Concurrent versus Sequential Chemotherapy and Radiotherapy in Limited Disease Small Cell Lung Cancer: A Retrospective Comparative Study

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Abstract. Background: Patients with limited-disease small cell lung cancer are treated with chemotherapy and chemotherapy combined with radiotherapy. Treatment schemes with curative intention include sequential or concurrent chemoradiotherapy, both combined with prophylactic cranial irradiation (PCI). It is unclear which scheme is superior. Patients and Methods: Until 2001, patients received 4-5 cycles of chemotherapy. In cases of no complete response, palliative radiotherapy (RT) was given in 13 fractions of 3 Gy (CT-RT group, N=26). A total of 89 patients did not receive RT after chemotherapy (CT group). After complete response, curatively intended RT was given, of 16×2.5 Gy, concurrently with PCI of 15×2 Gy (SCT-RT group, N=111). From 2001, 40 patients received 4-5 cycles of chemotherapy concurrently with RT of 25×1.8 Gy. PCI was applied to patients with complete response (CCT-RT group). Endpoints were median survival time (MST) and overall survival (OS). Results: MST of CT, CT-RT, SCT-RT and CCT-RT were 8.1, 12.5, 14.0 and 21.8 months, and 5-year OS 3.5, 4.8, 10.5 and 26.9%, respectively. Frequencies of brain metastasis after PCI in SCT-RT and CCT-RT patients were 16.4% and 8.7%, respectively. Conclusion: Concurrent chemoradiotherapy resulted in longer MST and higher OS than sequential chemoradiotherapy, chemotherapy with palliative radiotherapy or chemotherapy alone. Results may improve further by applying PCI at an earlier stage and increasing the RT dose.

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Key Words: SCLC limited disease, sequential chemoradiotherapy, concurrent chemoradiotherapy, prophylactic cranial radiotherapy, median survival time, overall survival.

Small cell lung cancer (SCLC) accounts for 13.8% of all lung cancer cases (1). SCLC is the most aggressive form of lung cancer, having greater potential to metastasize than other types of lung cancer. Nearly all patients (>95%) diagnosed with SCLC are current or ex-smokers (2). Staging systems divide SCLC into limited disease (LD) and extensive disease. About one third of SCLC patients have LD, by definition confined to one side of the chest, and the remaining patients have extensive disease. Without treatment, tumour progression in LD SCLC is rapid, with a median survival time (MST) of only a few months (3, 4). The role of chemotherapy (CT) has been extensively tested. Long-term survival in these cases is <10% (5, 6). For palliative reasons, thoracic radiotherapy (RT) was given to CT patients who did not respond completely to chemotherapy. Thoracic radiotherapy, given in addition to chemotherapy after complete response, resulted in significantly improved survival rates when compared to those treated with CT only (7, 8). Furthermore, it was noted that prophylactic cranial irradiation (PCI) improved survival of SCLC patients who achieved complete response following primary therapy (9-13). Takada et al. (14) reported results of a randomized multicenter trial and concluded that concurrent chemoradiotherapy (CCT-RT) is more effective than sequentially applied chemotherapy and radiotherapy (SCT-RT).

The main treatment regimen for LD SCLC nowadays consists of a combination of CT, thoracic RT and PCI. We retrospectively analysed treatment efficacy of patients with LD SCLC who underwent CT only, CT without complete response followed by palliative thoracic RT (CT-RT), SCT-RT or CCT-RT.

Patients and Methods

Patients. The database on pathologically confirmed LD-SCLC patients provided by the Comprehensive Cancer Centre (IKMN), Utrecht, the Netherlands, was analysed. Patients were treated in 10 regional hospitals in the period 1996-2005. RT was applied at the University Medical Centre Utrecht at Utrecht, the
Netherlands. A total of 89 patients received CT only, 26 patients with no complete response received palliative thoracic RT (CT-RT), and 111 patients who achieved complete response were referred for curatively intended radiotherapy (SCT-RT). Starting in 2001, 40 patients were offered CCT-RT. Patient characteristics are shown in Table I.

**Chemotherapy only and sequentially applied chemotherapy and radiotherapy.** The CT consisted of 4–5 cycles, given in a 3-week cycle, of cyclophosphamide (1.000 mg/m² on day 1), doxorubicin (45 mg/m² on day 1) and etoposide (100 mg/m² on days 1, 2 and 3) (CT group, N=89). When the chemotherapy did not result in a complete response as determined by bronchoscopy, CT scan and or chest X-ray, palliative thoracic irradiation with 13 fractions of 3 Gy, 4 fractions/week, was the preferred treatment (CT-RT group, N=26). The reasons for the 89 patients not receiving radiotherapy after CT were tumour progression during chemotherapy, pancytopenia, refusal of further therapy, worsening of patient’s condition or death.

