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ORIGINAL ARTICLE

Prognostic factors in limited-stage small cell lung cancer of patients treated with combined modality approach

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Summary

Purpose: *To evaluate the combined modality treatment results of patients with limited-stage small cell lung cancer (SCLC), who were treated and followed by the DE LCSG.*

Patients and methods: *Sixty-three patients with limited-stage SCLC diagnosed between April 1991 and December 2002 were included. All patients were treated with combined chemotherapy and thoracic radiotherapy. Median age was 59 years (range 36-84), and all patients were male except 4. Surgery was performed for diagnosis in 3 patients. Four cycles of chemotherapy (median) were administered, composed of cisplatin-etoposide (CE) (26 patients), cyclophosphamide-vincristine-adriamycin (CAV) (10 patients) or alternated CE and CAV (18 patients). Nine patients received various chemotherapy regimes other than CE and/or CAV. A total dose of 5000 cGy with 180-200 cGy daily fractions was given to the primary tumor and mediastinum, excluding the spinal cord after 4500 cGy. Prophylactic cranial irradiation (PCI) was performed in 13 (20%) patients. Overall survival (OS) and progression-free survival (PFS) were calculated, beginning from the date of diagnosis and the end of radiotherapy, respectively. Kaplan-Meier method was used for obtaining survival rates. Log-rank test and Cox proportional hazards model were used for univariate and multivariate analyses, respectively.*

Results: *Median follow-up time was 17 months (range 3-131). Median PFS and OS were 12 (range 1-131) and 17 (range 3-131) months, respectively. Two-year PFS and OS rates were 27 % and 38 %, respectively. During follow-up, 27 (43%) patients developed brain metastasis; among them only 3 had received PCI. Univariate analysis showed that addition of PCI significantly improved PFS (p=0.025) and advanced age was a favorable prognostic factor for OS (p=0.039). In the multivariate analysis, advanced age (p=0.034) and addition of PCI (p=0.004) were independent factors increasing PFS, however no significant prognostic factor influencing OS was found.*

Conclusion: *Our treatment results are in accordance with the relevant literature. It is also concluded that PCI should be given to all patients with complete response to chemotherapy. However, analysis of prognostic factors should be cautiously evaluated because of small number and heterogeneous distribution of patients in subgroups. Prospective studies are necessary for better determination of prognostic factors.*

Key words: chemotherapy, limited-stage small cell lung cancer, prognostic factors, radiotherapy

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Introduction

SCLC constitutes 20-25 % of all cases of lung cancer. The most prominent characteristics of SCLC are its rapid growth potential and the presence of metastasis at diagnosis. Due to its high sensitivity to chemotherapy and radiotherapy, treatment results are quite different when compared to other lung malignancies [1].

Limited-stage SCLC, characterized by involvement of the ipsilateral hemithorax is seen in 30-40 % of the patients with newly diagnosed SCLC. Most of the patients have extensive-stage disease at diagnosis.

As a result of the sensitivity of SCLC to chemotherapy and radiotherapy, combined modality treatment is the standard approach [2]. While the median survival is 6-12 weeks without any treatment, this rate reaches 18 months in limited stage and 7-9 months in extensive stage SCLC with the use of combined modality treatment [3,4].

This study aimed to evaluate the combined modality treatment results of patients with limited-stage SCLC, followed and/or treated by Dokuz Eylül Lung Cancer Study Group (DELCSG), and also to determine the factors influencing PFS and OS.

Patients and methods

Sixty-three patients with histologically proven limited-stage SCLC diagnosed between April 1991 and December 2002 were included in this study. Follow-up and/or treatment of all the patients were carried out by DELCSG. Median age was 59 years (range 36-84) and all patients were male except 4.

For staging complete blood count, serum biochemistry, chest X-ray, bronchoscopy, thoracic and cranial computerized tomography, abdominal ultrasonography, bone scintigraphy and bone marrow biopsy were performed in all patients. Surgery was performed in only 3 patients for diagnostic purposes while all of the patients received chemotherapy and thoracic radiotherapy. All patients received their radiotherapy in our department.

