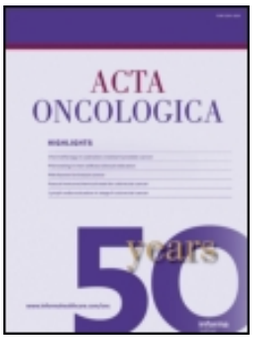

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ORIGINAL ARTICLE

Accelerated hyperfractionated radiotherapy and concomitant chemotherapy in small cell lung cancer limited-disease. Dose response, feasibility and outcome for patients treated in western Sweden, 1998–2004

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Abstract

Addition of thoracic radiation therapy (TRT) to chemotherapy (CHT) can increase overall survival in patients with small cell lung cancer limited-disease (SCLC-LD). Accelerated fractionation and early concurrent platinum-based CHT, in combination with prophylactic cranial irradiation, represent up-front treatment for this group of patients. Optimised and tailored local and systemic treatment is important. These concepts were applied when a new regional treatment programme was designed at Sahlgrenska University Hospital in 1997. The planned treatment consisted of six courses of CHT (carboplatin/etoposide) + TRT ± prophylactic cranial irradiation (PCI). Standard TRT was prescribed as 1.5 Gy BID to a total of 60 Gy during 4 weeks, starting concomitantly with the second or third course of CHT. However, patients with large tumour burdens, poor general condition and/or poor lung function received 45 Gy, 1.5 Gy BID, during 3 weeks. PCI in 15 fractions to a total dose of 30 Gy was administered to all patients with complete remission (CR) and "good" partial remission (PR) at response evaluation.

Eighty consecutive patients were treated between January 1998 and December 2004. Forty-six patients were given 60 Gy and 34 patients 45 Gy. Acute toxicity occurred as esophagitis grade III (RTOG/EORTC) in 16% and as pneumonitis grade I–II in10%. There were no differences in toxicity between the two groups. Three- and five-year overall survival was 25% and 16%, respectively. Median survival was 20.8 months with no significant difference between the two groups. In conclusion, TRT with a total dose of 60 or 45 Gy is feasible with comparable toxicity and no difference in local control or survival. Distant metastasis is the main cause of death in this disease; the future challenge is thus further improvement of the systemic therapy combined with optimised local TRT.

During the last century there was a change in treatment strategies for small cell lung cancer limited-disease (SCLC-LD), beginning with surgery, followed by radiation therapy (RT) and finally chemotherapy (CHT). Further progress was achieved when CHT and RT were combined, resulting in improved overall survival as described in two meta-analyses by Warde and Pignon in 1992 [1,2]. However, the optimal combination of these two treatment modalities is still not clear. There are many factors to be taken into account when combining CHT and RT in the treatment of SCLC, e.g. timing of RT (early vs. late), target absorbed dose, fractionation (conventional vs. accelerated) and target volumes for the thoracic RT. These issues have been the subjects of many studies aimed at establishing the optimal treatment for SCLC-LD [3–10].

Prophylactic cranial irradiation (PCI) was introduced, with favourable effects according to two large meta-analyses [11,12], due to the high risk of brain metastasis in this patient group.

Based on these results, a new regional treatment protocol was designed for SCLC-LD, in western Sweden. It consisted of platinum-based CHT in combination with accelerated RT at two different dose levels, 60 Gy and 45 Gy, the latter for patients with large tumour burdens and/or impaired pulmonary function. TRT was administered concurrently with the second or third course. The detailed treatment protocol is presented elsewhere.

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The primary aim of this retrospective study was to analyse the outcome of this treatment protocol, including overall survival, local control, feasibility and toxicity. The secondary aims were to study weather the total radiation dose was of importance, as well as to identify prognostic factors for therapy outcome.

Methods

During the period January 1998–December 2004, all patients with SCLC-LD were identified and treated according to the new treatment protocol consisting of chemotherapy with carboplatin (AUC 5, according to Calvert's formula, day 1) and etoposide (100 mg/m^2, day 1–3 i.v., or 120 mg/m^2 day 1–5 per os) as soon as possible after diagnosis. The choice of carbo- instead of cisplatin was based on the difference in toxicity and the lack of evidence of difference in efficacy [13–15]. TRT was given as 3D-CRT on linear accelerators with 6 MV photons. Patients were immobilised in vacuum pillows and a therapeutic computed tomography (CT) of the chest was performed. Planning target volume (PTV) was defined as the persisting tumour volume after previous chemotherapy as visualised on the therapeutic CT, with a 1.5–2.0 cm margin. Dose plans generally consisted of 3–5 fields and isocentric treatment technique was used. The fractionation was 1.5 Gy BID, with at least six hours between fractions. The planned dose was 60 Gy during 4 weeks but patients with large tumour burdens, poor lung function or impaired general condition were given 45 Gy, according to the clinician's judgement. Approximately one third of the patients were given 60 Gy to macroscopic tumour with margin and had an adjuvant target volume, including the mediastinal lymph nodes, treated to 45 Gy. In the following analyses the whole group of patients given 60 Gy is analysed together. TRT was administered concurrently with the second or third cycle of carboplatin/etoposide. Chemotherapy treatment continued after the TRT with the aim of administering a total of six cycles.