In cases of complete response, patients received thoracic RT with 16 fractions of 2.5 Gy/day, 5 fractions/week (SCT-RT group, N=111). The volume that was irradiated was based on the pre-treatment CT scan. Concurrently with the thoracic irradiation, PCI was applied consisting of 15 fractions of 2 Gy, 5 fractions/week.

**Concurrent chemoradiotherapy.** The chemotherapy consisted of 4 or 5 cycles, given in a 3-week cycle, of cisplatin (60 mg/m² on day 1) and etoposide (120 mg/m² on days 1, 2 and 3) (CT group, N=89). The chemotherapy did not result in a complete response as determined by bronchoscopy, CT scan and or chest X-ray, palliative thoracic irradiation with 13 fractions of 3 Gy, 4 fractions/week, was the preferred treatment (CT-RT group, N=26). The planning CT scan was made in the week before the start of the chemotherapy or in the first week of the first cycle. PCI was applied consisting of 15 fractions of 2 Gy, 5 fractions/week to patients with a complete response after completion of the chemotherapy.

**Tumour volume measurement.** The tumour dimensions of the SCT-RT and CCT-RT patients were taken from the CT diagnostic scan made prior to chemotherapy. The maximum diameter in the medio-lateral or ventro-dorsal direction was measured, d₁, as well as the maximum diameter in the cranial-caudal direction, d₂, i.e. the number n of CT slices in the cranial-caudal direction on which the tumour was visible, multiplied by the slice thickness t, dₙ=t. The tumour volume was calculated as V=0.5d₁²d₂ when d₁ was the smallest dimension or V=0.5d₁²d₂ when d₂ was the smallest dimension.

**Endpoints.** Primary endpoints were MST and overall survival (OS). The MST was defined as the time from the start of treatment, when half of the patients were found to be still alive. Overall survival time was defined as interval between start of treatment and death (from all causes) or last known follow-up. Secondary endpoints were tumour-related cause of death and frequency of metastasis.

**Statistics.** The Kaplan-Meier method was applied to determine the MST and the OS rates, and the log-rank (Mantel-Cox) test was used to compare treatment results. The $\chi^2$ test was applied to determine differences in metastasis frequency. Tests were performed using the Statistical Package for Social Sciences, version 13.0 (SPSS, Chicago, IL, USA).

### Table I. Patient characteristics: gender, age, and tumour volume.

<table>
<thead>
<tr>
<th>Gender</th>
<th>CT (N=89)</th>
<th>CT-RT (N=26)</th>
<th>SCT-RT (N=111)</th>
<th>CCT-RT (N=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>63 (70.8%)</td>
<td>16 (61.5%)</td>
<td>68 (61.3%)</td>
<td>26 (65%)</td>
</tr>
<tr>
<td>Female</td>
<td>26 (29.2%)</td>
<td>10 (38.5%)</td>
<td>43 (38.7%)</td>
<td>14 (35%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Mean±SD</td>
<td>68.3±8.8</td>
<td>63.9±9.0</td>
<td>63.1±9.7</td>
</tr>
<tr>
<td>Range</td>
<td>34.7-86</td>
<td>49.7-80.6</td>
<td>32-81.7</td>
<td>42-76</td>
</tr>
</tbody>
</table>

CT: Chemotherapy; CT-RT: CT and palliative thoracic radiotherapy; SCT-RT: sequentially applied chemoradiotherapy; CCT-RT: concurrently applied chemoradiotherapy; SD: standard deviation.

<table>
<thead>
<tr>
<th>Tumour volume before CT (cm³)</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT (N=89)</td>
<td>81</td>
<td>8-883</td>
</tr>
<tr>
<td>CT-RT (N=26)</td>
<td>40</td>
<td>16-526</td>
</tr>
</tbody>
</table>

CT: Chemotherapy; CT-RT: CT and palliative thoracic radiotherapy; SCT-RT: sequentially applied chemoradiotherapy; CCT-RT: concurrently applied chemoradiotherapy; SD: standard deviation.

### Table II. Median survival time and overall survival of patients treated with chemotherapy only, chemotherapy and thoracic radiotherapy, sequential, and concurrent chemoradiotherapy.

