

Karnofsky Performance Score and Radiation Dose Predict Survival of Patients Re-irradiated for a Locoregional Recurrence of Small Cell Lung Cancer

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Abstract. Aim: When patients with small cell lung cancer (SCLC) experience locoregional recurrence, surgery is often not employed as salvage therapy. Systemic chemotherapy and radiotherapy are often used. Many radiation oncologists are reluctant to deliver a second course of radiotherapy. However, select patients may benefit from re-irradiation. This study aimed to identify these patients. Patients and Methods: In patients receiving re-irradiation for a locoregional recurrence of SCLC, 11 potential prognostic factors were analyzed for survival. Results: Survival was positively associated with a Karnofsky performance score ≥ 80 ($p=0.003$) and a cumulative dose >90 Gy ($p=0.026$). A trend was observed for younger age, longer interval between first course of radiotherapy and re-irradiation, a greater dose of re-irradiation and for concurrent chemotherapy. Conclusion: Significant predictors of survival in patients re-irradiated for a locoregional recurrence of SCLC were identified. Patients with a good performance status can benefit from re-irradiation if administered in sufficient doses.

Patients with small cell lung cancer (SCLC) account for 10% to 25% of all patients with lung cancer (1). Since SCLC is a highly chemo- and radiosensitive tumor entity, surgery plays a less important role than for other solid tumor types, including non-small cell lung cancer (2). Radiotherapy is generally delivered to the primary tumor and the regional lymph nodes (3). When a patient experiences locoregional recurrence, surgery is rarely

employed for salvage therapy, with systemic agents and radiotherapy being more often employed.

When a second course of radiotherapy (re-irradiation) is considered, one must critically assess the tolerance doses of the organs at risk such as lungs, heart, spinal cord and esophagus (3). Since the tolerance of these organs is often already exhausted in such cases, the total dose of the second course of radiotherapy is usually lower than that of the first course, often resulting in a lesser treatment effect (3). This concern regarding excessive toxicity may ultimately hinder aggressive salvage therapy and worsen the already poor prognoses of patients requiring re-irradiation for recurrent SCLC. Most failures after initial therapy are at distant sites and radiation oncologists are often reluctant to deliver a second course of radiotherapy to patients with locoregional recurrence. However, it is possible that selected patients can benefit from re-irradiation in terms of longer survival. The current study was performed to define the outcome of patients re-irradiated for SCLC and to identify prognostic factors that help detect patients who appear to benefit the most from re-irradiation.

Patients and Methods

Data of 11 patients who required a second course of radiotherapy (re-irradiation) for locoregional recurrence of SCLC were analyzed for survival. Initial treatment consisted of 50 to 60 Gy of conventionally fractionated radiotherapy supplemented by one to four courses of chemotherapy with carboplatin and etoposide. No patient had distant metastases at the time of primary radiotherapy and at the time of re-irradiation. Eight patients had received prophylactic cranial irradiation. A total of 11 potential prognostic factors were investigated, namely gender, T-stage at initial diagnosis (T2-3 vs. T4), initial N-stage (N0-2 vs. N3), age at re-irradiation (<68 vs. ≥ 68 years, median age=68 years), pack years (≤ 40 vs. >40 years), interval between first course of radiotherapy and re-irradiation (<18 vs. ≥ 18 months, median=17 months), site of recurrence (lobe vs. mediastinum vs. other), Karnofsky performance score (≤ 70 vs. ≥ 80 , median=80), dose of re-irradiation

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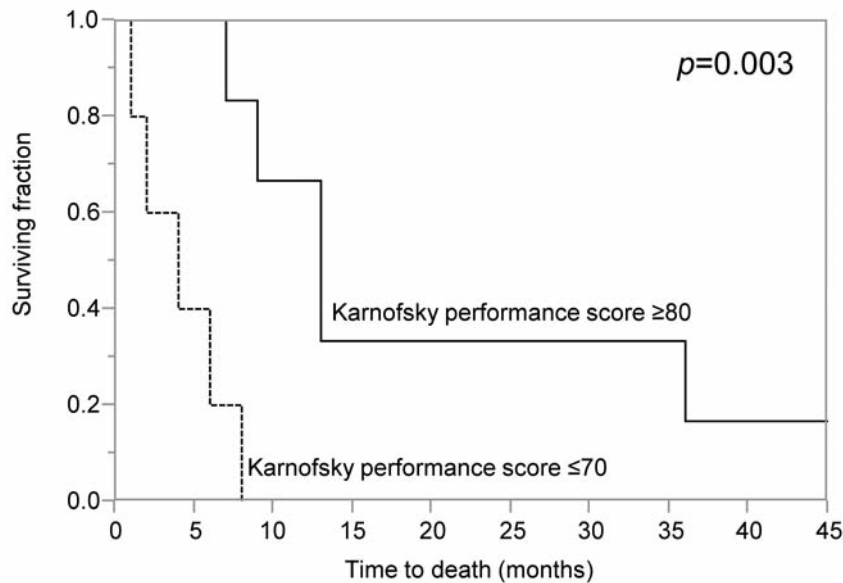


Figure 1. Kaplan–Meier curves of patients with a Karnofsky performance score of ≤ 70 and those patients with a score of ≥ 80 .

given as equivalent dose in 2 Gy fractions (EQD2; 28–30 Gy vs. 36–42 Gy), concurrent chemotherapy with topotecan (yes vs. no) and the cumulative (first radiotherapy plus re-irradiation) EQD2 (<90 Gy vs. 90 Gy vs. >90 Gy) (4). For the analyses of potential associations with survival, the Kaplan–Meier method and the log-rank test were used (5).

