Karnofsky Performance Score, Radiation Dose and Nodal Status Predict Survival of Elderly Patients Irradiated for Limited-disease Small-cell Lung Cancer

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Abstract. *Aim: Elderly patients require special consideration in oncology treatment. Small-cell lung cancer (SCLC) is a highly aggressive tumour with dismal prognosis. The present study focused on prognostic factors in elderly patients irradiated for limited-disease SCLC. Patients and Methods: In 36 patients aged ≥65 years, 11 factors were evaluated for the impact on survival, namely gender, Karnofsky performance score, body mass index, T-category, N-category, tobacco consumption, time from SCLC diagnosis to irradiation, smoking during irradiation, simultaneous chemotherapy, radiation dose and prophylactic cranial irradiation. Results: On multivariate analysis, Karnofsky performance score of >70 (p<0.001), N-category 0-2 (p≤0.001) and total radiation dose of >52 Gy (p=0.011) were significantly associated with better survival. Conclusion: Significant predictors of survival in elderly patients irradiated for limited-disease SCLC were identified. A radiation dose of >52 Gy resulted in improved survival when compared to lower doses.*

Demographic change with increasing numbers of elderly patients has an impact on oncology treatment and requires special attention due to higher comorbidity index and divergent prognosis (1-7). Patients with small-cell lung cancer (SCLC) represent 10-25% of all patients with lung cancer. Of all patients with SCLC, 50-68% of patients are diagnosed at the age of 65 years or older (8-11). These elderly patients are generally characterized by a higher comorbidity index, reduced organ function and a reduced bone marrow reserve when compared to younger patients. Furthermore, the prognoses of elderly patients with SCLC were reportedly significantly worse than in younger patients (7, 10). Thus, patients aged ≥65 years should be considered as a separate group.

For patients with SCLC, radiochemotherapy is the standard treatment in cases with limited disease (12). However, many elderly patients cannot tolerate intensive treatment regimens (7, 10). The intensity of such a treatment regimen should always be adjusted to individual patient factors such as co-morbidity, performance score and a patient's estimated remaining life span. Thus, in order to select the most appropriate treatment regimen for an individual elderly patient with SCLC, it would be helpful to be able to estimate the survival time. Such estimations would be considerably facilitated by the knowledge of significant prognostic factors. The present study was performed in order to identify such predictors in a cohort of elderly patients presenting with limited-disease SCLC and contribute to the individualisation of their treatment.

Patients and Methods

Thirty-six elderly patients with SCLC who were treated with radiochemotherapy for the primary tumour and involved lymph nodes were included in this retrospective study. The median age was 69.5 years and all patients were 65 years or older when radiochemotherapy was started. Chemotherapy consisted of two to six courses of etoposide (120 mg/m^2 on days 1-3) plus either cisplatin (60-80 mg/m^2 on day 1) or carboplatin (area under the curve of 6 on day 1). One patient refused the planned chemotherapy. Prophylactic cranial irradiation (PCI) following radiochemotherapy was part of the treatment program for 26 (72%) patients.

The total radiation doses were calculated as equivalent doses in 2 Gy fractions (EQD2) (3). Two EQD2 levels (≤52 *vs.* >52 Gy) and 10 additional characteristics were analysed for potential associations with survival. These 10 characteristics were gender (male *vs.* female), Karnofsky performance score (≤70 *vs.* >70), body mass index (<20 *vs.* ≥20 kg/m^2), T-category (1-3 *vs.* 4), N-category (N0-2 *vs.* 3), pack years (<40 *vs.* ≥40 years), time between first diagnosis

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Table I. *Analyses of survival of patients with small-cell lung cancer (SCLC).*

Characteristic	Survival at			*p*-Value[a]	
	1 Year (%)	2 Year (%)	3 Year (%)	Univariate analysis	Multivariate analysis
Gender					
Female (n=10)	70	20	0		
Male (n=26)	58	23	15	0.87	
Karnofsky performance score					
≤70 (n=12)	17	0	0		
>70 (n=24)	75	38	17	**<0.001**	**<0.001**
Body mass index, kg/m^2					
<20 (n=4)	50	25	0		
≥20 (n=32)	56	25	13	0.23	
T-Category					
1-3 (n=25)	56	28	16		
4 (n=11)	55	18	0	0.50	
N-Category					
0-2 (n=27)	67	33	15		
3 (n=9)	22	0	0	**0.005**	**0.018**
Pack years					
<50 (n=25)	52	16	12		
>50 (n=11)	64	46	9	0.40	
Time from diagnosis of SCLC to irradiation					
≥2 Months (n=29)	62	28	10		
<2 Months (n=7)	29	14	14	0.62	
Smoking during irradiation					
Yes (n=8)	38	13	0		
No (n=28)	61	29	14	0.15	
Concurrent chemotherapy					
Yes (n=13)	54	23	15		
No (n=23)	57	26	7	0.13	
Radiation dose (EQD2)					
≤52 Gy (n=14)	54	15	0		
>52 Gy (n=22)	57	30	17	**0.029**	**0.007**
Prophylactic cranial irradiation					
Yes (n=26)	69	35	15		
No (n=10)	20	0	0	**0.001**	0.75

[a]According to log-rank test for univariate and Cox regression for multivariate analysis. Significant values are shown in bold.

of SCLC and start of radiotherapy (<2 *vs.* ≥2 months), smoking during radiotherapy (no *vs.* yes), concurrent chemotherapy (yes *vs.* no) and prophylactic cranial irradiation (yes *vs.* no).