Treatment evaluation after end of therapy included chest x-ray, CT of the chest and brain and, for the majority of patients, a bronchoscopy. If there was a complete response (CR) or "good" partial response (PR), PCI was administered as follows: 2 Gy, once daily, 5 days a week to a total of 30 Gy. Patients were followed up every 3 months with chest x-ray or CT for the first 2 years and subsequently every 6 months.

Data concerning age, sex, tumour stage, Karnofsky performance status, lung function, chemotherapy, number of CHT cycles, irradiated volume, toxicity, PCI, response, local control and cause of death have been retrospectively compiled.

Statistics

The overall survival rates were analysed according to the Kaplan Meier method and are measured from the date of diagnosis. Possible differences between comparable groups, for example males and females, were examined by log-rank test. Possible differences between non-comparable groups were examined by cox-regression test where confounding factors were taken into account. This method was used concerning the groups receiving different dose levels. Univariate and multivariate analyses for possible prognostic factors were performed.

Results

Patient characteristics

The whole material consisted of 80 patients. The median age was 65, ranging from 38 to 83, and there was a slight predominance of women (56%). Patients were given an average of 5.6 cycles of chemotherapy and the TRT was administered concurrently with the third CHT cycle (range 2–6). Thirty-four patients received 45 Gy, for the reasons mentioned previously, and 46 patients were given 60 Gy. The two groups (60 and 45 Gy) are presented in Table I. In addition to differences in tumour stage (TNM) and pulmonary function, patients also differed with respect to Karnofsky performance status and irradiated volume; the high-dose group had a better performance status and smaller treated volumes. This group also included more patients with N0 disease, fewer females and the patients were slightly younger than in the 45 Gy group.

Table I. Characteristics of the two dose groups.

	60 Gy	45 Gy
n =	46 patients	34 patients
Age	62 (mean)	69 (mean)
	38–77 (range)	45–83 (range)
Sex	52% females	62% females
	48% males	38% males
FEV1%	77 (mean)	70 (mean)
	51–112 (range)	40–129 (range)
Karnofsky	93.5 (mean)	85.6 (mean)
	75–100 (range)	70–100 (range)
PTV cm3	681 (mean)	746 (mean)
	324–1457 (range)	180–1616 (range)
Number of chemotherapy cycles	5.7 (mean)	5.5 (mean)
	3–7 (range)	3–6 (range)
$T_{1\text{-}3}N_0M_0$	7 patients	1 patient
$T_4N_+M_0$	39 patients	33 patients
Percent given PCI	54%	56%

Both groups were given the same number of chemotherapy cycles.

Radiotherapy-related acute toxicity

The major acute side effect was esophagitis: 15% of the 45 Gy group and 17% of the 60 Gy group suffered grade 3 esophagitis, as defined by the EORTC/RTOG (requires i.v. nutrition or nasogastric tube). Regarding pulmonary reactions, only 11% contracted some kind of pneumonitis with a maximum severity of grade 2. No grade 4 or 5 radiotherapy-related acute toxicity occurred.

Radiotherapy-related late toxicity

The prevalence of late lung toxicity with fibrosis and impaired lung function is hard to estimate as it has not been specifically studied. One patient in the 60 Gy group had a late esophageal stenosis.

Response

Evaluation of treatment response by chest x-ray and CT, as described above, was based on the RECIST criteria [16]. Assessment of treatment response by chest x-ray might be obscured by radiotherapy-induced fibrosis. In the high-dose group there was 33% CR, 58% PR, 0% stable disease (SD) and 9% progressive disease (PD). The corresponding figures in the lower-dose group are 35% CR, 55% PR, 0% SD and 10% PD, indicating no significant difference in treatment response between the two groups.

We did not observe any significant difference in local control, defined as freedom from progression on CT or chest x-ray at last follow-up. Local control was maintained in 70% of the high-dose group and 65% of the low-dose group.

Survival

The overall survival was analysed using the Kaplan-Meier method and is shown in Figure 1. The 3-year and 5-year survival was 25% and 16%, respectively, with a median survival of 20.8 months. The survival for the two different dose levels is shown in Figure 2. A cox-regression analyse integrating five confounding factors (sex, lung function, PTV, performance status and age) did not show any survival difference between the groups. The median follow-up was 36 months (range 10–72).

