Impact of the Radiation Dose on Survival after Radiochemotherapy for Small-cell Lung Cancer

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Abstract. *Aim: Radiochemotherapy for small-cell lung cancer may not be sufficiently tolerated by all patients. To contribute to better personalization of the radiochemotherapy programs, this study compared two radiotherapy doses and 10 characteristics for survival. Patients and Methods: In 71 patients receiving radiochemotherapy for small-cell lung cancer, the radiation dose given as equivalent dose in 2 Gy fractions (EQD2: <56 vs. ≥56 Gy) plus 10 characteristics, namely gender, age, Karnofsky performance score, T-category, N-category, tumor stage, pack years, smoking during radiotherapy, respiratory insufficiency and hemoglobin prior to radiotherapy, were evaluated for survival. Results: On multivariate analysis, EQD2 ≥56 Gy (p=0.003), female gender (p=0.029), Karnofsky performance score >70 (p<0.001), very limited disease (p=0.043) and pre-radiotherapy hemoglobin ≥12 g/dl (p=0.044) were significantly associated with better survival. Conclusion: This study identified several independent predictors of survival after radiochemotherapy of small-cell lung cancer. A radiation dose of ≥56 Gy resulted in better survival than lower doses.*

Small-cell lung cancer accounts for up to 25% of all lung cancer (1). Radiochemotherapy is the standard treatment for patients with limited disease (T3-4 or N2-3 M0) and can be a reasonable alternative for patients with unresectable very limited disease (2). Since radiochemotherapy may be associated with significant toxicity, including fatigue, nausea, radiation-induced pneumonitis or chemotherapy-induced pancytopenia, nephrotoxicity and peripheral polyneuropathy, such an intensive treatment regimen may not be sufficiently tolerated by all patients. To avoid over- or undertreatment, it is important to know the optimal doses of both radiotherapy and chemotherapy for these patients. To contribute to this knowledge, the current study compared two different dose levels of radiotherapy with respect to survival. Furthermore, in order to achieve the best possible treatment results, personalization of the radiochemotherapy program is recommended and should take into consideration the remaining lifespan of the patients concerned. Therefore, this study investigated ten further characteristics in addition to the radiation dose that might be associated with the survival prognoses of patients with SCLC.

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Patients and Methods

Seventy-one SCLC patients treated with radiochemotherapy for primary tumor and involved lymph nodes were included in this retrospective study. 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 (AUC 6 on day 1). Two patients refused the planned chemotherapy. Prophylactic cranial irradiation (PCI) following radiochemotherapy was part of the treatment program and administered to 54 patients. Seventeen patients did not receive PCI due poor performance status or death prior to the start of PCI.

The radiation dose was given as equivalent dose in 2 Gy fractions (EQD2) (3). The EQD2 (<56 *vs.* ≥56 Gy) and 10 characteristics were analyzed for potential associations with survival. These 10 characteristics were gender, age (≤64 *vs.* ≥65 years; median=65 years), Karnofsky performance score (≤70 *vs.* >70), T-category (T1-2 *vs.* T3-4), N-category (N0-1 *vs.* N2-3), stage (very limited disease *vs.* limited disease), pack years (< 40 *vs.* ≥40 years), smoking during radiotherapy (no *vs.* yes), respiratory insufficiency (no *vs.* yes), and hemoglobin prior to radiotherapy (<12 *vs.* ≥12 g/dl).

The univariate analyses of these factors with respect to survival were performed using the Kaplan–Meier method and the log-rank test (4). The characteristics that showed a significant association with survival ($p<0.05$) were additionally included in a multivariate (Cox regression) analysis.

Results

In the univariate analyses, better survival was associated with an EQD2 ≥56 Gy ($p=0.045$), female gender ($p=0.032$), a Karnofsky performance score of >70 ($p<0.001$), very limited

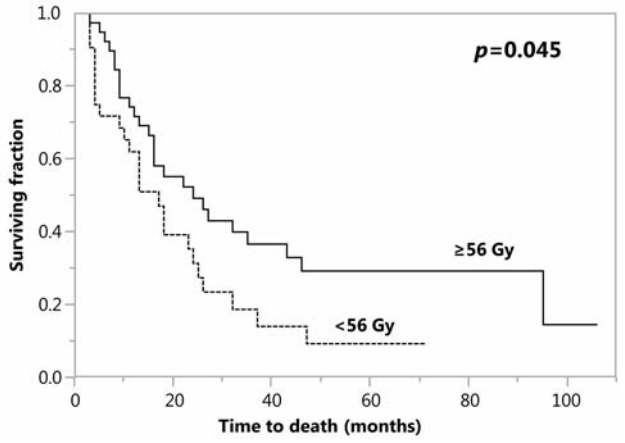

Figure 1. *Kaplan–Meier curves of patients receiving an equivalent dose in 2 Gy fractions of ≥56 Gy compared to patients treated with doses <56 Gy.*

disease (p=0.041), smoking fewer than 40 pack years (p=0.036), no smoking during radiotherapy (p=0.009), and a pre-radiotherapy hemoglobin of ≥12 g/dl (p=0.035). The results of the univariate analyses are given in Table I.