Results

The 1-year and 2-year survival rates for the entire cohort were 36% and 18%, respectively. The median survival after re-irradiation was 8 months. According to the survival analyses, survival was positively associated with a Karnofsky performance score of ≥ 80 ($p=0.003$, Figure 1) and a cumulative EQD2 of >90 Gy ($p=0.026$). In addition, a trend ($p<0.20$) towards improved survival was observed for younger patients (<68 years; $p=0.13$), with a longer (≥ 18 months) interval between first course of radiotherapy and re-irradiation, a greater (36–42 Gy) dose of re-irradiation ($p=0.16$) and concurrent chemotherapy with topotecan ($p=0.19$). The results of the analyses of survival are summarized in Table I.

Discussion

In patients with SCLC, surgery plays a minor role compared to patients with many other types of solid tumors, even in cases of recurrent disease. Since SCLC is very chemosensitive, systemic agents are important for the treatment of both metastatic disease and locoregional recurrence (2). Several new second-line regimens have been

introduced (6, 7). However, despite these new approaches, the prognosis of patients with recurrent SCLC is poor. In recent years, the development of personalized treatment regimens has been recognized as an additional option to improve the outcome of patients with cancer. In order to achieve this goal, a clear understanding of prognostic factors is essential. Several preclinical markers have been identified, such as nuclear survivin expression and the alternatively spliced actinin-4 variant (8, 9). Furthermore, prognostic factors have already been found for clinical conditions such as brain metastases from SCLC (10–12). The options of re-irradiation of the primary tumor/regional lymph nodes in cases of locoregional recurrence can be limited due to the potential damage to organs at risk. Potential sequelae may include, for example, pneumonitis, lung fibrosis, pericarditis, myelopathy, esophagitis and fistula. Therefore, re-irradiation to the thorax requires delivery using extraordinary clinical and radiobiological experience and modern high-precision radiation techniques. Many radiation oncologists are quite reluctant to administer a second course of thoracic irradiation. However, selected patients could benefit from re-irradiation. In order to properly identify these patients, prognostic factors are important. In the present study, the Karnofsky performance score (≥ 80 vs. ≤ 70) proved to be the most significant predictor of survival, followed by the cumulative radiation dose (>90 Gy vs. 90 Gy and <90 Gy). When combining both factors, in patients with a Karnofsky performance score of ≥ 80 and cumulative radiation dose of >90 Gy, the 2-year survival rate was 100%. Thus, patients with a good performance status at the time of their

Table I. Analyses of survival (*p*-values according to log-rank test).

Factor	At 1 year (%)	At 2 years (%)	<i>p</i> -Value
Gender			
Female (N=4)	25	25	0.63
Male (N=7)	43	14	
Initial T-stage			
T2-3 (N=6)	33	17	0.52
T4 (N=5)	40	20	
Initial N-stage			
N0-2 (N=8)	38	13	0.96
N3 (N=3)	33	33	
Age at re-irradiation			
<68 Years (N=5)	40	40	0.13
≥68 Years (N=6)	33	0	
Pack Years			
≤40 Years (N=7)	43	20	0.43
>40 Years (N=4)	25	0	
Interval from first radiotherapy to re-irradiation			
<18 Months (N=6)	17	0	0.11
≥18 Months (N=5)	60	40	
Site of locoregional recurrence			
Lobe (N=5)	40	0	0.88
Mediastinum (N=4)	25	25	
Other (N=2)	50	50	
Karnofsky performance score			
≤70 (N=5)	0	0	0.003
≥80 (N=6)	67	33	
Dose of re-irradiation			
28-30 Gy (N=6)	17	0	0.16
36-42 Gy (N=5)	60	40	
Concurrent chemotherapy (topotecan)			
Yes (N=3)	67	33	0.19
No (N=8)	25	13	
Cumulative dose of first radiotherapy plus re-irradiation			
<90 Gy (N=3)	0	0	0.026
90 Gy (N=5)	40	0	
>90 Gy (N=3)	67	67	

recurrence of SCLC appear to benefit from re-irradiation for a considerable time if they receive appropriate radiation doses. The main limitation of this study was its retrospective design, which could introduce uncontrolled biases, and the small sample size, which reduced the power to detect differences should they exist between the studied groups.

In conclusion, this study identified significant predictors of survival in patients re-irradiated for locoregional recurrence of SCLC. Patients with a good performance status appear to benefit from re-irradiation, which ought to be administered at sufficiently high doses. Re-irradiation should ideally be performed in an experienced and well-equipped radiation oncology Center.

Conflicts of Interest

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

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