We also analysed potential prognostic factors for survival. The only significant variable found was the administration of PCI; the 3- and 5-year survival was 39% and 20% vs. 15% and 15%, respectively ($p = 0.002$). However, the reason for this is obvious as only good responders after primary treatment were given PCI (Figure 3).

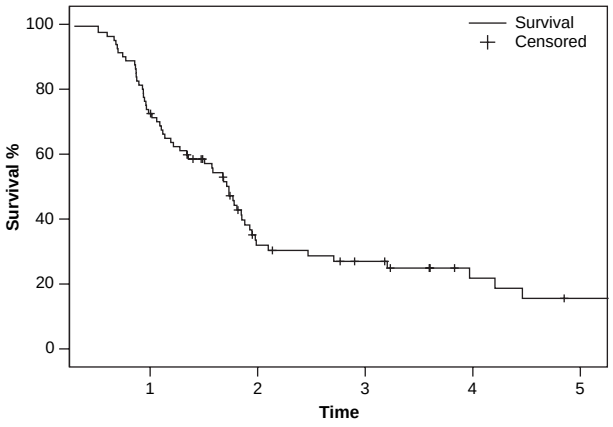

Figure 1. Overall survival (%).

We did observe trends towards improved survival in patients with better lung function (higher FEV1%), patients given radiotherapy early in the treatment regimen, patients in whom local control was achieved after completion of the therapy and patients with N0 disease. The latter group is, however, rather small in SCLC. It is notable that seven of eight patients with N0 disease were given 60 Gy. There was a clear trend towards improved survival in females (3- and 5-year survival 33% and 24%, respectively) compared with males (20% and 7%, respectively), but this difference did not reach significance ($p = 0.09$) (Figure 4). We did not observe any significant differences after univariate or multivariate analyses regarding age and number of chemotherapy cycles.

Cause of death

The two groups did not differ substantially regarding cause of death; the main cause was distant metastasis, especially brain metastases (Table II). No

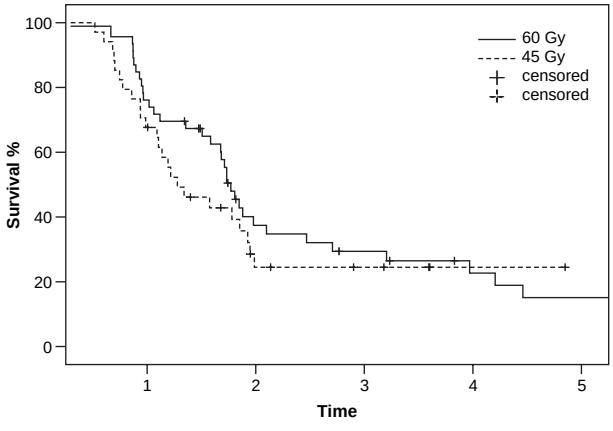

Figure 2. Survival (%), divided in two dose-groups.

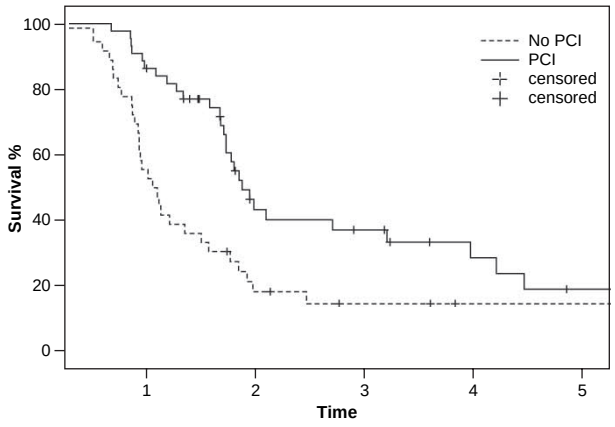

Figure 3. Survival (%), comparison between PCI patients and Non-PCI patients.

treatment related deaths were observed in either group.

Discussion

CHT in combination with TRT is considered to be standard treatment for SCLC-LD [1,2]. Factors such as timing and sequencing of TRT, fractionation, optimal doses of both CHT and TRT and treatment volumes to be irradiated, are among the important topics attaining much interest in clinical SCLC research [17,18].

Several studies have focused on the question of TRT timing. The data are somewhat contradictory, but two meta-analyses show a significant difference between early vs. late TRT [4,10]. This effect was more evident for accelerated and hyperfractionated therapy combined with platinum-based chemotherapy. Regarding sequential or concurrent TRT, there seems to be an advantage to protocols with concurrent therapy [3,19,20].