According to the SCLC Treatment Protocol activated by DELCSG in 1991, response was evaluated at the end of the 2nd cycle of chemotherapy. Regimens used were CE (etoposide 80-100 mg/m^2/day, days 1-3 by short i.v. infusion plus cisplatin 75-100 mg/m^2 with pre- and posthydration on day 1, every 3 weeks) alternating with CAV (cyclophosphamide 1,000 mg/m^2, doxorubicin 45 mg/m^2 and vincristine 2 mg total dose, all given i.v. on day 1 and repeated every 3 weeks). When no response to chemotherapy was seen, thoracic radiotherapy was started. In case of response to chemotherapy, an additional 2 cycles were given and thoracic radiotherapy was started within 4 weeks after the end of the 4th course of chemotherapy. The same chemotherapy was continued after radiotherapy in responding patients up to a total of 6 cycles (4 pre- and 2-post radiotherapy). Patients referred to our institution only for radiotherapy had received various chemotherapy regimens other than those described above. Patients with complete response to the combined treatment were also offered PCI. However, some of the complete responders refused PCI because of their low socioeconomic status.

After simulation and considering the size of the tumor prior to chemotherapy, the radiotherapy field included the primary tumor and mediastinum and, in the presence of massive mediastinal involvement, the supraclavicular region was also included. Normal lung tissue was protected by individualized cerrobend blocks. Tumors were irradiated using linear accelerator energies. A total dose of 5000 cGy with 180-200 cGy daily fractions was given to the primary tumor and mediastinum, using two isocentric parallel opposed AP-PA fields. The spinal cord was excluded from the field at 4500 cGy using two isocentric parallel opposed oblique fields. PCI was given using two parallel opposed fields with daily fractions of 200 cGy up to a total dose of 2000-3000 cGy in 2-3 weeks.

Follow-up was regularly performed every 3 months. Death dates of the patients were determined by contacting the patient relatives on telephone. OS and PFS were calculated from the date of diagnosis and the end of radiotherapy, respectively. Kaplan-Meier method was used for obtaining survival rates. Log-rank test and Cox proportional hazards model were used for univariate and multivariate analyses, respectively. Age ($\leq$ 55 vs. > 55 years), sex, weight loss of more than 10% in the last 6 months (absent vs. present), number of chemotherapy cycles ($\leq$ 4 vs. > 4), type of chemotherapy regimen, radiotherapy administration from the time of diagnosis ($\leq$ 5 vs. > 5 months), response to treatment, addition of PCI (absent vs. present) were the factors put into univariate and multivariate analyses.

Results

Patient characteristics are summarized in Table 1. Weight loss of more than 10% in the last 6 months was observed in 13 (20.6 %) patients at the time of diagnosis. Karnofsky performance status of all the patients was above 70 due to their being eligible for combined modality treatment. Sixty percent of the patients were older than 55 years (Table 1).

Surgery was performed in 3 patients in whom histological diagnosis could not be obtained with conventional methods. Surgical procedures were wedge resection (1 patient), lobectomy (1 patient) and pneumonectomy (1 patient).

Table 1. Patient characteristics

Characteristic	*n (%)*
Age (years)	
≤ 55	25 (40)
> 55	38 (60)
Sex	
male	59 (94)
female	4 (6)
Weight loss (>10%)	
yes	13 (20)
no	50 (80)

Treatment characteristics are demonstrated in Table 2. Patients with proven limited-stage SCLC were given 2-12 cycles (median 4) of combination chemotherapy. Distribution according to chemotherapy schemes were CE 26 (42%) patients, CAV 10 (16%) patients or alternated CE and CAV 18 (28%) patients. Nine (14%) patients received various chemotherapy regimes other than CE and/or CAV. Twenty-five (40%) patients received more than 4 cycles of chemotherapy.

Following chemotherapy, radiotherapy started at a median of 5 months (range 2-16) from the time of diagnosis. Median thoracic radiotherapy dose was 5000 cGy (range 400-6170). One patient did not complete radiotherapy because of sudden death after the 3rd fraction. Median dose of PCI was 3000 cGy (range 2000-3000).

Median follow-up time was 17 months (range 3-131). During follow-up, 35 patients developed distant metastasis. The distribution according to the site of distant metastases was as follows: brain metastasis 27 (43%) patients, liver metastasis 6 (9%) patients, and bone metastasis 2 (3%) patients. Among the 27 patients with brain metastasis only 3 had received PCI.