<table>
<thead>
<tr>
<th>Evaluable patients</th>
<th>CT (N=77)</th>
<th>CT-RT (N=21)</th>
<th>SCT-RT (N=95)</th>
<th>CCT-RT (N=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MST±SE (month)</td>
<td>8.1±0.9</td>
<td>12.5±1.0</td>
<td>14.0±0.6</td>
<td>21.8±3.2</td>
</tr>
<tr>
<td>95% Confidence interval</td>
<td>6.6-9.9</td>
<td>10.6-14.4</td>
<td>12.9-15.1</td>
<td>15.5-28.0</td>
</tr>
<tr>
<td>Overall survival ± SE (%)</td>
<td>32.5±5.3</td>
<td>52.4±10.9</td>
<td>67.4±4.8</td>
<td>75.0±6.8</td>
</tr>
<tr>
<td>1-Year</td>
<td>5.2±2.5</td>
<td>4.8±4.6</td>
<td>17.3±3.9</td>
<td>32.2±7.7</td>
</tr>
<tr>
<td>5-Year</td>
<td>3.5±2.2</td>
<td>4.8±4.6</td>
<td>10.5±3.2</td>
<td>26.9±8.1</td>
</tr>
</tbody>
</table>

CT: Chemotherapy; CT-RT: CT and palliative thoracic radiotherapy; SCT-RT: sequentially applied chemoradiotherapy; CCT-RT: concurrently applied chemoradiotherapy; MST: median survival time; SE: standard error.

### Results

**Patient population.** The groups of patients did not differ significantly from one another with respect to the distribution of gender and age ($p>0.05$), although the percentage of males and mean age were higher in the CT group. The tumour volumes as derived from the CT diagnostic scans of 43 SCT-RT patients and 23 CCT-RT patients show some differences, with relatively larger tumour volumes being present in the SCT-RT group (Table I).

**Chemotherapy only.** In the group of 89 patients who received CT only, 12 patients were lost to follow-up. Of the 77 evaluable patients, the MST was 8.1 months. The 1-, 3- and 5 year OS were 32.5, 5.2 and 3.5%, respectively (Table II; Figures 1-3).
The radiological response after CT was evaluated: 6 patients had complete response, of whom 2 were long-term survivors (more than 5 years). All other patients had partial response, stable or progressive disease. In the database, no information on tumour volumes was available.

Chemotherapy followed by thoracic radiotherapy. Twenty-six patients received palliative thoracic radiotherapy. Five patients were lost to follow-up. One long-term survivor was identified. The MST of 21 patients was 12.5 months. The 1-, 3- and 5-year OS were 52.4, 4.8 and 4.8%, respectively (Table II; Figures 1-3). Data on tumour volume were not recorded in the IKMN database.

Sequential chemotherapy and radiotherapy. Of the 111 SCT-RT patients, 16 were lost to follow-up. Of the 95 evaluable patients, the MST was 14.0 months and the 1-, 3- and 5-year OS were 67.4, 17.3 and 10.5%, respectively (Table II; Figures 1-3). The median tumour volume of 43 patients, measured from the CT scans, was 81 cm$^3$ (Table I).

Of 69 patients, more detailed information on the interval between the end of the chemotherapy and the start of the RT, as well as on the total overall treatment time (OTT), was available. The interval between the end of CT and the start of RT ranged between 25 and 194 days, with a mean of 66 days. The mean OTT was 182 days (Table III). Sixty-seven out of these 69 SCT-RT patients (97%) had a complete response, and 2 a partial response. The complete responders received PCI, however, 11 patients (16.4%) developed brain metastases after PCI.

In 59 patients, the cause of death was known and was tumour related in 45 patients (76.3%). Local recurrence was present in 19 patients (42%), 7 of whom also had distant metastases. The remaining 26 patients developed distant metastases.

Concurrent chemoradiotherapy. The median tumour volume at the start of the CCT-RT of 23 patients was 40 cm$^3$ (Table I). The mean OTT was 159 days and the range 123-197 days. Without PCI, the OTT was 88 days, with a range of 42-128 days. This implies that not all patients received the planned CT in the treatment time of 65 days (4 cycles of 3 weeks) or 86 days (5 cycles). The MST of patients with a shorter OTT than the median treatment time of 91 days was 15.3 months. The other patients had an MST of 24.1 months. The overall MST

![Figure 1. Cumulative survival as a function of time after start of treatment. Curve 1: chemotherapy (CT) only; curve 2: CT and palliative thoracic radiotherapy (CT-RT); curve 3: sequentially applied chemotherapy and radiotherapy (SCT-RT) and curve 4: concurrently applied chemoradiotherapy (CCT-RT).](image1)