Is fractionation of importance in SCLC? Initial studies from 1999 showed a benefit from accelerated treatment [6,8], but no difference was found in a

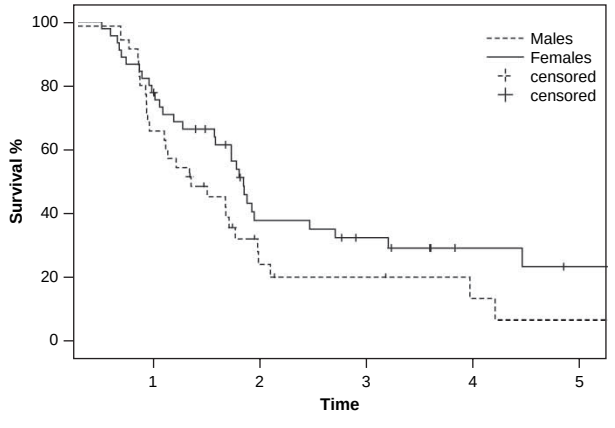

Figure 4. Survival (%), comparison between males and females.

Table II. Cause of death in the two dose groups.

%	60 Gy	45 Gy
Distant metastases (Brain)	68 (44)	75 (33)
Local recurrence	12	13
Other disease	18	4
Unknown	3	8

comparison between treatment once or twice daily in a meta-analysis the same year [7]. Bonner et al. concluded that when TRT is delayed until the fourth EP cycle, irradiation twice daily did not result in improvement of local control or survival, compared to once daily [21]. However the previously mentioned meta-analysis by Fried et al. established the superiority of accelerated hyperfractionated RT [4].

Concerning total dose, a study by Coy et al. compared two dose levels, 25 Gy vs. 37.5 Gy, showing a significantly improved local control in the higher-dose group, but no difference in survival [9]. A study comparing TRT regimens, 30 Gy (2 Gy once daily) administered to patients with extensive disease and 60 Gy to patients with LD, also found improved local control in the high-dose group [22]. A recent phase II study by Bogart et al. showed that 70 Gy with conventional fractionation is feasible in SCLC-LD [23].

The majority of the questions mentioned above were addressed when a new treatment programme for patients with SCLC-LD was introduced in western Sweden in 1997. Many clinicians consider the administration to this patient population of 1.5 Gy BID to a total of 60 Gy during 4 weeks, combined with chemotherapy, as impossible and associated with unacceptable toxicity. However, our results in the 80 patients treated according to this protocol indicate that it is indeed feasible. The main toxicity problem is grade 3 esophagitis, afflicting 15% and 17%, respectively, in the two dose groups, an acceptable rate, in our opinion, when appropriate supportive care is offered to the patients. The 3- and 5-year overall survival – 25% and 16%, respectively – is comparable with results of the majority of modern SCLC-LD studies [24]. Overall survival is quite similar in the two groups, although there is a negative selection in the lower-dose group. No substantial difference regarding local control was observed either. A possible explanation for this is the relatively small number of treated patients. Our low-dose group (45 Gy BID) received a higher biological dose than in other comparative studies in which the low-dose groups were given about 25–30 Gy [9,22]. However, it might well be that there is no dose-response relationship in SCLC-LD at doses above 45 Gy BID.

The trend towards improved survival observed in patients given early concurrent treatment is in accordance with previously published data. We did not have an upper age limit for inclusion; the oldest patient treated was 83 years old. In this analysis, age was not found to be a significant prognostic factor and older patients benefit from this treatment similarly to the younger population. Age has been reported to be an uncertain criterion for outcome and tolerability of treatment in SCLC-LD [25].

PCI is beneficial to responding patients and yields a statistically significant survival advantage, even in this relatively small material in which a 3- and 5-year survival of 39% and 20% vs 15 and 15%, respectively, was found. The reason for this is obvious, however, as only good responders after primary treatment were given PCI.

Distant metastasis is the main problem in SCLC and the main cause of death (about 70%) in our study. New chemotherapeutic agents and novel treatment approaches are under intensive investigation. Encouraging results have been reported, among others, by Arriagada and Thatcher who have shown that slightly higher chemotherapy doses and the supplement of an additional chemotherapeutic agent lead to significantly improved survival [26,27]. Even if the frequency of distant relapse can be reduced, local control is a prerequisite for long-term survival and it is therefore necessary to optimise local treatment as much as possible. This retrospective study has shown that it is possible to escalate the local absorbed dose and use an alternative fractionation regimen in combination with early administration of modern combination chemotherapy in the treatment of SCLC-LD, with acceptable toxicity. We consider these results to be important when new multi-national trials for further optimisation and standardisation of radiotherapy for SCLC-LD are designed.

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