Median PFS was 12 months (range 1-131), whereas median OS was 17 months (range 3-131). One, 2- and 5-year PFS rates were 46%, 27% and 12.7%, respectively (Figure 1). One, 2- and 5- year OS rates were 66.6 %, 38 % and 13.9 %, respectively (Figure 2). The median OS rate of 35 patients who developed distant metastasis during follow-up was 17 months (range 3-92), while the median OS rate after the metastasis

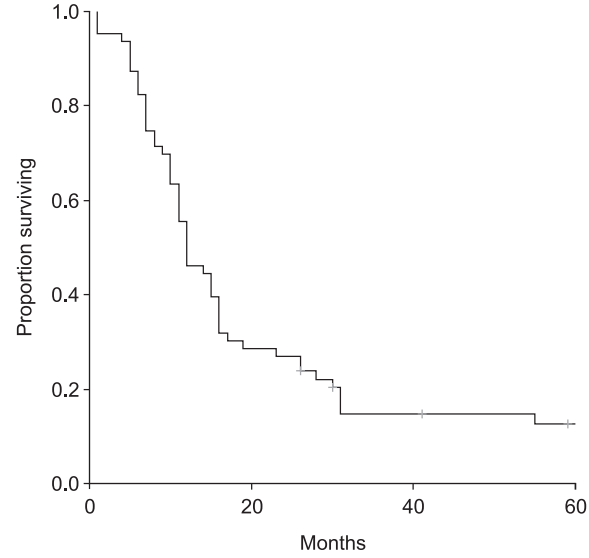

Figure 1. Progression free survival.

Table 2. Treatment characteristics

Characteristic	*n (%)*
Chemotherapy	
CE*	26 (42)
CE-CAV†	18 (28)
CAV	10 (16)
Other	9 (14)
Number of chemotherapy cycles	
≤ 4	38 (60)
> 4	25 (40)
Radiotherapy timing from the date of diagnosis (months)	
≤ 5	38 (60)
> 5	25 (40)
PCI§	
yes	13 (21)
no	50 (79)

*cisplatin-etoposide; †cyclophosphamide-adriamycin-vincristine; §prophylactic cranial irradiation

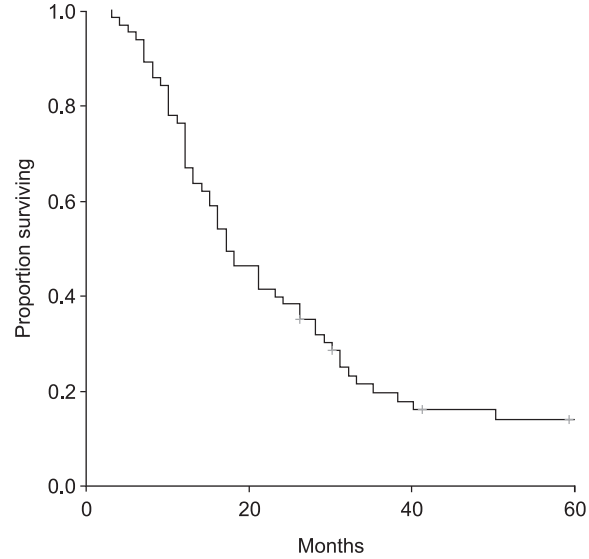

Figure 2. Overall survival.

Table 3. Univariate analysis for progression free survival

Factor	*n (%)*	*Survival (months)*	*p-value*
Age (years)			
≤ 55	25 (40)	11	0.07
> 55	38 (60)	12	
Sex			
male	59 (94)	12	0.055
female	4 (6)	55	
Weight loss (> 10%)			
yes	13 (20)	11	0.74
no	50 (80)	12	
Chemotherapy			
CE	26 (42)	12	0.75
CE – CAV	18 (28)	9	
CAV	10 (16)	16	
Other	9 (14)	22	
Number of chemotherapy cycles			
≤ 4	38 (60)	12	0.55
> 4	25 (40)	12	
Radiotherapy timing from the date of diagnosis (months)			
≤ 5	38 (60)	12	0.48
> 5	25 (40)	12	
Response to treatment			
complete response	26 (41)	15	0.12
partial response	32 (50)	11	
no response	3 (5)	6	
unknown	2 (4)	12	
PCI			
yes	13 (21)	28	0.025
no	50 (79)	11	

For abbreviations, see footnote of Table 2

Table 4. Univariate analysis for overall survival

Factor	*n (%)*	*Survival (months)*	*p-value*
Age (years)			
≤ 55	25 (40)	15	0.039
> 55	38 (60)	21	
Sex			
male	59 (94)	17	0.09
female	4 (6)	82	
Weight loss (> 10%)			
yes	13 (20)	17	0.94
no	50 (80)	17	
Chemotherapy			
CE	26 (42)	16	0.70
CE – CAV	18 (28)	17	
CAV	10 (16)	17	
Other	9 (14)	27	
Number of chemotherapy cycles			
≤ 4	38 (60)	17	0.83
> 4	25 (40)	17	
Radiotherapy timing from the date of diagnosis (months)			
≤ 5	38 (60)	17	0.56
> 5	25 (40)	21	
Response to treatment			
complete response	26 (41)	21	0.45
partial response	32 (50)	15	
no response	3 (5)	5	
unknown	2 (4)	7	
PCI			
yes	13 (21)	31	0.06
no	50 (79)	16	

For abbreviations, see footnote of Table 2

development was 5 months (range 1-35). Seven patients are still disease-free for 26-131 months (median 52).