In the multivariate analysis, EQD2 (p=0.003), gender (p=0.029), Karnofsky performance score (p<0.001), tumor stage (p=0.043) and pre-radiotherapy hemoglobin (p=0.044) were significantly associated with survival (Table I). Pack years (p=0.30), and smoking during radiotherapy (p=0.31) were not significant in the Cox regression analysis. Figure 1 shows Kaplan-Meier curves from univariate analysis of these factors with respect to patient survival.

Discussion

The treatment of small-cell lung cancer has considerably improved due to new treatment approaches (5, 6). The vast majority of patients presenting with limited disease receive definitive radiochemotherapy. This approach is also reasonable for patients with very limited disease who are not suitable for thoracic surgery or refuse resection of their tumor. The optimal radiation dose for limited or very limited small-cell lung cancer still needs further clarification. Since radiochemotherapy is quite aggressive and may not be well tolerated by all patients, it is important to identify a dose which is both effective and not too toxic. A phase II trial demonstrated that high-dose radiotherapy (60 Gy in 40 fractions, two fractions per day) combined with cisplatin and etoposide resulted in a favorable median survival time of 22 months (7). However, 95% of the patients experienced grade 3 or greater toxicity, and 80% grade 4 or greater. These data support the idea of tailoring the radiochemotherapy program to the particular situation and characteristics of each individual patient. The present study compared two dose (EQD2) groups, <56 Gy and ≥56 Gy, with respect to survival. According to the results, doses of 56 Gy or more resulted in significantly greater survival rates than at a dose of <56 Gy. These findings agree with the results of the previous phase II trial.

Further improvement of the treatment of small-cell lung cancer may be achieved with better individualization of the treatment approaches taking into account prognostic factors (8-10). Therefore, in addition to the radiation dose, this study investigated 10 additional characteristics for a potential association with survival. Gender, Karnofsky performance score, tumor stage and pre-radiotherapy hemoglobin were significant independent predictors of survival. In a previous pooled analysis of the data of 14 small-cell lung cancer trials, gender was a significant prognostic factor of survival in patients with limited disease (11). Performance status had a significant impact on survival only in patients with extensive disease. In the present study, the pre-radiotherapy hemoglobin level was a significant predictor of survival. The finding that anemia was associated with poorer survival can be explained by the fact that the effect of radiotherapy depends on tumor oxygenation. Anemia results in tumor hypoxia, which has a negative impact on the production of radiation-induced cytotoxic free radicals. These radicals are mandatory for both DNA damage and tumor-cell kill (12). These data reveal that the results of the present study are consistent with data which has been already reported in the literature (11, 12).

In conclusion, this study identified several independent predictors of survival after radiochemotherapy of small-cell lung cancer, which may guide physicians when aiming to tailor the treatment to an individual patient's specific situation. A radiation dose of 56 Gy or more resulted in significantly better survival than doses <56 Gy. Therefore, patients with SCLC, particularly those treated with curative intention, should receive maximum supportive care in order to ensure that they can receive a radiation dose of at least 56 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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Table I. *Survival rates at 1 and 3 years after radiochemotherapy for small-cell lung cancer.*

Characteristic	Survival		*p*-Value	
	At 1 year (%)	At 3 years (%)	Univariate analysis	Multivariate analysis
Radiation dose (EQD2)				
<56 Gy (n=32)	62	19		
≥56 Gy (n=39)	72	37	0.045	0.003
Gender				
Female (n=26)	85	46		
Male (n=45)	57	19	0.032	0.029
Age				
≤64 Years (n=34)	73	34		
≥65 Years (n=37)	62	24	0.13	---
Karnofsky performance score				
≤70 (n=17)	18	0		
>70 (n=54)	83	37	<0.001	<0.001
T-Category				
T1-2 (n=26)	69	47		
T3-4 (n=45)	66	19	0.17	---
N-Category				
N0-1 (n=12)	83	65		
N2-3 (n=59)	64	21	0.07	0.12
Stage				
Very limited disease (n=7)	100	86		
Limited disease (n=64)	64	21	0.041	0.043
Smoking history				
<40 Pack years (n=32)	78	41		
≥40 Pack years (n=39)	58	18	0.036	0.30
Smoking during radiotherapy				
No (n=53)	72	35		
Yes (n=18)	55	8	0.009	0.31
Respiratory insufficiency				
No (n=59)	69	32		
Yes (n=12)	57	12	0.10	---
Hemoglobin before radiotherapy				
<12 g/dl (n=33)	52	19		
≥12 g/dl (n=38)	81	37	0.035	0.044

EQD2: Equivalent dose in 2 Gy fractions.

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