![Figure 2. Median survival time (MST) of patients treated with chemotherapy (CT) only, CT and palliative thoracic radiotherapy (CT-RT), sequential applied chemotherapy and radiotherapy (SCT-RT), and concurrently applied chemoradiotherapy (CCT-RT). Error bars indicate standard deviation.](image2)

![Figure 3. Overall survival at 1, 3 and 5 years of patients treated with chemotherapy (CT) only, CT and palliative thoracic radiotherapy (CT-RT), sequentially applied chemotherapy and radiotherapy (SCT-RT), and concurrently applied chemoradiotherapy (CCT-RT). Error bars indicate standard deviation.](image3)
was 21.8 months and the 1-, 3- and 5-year overall survival were 75, 32.2 and 26.9%, respectively (Table II; Figures 1-3).

Five patients received PCI of 8 fractions of 3.5 Gy in two weeks because of the presence of brain metastases at the end of chemotherapy.

After CCT-RT, 24 (60%) out of the 40 patients had a complete response; 23 patients received PCI. Later, brain metastases were observed in 2 (8.7%) out of the 23 patients who received PCI.

The causes of death in 25 (89.3%) out of 28 evaluable patients were tumour related. Ten patients (40%) had local recurrence, of whom 2 also had distant metastases. The remaining 15 patients developed distant metastases.

Discussion

The observed results of patients who received CT only are in line with results obtained by others (5, 6). The combination chemotherapy with RT improved the results significantly. In our patients, when chemotherapy was followed by palliative RT, the MST increased significantly (p<0.05) from 8.1 to 12.5 months, with curatively intended RT to 14 months, and with CCT-RT to 21.8 months. The MST of the CCT-RT group was significantly longer than those of the other treatment groups. In addition the 5-year survival increased, from 3.5% (CT) to 10.5% (SCT-RT) and to 26.9% for the CCT-RT. OS was significantly higher in the CCT-RT group as compared to the SCT-RT group (p=0.016).

The SCT-RT and CCT-RT groups did not differ significantly with respect to the distribution of gender and age. The pre-treatment tumour volumes in the CCT-RT group were smaller than in the SCT-RT group as shown by the median values (Table I).

Our data for CCT-RT patients showed an MST of 21.8 months; and 2- and 5-year survivals of 44.1% and 26.9%, respectively. Our results with CCT-RT are comparable with those of others (14-18). Takada et al. reported on a randomized multicenter trial (14). The MSTs they noted were 19.7 months with SCT-RT and 27.2 months with concurrent therapy. The 2-, 3- and 5-year survival rates for SCT-RT were 35.1, 20.2 and 18.3%, respectively, and for CCT-RT 54.4, 29.8 and 23.7%, respectively (Table IV). Baas et al. (15) concluded that combination of CT with concurrent involved-field RT is an effective treatment for LD SCLC. The 2- and 5-year survival rates were 47 and 27%, respectively. The MST was 19.5 months. Park et al. (16) reported differences between concurrent or sequential chemoradiotherapy in overall response rates (78% versus 63%, respectively, p=0.13) and MST (mean 18.3 months versus 13.2 months, respectively, p=0.33) (Table IV). However, the data were limited and with only 51 patients, the trial was likely underpowered to detect a statistical significant survival difference; at any rate, the trend is that a concurrently applied scheme yields better results. Turrisi et al. (17) reported for a single and a twice-daily RT scheme for CCT-RT patients MSTs of 19 and 23 months; for the 2-year survival 41 and 47%, and for the 5-year survival 16 and 26%, respectively (Table IV). De Ryuyscher et al. (18) also concluded that with platinum CT, early chest RT (i.e. RT started within 30 days after start of the CT) resulted in higher survival rates than when RT was applied later.

In our study, we noted that the OTT in the SCT-RT group, when compared to that of the CCT-RT group, was significantly longer. This is caused by the time required for restaging procedures (CT scan, chest X-ray, bronchoscopy) and referring the patient for radiotherapy. SCLCs have a
shorter tumour volume doubling time when compared to that of squamous cell carcinoma and adenocarcinoma (23 days versus 88 and 161 days, respectively) (19-21). Accelerated growth during the time interval may cause a substantial tumour volume increase. For example, in an earlier study (22) we observed accelerated tumour growth for non-small cell lung carcinomas in the interval between the end of induction chemotherapy and start of radiotherapy. The mean tumour volume-doubling time was about half that of non-treated tumours. Therefore, analogous to non-small cell lung cancer, the OTT in SCLC must be shortened or RT must be given concurrently with the CT.