Univariate analysis showed that addition of PCI significantly improved PFS (p=0.025) and avanced age was a favorable prognostic factor for OS (p=0.039) (Tables 3,4). In the multivariate analysis, advanced age (p=0.034) and addition of PCI (p=0.004) were significant factors increasing PFS; however, no significant prognostic factor was found affecting OS (Tables 5,6).

Discussion

The contemporary therapy of SCLC is combined-modality treatment consisting of chemotherapy and radiotherapy. Chemotherapy is basically used to control systemic disease and radiotherapy is applied to increase locoregional control. Intrathoracic recurrence rates reaching 75-80 % with chemotherapy alone are reported to decrease to 30-60 % with the addition of radiotherapy [5]. Addition of radiotherapy to chemotherapy results also in an improvement in survival by increasing local and regional disease control [6].

In the meta-analysis of thoracic radiotherapy for limited-stage SCLC carried out by Pignon and et al., 3-year OS rate was 8.9% in the chemotherapy-alone group, while this rate was 14.3% in the combined-therapy group where radiotherapy was added [6]. The 5.4 % survival advantage due to the addition of radiotherapy made the combined approach to become standard of care [6]. In our study, the 3-year OS rate of 19.4 % with combined approach is in accordance with the previously mentioned meta-analysis.

Table 5. Multivariate analysis for progression free survival

Factor	*n (%)*	*Survival (months)*	*p-value*
Age (years)			
≤ 55	25 (40)	11	0.034
> 55	38 (60)	12	
Sex			
male	59 (94)	12	0.14
female	4 (6)	55	
Weight loss (> 10%)			
yes	13 (20)	11	0.82
no	50 (80)	12	
Chemotherapy			
CE	26 (42)	12	0.27
CE – CAV	18 (28)	9	
CAV	10 (16)	16	
Other	9 (14)	22	
Number of chemotherapy cycles			
≤ 4	38 (60)	12	0.52
> 4	25 (40)	12	
Radiotherapy timing from the date of diagnosis (months)			
≤ 5	38 (60)	12	0.52
> 5	25 (40)	12	
Response to treatment			
complete response	26 (41)	15	0.88
partial response	32 (50)	11	
no response	3 (5)	6	
unknown	2 (4)	12	
PCI			
yes	13 (21)	28	0.004
no	50 (79)	11	

For abbreviations, see footnote of Table 2

Table 6. Multivariate analysis for overall survival

Factor	*n (%)*	*Survival (months)*	*p-value*
Age (years)			
≤ 55	25 (40)	15	0.07
> 55	38 (60)	21	
Sex			
male	59 (94)	17	0.08
female	4 (6)	17	
Weight loss (> 10%)			
yes	13 (20)	17	0.90
no	50 (80)	17	
Chemotherapy			
CE	26 (42)	16	0.42
CE – CAV	18 (28)	17	
CAV	10 (16)	17	
Other	9 (14)	2	
Number of chemotherapy cycles			
≤ 4	38 (60)	17	0.79
> 4	25 (40)	17	
Radiotherapy timing from the date of diagnosis (months)			
≤ 5	38 (60)	17	0.81
> 5	25 (40)	21	
Response to treatment			
complete response	26 (41)	21	0.96
partial response	32 (50)	15	
no response	3 (5)	5	
unknown	2 (4)	7	
PCI			
yes	13 (21)	31	0.057
no	50 (79)	16	

For abbreviations, see footnote of Table 2

Various prognostic factors have been analyzed in patients with SCLC including age [7-10], gender [7,11,12], weight loss [7,9], performance status [9,11,13,14], serum sodium level [9,13], serum lactate dehydrogenase level [7,10,11,13,14], serum alkaline phosphatase level [7], molecular markers [15-18], number of chemotherapy cycles [10], type of chemotherapy scheme [19], radiotherapy timing [20], response to treatment [19] and addition of PCI [9,19,21-27].

Age has been inconsistently reported as a prognostic factor in SCLC. Christodoulou et al. reported that age ≥ 60 years was a poor prognostic factor for response to treatment in SCLC on multivariate analysis [7]. Age was demonstrated as an independent prognostic factor in OS in the study performed by Work et al. [9] and Jacoulet et al. [8]; however, this was not verified by Ludbrook et al. [10]. In our study age was not an OS prognosticator in multivariate analysis, however advanced age positively affected PFS. This unexpected finding may be the result of the small number of patients in our study.