The univariate analyses of these factors with respect to survival were performed using the Kaplan–Meier method and the log-rank test (13). The characteristics that showed a significant association with survival ($p<0.05$) were additionally included in a multivariate (Cox regression) analysis.

Results

Median survival in the entire cohort was 17 months. The results of both the univariate and the multivariate analyses of survival are summarized in Table I. In the univariate analyses, a significantly positive association with survival was found for a Karnofsky performance score of >70 ($p<0.001$), N-category 0-2 ($p=0.005$), administration of PCI ($p=0.001$) and a radiation dose (EQD2) of >52 Gy ($p=0.029$, Figure 1). Consequently, these factors were included in the multivariate analysis (Cox regression model). On multivariate analysis, Karnofsky performance score of >70 ($p<0.001$), N-category 0-2 ($p=0.018$) and a radiation dose (EQD2) of >52 Gy ($p=0.007$) achieved significance and were, therefore, identified as independent positive prognostic factors.

Discussion

The proportion of elderly patients in oncology is constantly increasing. This fact has to be taken into account regarding current research obstacles, individualized care and potential impact of comorbidities on patient prognosis and treatment

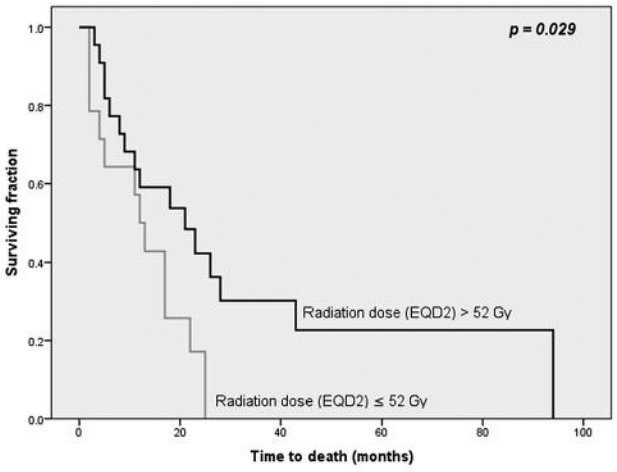

Figure 1. *Kaplan–Meier curves of patients according to radiation dose (EQD2).*

benefit. This also applies to patients with SCLC. Several biomarkers have been found to have an impact on prognosis of such patients (14, 15). Radiochemotherapy represents the currently most effective treatment option for LD-SCLC. Most patients are not suitable for thoracic surgery or refuse surgical resection. However, radiochemotherapy is a relatively aggressive treatment, which may not be tolerated by elderly patients. The treatment for elderly patients should ideally be effective but not burdensome or too toxic. In a phase II trial, patients were treated with high-dose radiotherapy (60 Gy in 40 fractions, two fractions per day) combined with cisplatin and etoposide and experienced a favourable median survival time of 22 month (16). However, 80% of the patients developed grade 4 or greater toxicity. Thus, careful selection of patients, particularly of elderly patients, is mandatory to achieve optimal results. Prognostic factors of survival need to be identified to optimize treatment allocation in respect of the patient's prognosis. A retrospective study of elderly patients with SCLC showed that extensive-disease SCLC and fewer than four cycles of chemotherapy were independent negative prognostic factors (11). In contrast, the performance status was not a prognostic factor in this study, but was reported to be of prognostic significance in other studies (7, 17). The findings of our present study agree with those of the latter two studies (7, 17) that showed the performance status to be an independent prognostic factor.

PCI is a standard part of the treatment of patients with LD-SCLC who achieved complete response after radiochemotherapy. In the present study, PCI was significantly associated with survival on univariate analysis but not on multivariate analysis. This finding might be explained by the fact that PCI was administered preferentially to patients with a good performance status.

The prognostic impact of the N-category is controversial. Reyman *et al*. found no negative prognostic impact for patients with N3 category *vs*. N0-2 category (17). In contrast to these findings, our study showed that N3 category (vs. N0-2 category) was an independent negative prognostic factor.

The optimal radiation dose for elderly patients with LD-SCLC is unclear. The present study compared two dose groups, ≤52 Gy and >52 Gy, with respect to survival. According to the results, radiation doses of more than 52 Gy resulted in a significantly better survival rate than at doses of ≤52 Gy. This is an important finding, since taking into account age and co-morbidities, radiation oncologists may tend to use radiation doses lower than 52 Gy which, according to the results of this study, appear not to be sufficient. However, the retrospective nature of the present study and the relatively small number of patients should be considered when interpreting these results.

In conclusion, several independent prognostic factors of survival were identified for elderly patients with LD-SCLC and can guide physicians in optimizing individual treatment for these patients. A radiation dose (EQD2) of more than 52 Gy resulted in significantly better survival rates than lower doses. Thus, elderly patients, particularly those treated in curative intention, should receive optimal supportive care ensuring that the patients can receive a radiation dose of greater than 52 Gy.

Conflicts of Interest

On behalf of all Authors, the corresponding Author states that there is no conflict of interest related to this study.

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