PCI has been shown to be effective in preventing cerebral metastasis (9, 11) and in improving survival when applied to patients with LD SCLC who had achieved a complete response after primary therapy. Even in cases with extended disease SCLC, PCI improved the survival (12, 23).

In our study, SCT-RT patients received PCI on an average of 159 days after the start of the CT, and the CCT-RT patients on an average of 139 days. The frequency of brain metastasis in patients who received PCI was 16.4% for the SCT-RT patients and 8.7% in CCT-RT patients. Although not statistically different, this may indicate that early PCI is warranted. For example, PCI may start about two weeks after the CT instead of the 7-9 weeks after the end of CT for the CCT-RT and SCT-RT patients, preventing a mean of about 5-7 weeks of cell proliferation, respectively. Furthermore, it may also be important that delay of RT of the primary tumour may also allow ongoing cumulative risk of metastatic events in the brain.

In the present study, the OTTs, without PCI, of concurrently treated patients were in the range of 42-128 days. There are several reasons why this range is that large. An OTT of about 65 days (4 cycles of 3 weeks) or 86 days (5 cycles of 3 weeks) was expected. The OTTs in excess of 86 days were a consequence of interruptions in the treatment caused by side-effects. The patients with the relatively short OTT did not receive the planned full course chemotherapy because of severe chemotherapy side-effects. In this group of patients, the mean survival time is expected to be shorter than that in the group of patients who received the planned course of CT. The MST was indeed lower for the patients with the short OTT as compared to those with a long OTT; 15.3 versus 24.1 months. It indicates the importance of having the planned chemotherapy course.

When the PCI is included in the OTT of CCT-RT patients, the mean OTT is 159 days. Here again the interval between the end of the CT and start of the PCI was relatively long. The mean interval was 55 days, the median 48, and the range 27-109 days. Restaging procedures and referring the patient again to the department of radiotherapy likely caused the delay. However, the total OTT was shorter than that of SCT-RT with a mean value of 182 days. The question can be raised whether the interval between the end of CT and start of the PCI can be shortened. In the interval, micrometastases not recognizable on CT scan may grow to a size for which the total PCI dose of 30 Gy is not sufficient to kill all cells. From the radiobiological point of view, a dose of 30 Gy may eliminate all tumour cells with a volume of up to 1 mm³, larger sizes harbouring more than 106 cells may still not be recognizable on the CT or MRI scan but will still survive the PCI dose.

The local recurrence rate after SCT-RT and CCT-RT was practically identical, about 40%. The biological effective dose of RT, with OTT taken into account, was also comparable, about 50 Gy. In future, it would be worthwhile to increase the RT dose to lower the recurrence rate.

Our results indicate that CCR-RT resulted in a significantly longer MST and higher survival rate than did SCR-RT. These results are comparable with those of others. However, in this retrospective study some of the baseline data of the CCT-RT group were slightly different from those of the SCT-RT group: the follow-up time was shorter, the mean age lower and the median tumour volume smaller.

<table>
<thead>
<tr>
<th>Reference number</th>
<th>MST (months)</th>
<th>OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SCT-RT</td>
<td>CCT-RT</td>
</tr>
<tr>
<td>14</td>
<td>19.7</td>
<td>27.2</td>
</tr>
<tr>
<td>15</td>
<td>19.5</td>
<td>19.5</td>
</tr>
<tr>
<td>16</td>
<td>13.2</td>
<td>18.3</td>
</tr>
<tr>
<td>17*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present study</td>
<td>14.0</td>
<td>21.8</td>
</tr>
</tbody>
</table>

SCT-RT: Sequentially applied chemotherapy and radiotherapy; CCT-RT: concurrently applied chemoradiotherapy; OS: overall survival; MST: median survival time. *Results of once-daily and twice-daily thoracic radiotherapy, respectively.

Table IV. Median survival time and overall survival at 2, 3 and 5 years of patients treated with sequentially and concurrently applied chemoradiotherapy. Results of several studies.
Only in a randomized trial can these differences in baseline data be avoided. Furthermore, cyclophosphamide-based CT has been demonstrated as being inferior to etoposide and cisplatin in a randomized trial where the sequence of CT and RT was kept constant (24). Improvements of CT technology and change in CT may also result in improved OS of the concurrent therapy cohort as compared to the sequential therapy cohort.

In conclusion, the concurrently applied CT resulted in longer MST and higher survival rates than sequentially applied CT and RT. Results may improve further by applying PCI at an earlier stage and by increasing the RT dose.

References


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