, this result is based on a post hoc analysis, as we had not planned this subgroup analysis beforehand. At 5 years, the survival was significantly higher when chest radiotherapy was given early, representing a 5-year survival rate of 20.2% for early versus 13.8% for late thoracic radiotherapy. Exclusion of the non-platinum based trial can be advocated, as many arguments plead against this approach: one phase III trial [26] and two meta-analysis [27, 28] pointed at superior outcome with platinum based chemotherapy for LS-SCLC, and there is increased toxicity when radiation is delivered with anthracyclines [29].
However, the results of this review should be interpreted with caution. First, the 5-year survival data rely to a large extent on the NCI-C trial [19]. A subsequent large English study [18] with the same design and therapeutic regimen as the NCI-C trial, failed to show a survival difference at 3 years between early and late chest radiotherapy. It remains to be seen whether the 5-year survival will be different in this trial, for in two of the large phase III trials [19, 24] the long-term benefit of early [19] or accelerated [24] radiotherapy was only apparent from 3 years post-treatment onwards. Second, the studies with the highest reported dose intensity of chemotherapy seem to have the highest survival rates and show the largest differences between early and late chest radiotherapy [15, 19, 20]. Although it has not been shown convincingly that accelerating the delivery of chemotherapy improves survival [30–32], decreasing the interval between cycles from a 4-weekly to a 3-weekly schedule lead to superior survival in one study [33]. Therefore it appears that in order to have a benefit of early chest radiotherapy, an effective systemic treatment as well as a 2-year survival of at least 30% should be achieved. It is not unlikely that the beneficial effect of early chest radiation may only be observed in those patients in a good general condition, thoroughly staged and able to have a good compliance for an intensive, effective chemotherapy regimen combined with chest radiotherapy. However, this hypothesis cannot be proved by the available data. As a consequence, there is no definitive proof that early chest radiotherapy confers a survival benefit.

When the overall treatment time of chest radiation was less than 30 days, the 5-year survival was significantly [15, 19, 20] in favour for early chest radiotherapy, but not the 2-year survival [15, 17–20]. As the results at 5 years are to a large extent driven by Murray’s trial [19], but not confirmed in the UK trial of James et al. [18] at 3 years, these results should also be interpreted with caution. No firm conclusion can be drawn as to whether the overall treatment time of chest radiotherapy affects survival or not.

Local tumour control was never significantly different between early versus late chest radiotherapy. These results are difficult to interpret, because there was neither a uniform definition of local tumour control nor of the methods to assess it. Moreover, the limitations of chest X-rays or CT scans to assess the control of lung cancer treated with combined chemotherapy and radiotherapy are well known. All of these may have resulted in an unreliable assessment of the local tumour control.

Keeping all caveats for comparing local toxicity between studies in mind, severe pneumonitis was not significantly different between early or late chest radiotherapy. Severe oesophagitis, however, was more likely to occur when chest radiotherapy was delivered early.

Severe leukaemia was significantly more frequent in patients receiving early chest radiotherapy. This may be due to the increased bone marrow damage of delivering concurrent chemotherapy and chest radiotherapy, which both cause leukaemia. Severe thrombocytopenia was not significantly different between early or late chest irradiation when all studies were considered.

Our results are somewhat different from those of another meta-analysis [34] that concluded that chest radiotherapy delivered within the first 9 weeks after starting chemotherapy conferred a survival benefit at 2 years. However, in this study, the definition of early and late radiotherapy was different from ours (9 weeks in the latter study vs. 30 days in the present one) as well as the definition of the type of thoracic radiotherapy (conventional or hyperfractionated in the latter study vs. the overall treatment time of radiotherapy in the present one) and the large UK study [18] was a priori not included. Besides, this latter study did not adjust for heterogeneity between trials included in the meta-analysis, and as a result, small confidence intervals with a higher chance to obtain significant statistically differences between groups.

In conclusion, the data indicates that early radiotherapy (beginning within 30 days after the start of chemotherapy) is associated with a better 5-year survival rate, especially if the overall treatment time of chest radiotherapy is less than 30 days. The possible benefit of early chest radiotherapy for achieving a 5-year survival should be viewed with caution. Early chest radiotherapy could be more effective but the potential influence of patient selection and of the systemic treatment should be taken into account. In view of the many uncertainties, further research is needed. However, the results support the idea that delivering chest radiotherapy early, especially in combination with a short overall treatment time, may improve survival. It can be argued that the overall duration of the treatment may be one of the most important outcomes with regard to survival. We therefore think that it would be of major interest to investigate in new trials the role of the overall treatment time of the radio-chemotherapy ‘package’ as a whole.

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