Female gender has been reported to be a favorable predictor for complete response to treatment but not for survival [7]. However, Crown et al. suggested that female gender influenced OS in a positive manner [12]. This observation was repeated in the study of SWOG where female gender was an independent favorable predictor of 2-year survival considering the database of 2501 patients consecutively enrolled in SCLC trials since 1976 [11]. In our study gender was an insignificant factor for PFS and OS, although there was a trend for significance for PFS. However, it should be noted that there were only 4 (6%) female patients in our study group compared with males (94%), a fact that prevents definite conclusions regarding gender.

Weight loss has been suggested as a significant predictor of survival in SCLC [9]. Christodoulou et al. observed that weight loss was a poor predictor for response to treatment but not for survival [7]. Also, in our study weight loss was not shown to influence survival.

Performance status is a well known prognostic factor for survival in lung cancer. Also in SCLC, good performance status at the time of diagnosis has been emphasized as a favorable parameter on survival [9,11,13,14]. Since all of the patients in our study had Karnofsky performance status of 70 or more, it was impossible for us to perform an analysis including performance status.

Serum sodium, lactate dehydrogenase and alkaline phosphatase levels at diagnosis could not be studied in our patient population because of the lack of some data, especially in patients referred from different institutions. Also, in our study molecular markers were not intended to be studied as potential prognostic factors.

The number of chemotherapy cycles has been examined in the Ludbrook et al. study in 2003 [10]. On multivariate analysis, they found that administration of ≥ 4 cycles of chemotherapy was a favorable prognostic factor for OS in patients with limited-stage SCLC. In our analysis, the number of chemotherapy cycles did not affect PFS or OS.

In the Dosoretz et al. series of 194 consecutive patients with limited-stage SCLC, patients receiving a combination of CE and CAV experienced a 3-year DFS of 31% vs. 14% for CAV only and 18% for CE only ($p=0.0004$). Receiving CE and CAV still remained as a prognostic factor in the multivariate analysis ($p=0.01$) [19]. In our study a similar comparison was also performed, however no difference was found in survival rates depending on the type of chemotherapy regimen.

Our treatment protocol was altered after the year 2002 as concomitant chemoradiotherapy instead of sequential chemotherapy and radiotherapy. In this article we present the results of the previous protocol involving sequential combined modality approach. Timing of radiotherapy from the date of diagnosis plays a major role in the prognosis of limited-stage SCLC [20]. Early initiation of radiotherapy usually involves concomitant use of radiotherapy and chemotherapy. In this case both the early registration and also potentiation (radiosensitization through the use of concomitant chemotherapy) of locoregional therapy are the most important reasons of improved survival when compared to the late initiation of radiotherapy which usually involves sequential combined modality approach as shown in Kamath et al. study [20]. Despite the fact that all our patients received sequential thoracic radiotherapy after chemotherapy, we attempted to analyze the early initiation of radiotherapy and could not demonstrate any beneficial effect in PFS or in OS. This might be due to the absence of concomitant approach in the series as well as to the small number of patients in each group.

Response to treatment has been reported as an independent prognostic factor for OS in the Dosoretz et al. study [19], while this was not confirmed in our study. The relatively small number of patients in our study might have masked the prognostic significance of response to treatment.

Brain metastasis at presentation is encountered in 8-10 % of SCLC patients and reaches 80 % in patients who have lived more than 2 years from the time of diagnosis [28]. In our series, with a median follow-up of 17 months, the percentage of patients developing brain metastasis is 43 %.

While many authors reported that PCI had no significant effect on survival [21,25-27], others suggested the opposite [9,19,22-24]. The meta-analysis performed by Auperin et al. tried to answer whether PCI improved survival in SCLC patients being in complete remission [29]. In this meta-analysis involving 987 patients, PCI was found to cause a 5.4 % increase in the 3-year OS rate (15.3 % in the control group vs. 20.7 % in the treatment group). Also disease-free survival was increased with the addition of PCI [29]. Addition of PCI was also an independent predictor of increased PFS but not of OS in our series. However, it should be noticed that only 13 patients received PCI in our series which might have affected the result of multivariate analysis for OS.

Conclusion

Our treatment results obtained by thoracic radiotherapy given after combination chemotherapy are in accordance with the relevant literature. It is also concluded that PCI should be given to all patients with complete response to chemotherapy. However, analysis of prognostic factors should be cautiously evaluated because of small number and heterogeneous distribution of patients in subgroups. Prospective studies with large number of patients are necessary for better determination of prognostic factors.

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