Original Article

Prognostic factors and outcome of reirradiation for locally recurrent small cell lung cancer—a multicenter study

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Background: The prognosis of patients with recurrent small cell lung cancer (SCLC) remains poor and treatment options are limited. We performed a multi-institution retrospective cohort study to evaluate the outcome of thoracic reirradiation, identify prognostic factors and assess treatment-related toxicity.

Methods: Data of 33 patients re-irradiated for recurrent SCLC at 4 international university hospitals, were analysed. Overall survival (OS) acute and late toxicities were evaluated and prognostic factors for reirradiation were identified.

Results: Reirradiation (Re-RT) was performed at a median interval time of 24 months after the first thoracic radiotherapy series. Median survival after reirradiation was 7 months (range, 1–54 months). The Re-RT dose in EQD2 ranged from 20 to 87.50 Gy with a median of 32.50 Gy. The 1- and 2-year OS were 33% and 17%, respectively. Patients with a good performance status (KPS >70%), absence of extrathoracic disease, reirradiation dose (EQD2) of >40 Gy and a cumulative dose of first plus second series of radiotherapy (EQD2) >90 Gy were associated with improved OS. Acute pulmonary Grade 1–2 toxicity from re-irradiation was recorded in 11 patients (33%) and grade 3 acute toxicity was encountered 1 patient (3%).

Conclusions: Reirradiation for locoregionally recurrent SCLC is safe and shows promising outcomes. Patients reirradiated with doses >40 Gy experienced more favourable survival rates. In contrast, patients with a poor performance status or extrathoracic disease have a poor prognosis and Re-RT should be considered only for symptom control in this group.

Keywords: Small cell lung cancer (SCLC); recurrence; reirradiation; outcome; prognostic factor

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Introduction

Small cell lung cancer (SCLC) represents 10% to 25% of all lung cancers and is considered to be a highly aggressive malignancy with early local recurrences and distant metastases (1-3). In limited stage SCLC, a multimodal treatment including chemoradiotherapy followed by prophylactic cranial irradiation is the standard of care and shows high rates of complete and partial remissions (4,5).

However, loco-regional recurrence and distant failure are often seen during follow-up after primary treatment. Retreatment options such as cytotoxic or targeted agents and surgery are limited or frequently result in less favourable outcomes (2,6,7). European guidelines recommend re-administering of the first-line chemotherapy regimen (platinum/etoposide combinations) for relapse >6 months after completion of initial therapy (5). For relapse ≤6 months after initial therapy, sequential treatment with single agents is recommended (5). Despite many clinical trials using cytotoxic or targeted agents or immune checkpoint inhibitors, the prognosis of patients with recurrent SCLC is still poor with overall survival (OS) rates of <40% at 6 months and<10% at 12 months, respectively (8). Reirradiation has the potential to provide sufficient local control, and patients without extrathoracic disease may experience long-term survival. In the past, reirradiation was challenging due to concerns regarding toxicities and the inability to safely deliver sufficient doses during the second course of radiotherapy (9).

As a result of modern radiation techniques and image-guidance, reirradiation for thoracic malignancies has become safer and has shown promising outcomes in patients with recurrent non-small cell lung cancer (NSCLC) (10-12). In contrast, data for recurrent SCLC are scarce (3,11-16). We performed a multi-institution retrospective cohort study to evaluate the outcome of reirradiation, identify prognostic factors and assess treatment-related toxicity in this group of patients.

Methods

Patients

Data of 33 patients with a loco-regional recurrence of SCLC, who underwent reirradiation at 4 university hospitals in Germany, Japan, Turkey and USA between 2008 and 2015, were collected. This study received approval by each local Ethical Committee and was based on a retrospective analysis of patient records. Data regarding patient characteristics at initial irradiation and reirradiation, outcomes and treatment-related toxicity were evaluated.

Initial diagnosis and treatment

All patients were diagnosed with a histologically confirmed SCLC between 2004 and 2013. Initial stage was considered very limited disease in 14 patients, limited disease in 17 patients and extensive disease in 2 patients according to the classification of the Veterans Administration Lung Study (17). Initial treatment consisted of concurrently chemoradiotherapy (platinum-based chemotherapy (cisplatin/carboplatin) with etoposide) in 91% of all patients. Two patients with extensive stage disease received palliative radiation for superior vena cava syndrome with sequential chemotherapy (carboplatin and etoposide). Thoracic radiotherapy was given twice-daily with a single dose of 1.5 Gy according to Turrisi *et al.* (18) in 13 (39%) patients, normofractionated with an EQD2 ≥60 Gy in 7 (21%) patients (61%) or in palliative intention with a median EQD2 of 54 Gy (range, 13–58 Gy) in 13 (39%) patients (*Table 1*). Prophylactic cranial irradiation after definitive chemoradiotherapy was applied in 76% of the patients.

Diagnosis and treatment at recurrence

The diagnosis of a thoracic recurrence was made by experienced radiologists based on computed tomography (CT) or PET-CT imaging, with or without pathologic confirmation.

Reirradiation was applied to the availability of each center with three-dimensional conformal radiotherapy (3D-CRT) or intensity modulated radiotherapy (IMRT). Different reirradiation doses and fractionations were employed in relation to the tumor volume, and the proximity of organs at risk (OARs) and previous exposure. In order to compare the administered radiation dose of all patients the equivalent dose in 2 Gy fractions (EQD2) using α/β ratio of 10 was calculated for all radiation courses (initial- and re-irradiation, cumulative dose). Reirradiation doses ranged from 20 to 87.50 Gy (median: 32.50 Gy). Concurrent chemotherapy was given in 3 patients (9%) using topotecan. Further systemic treatment after the end of reirradiation was given in 7 patients (21%).

Evaluation of prognostic factors

A total of nine potential prognostic factors were investigated including gender, age at reirradiation (≤65 versus >65 years), time interval between end of first and second

Table 1 patient characteristics at initial irradiation

Variables	Number of patients	Proportion (%)
Age, years		
≤65	22	67
>65	11	33
Gender		
Female	21	64
Male	12	36
T stage		
1–2	10	30
3–4	13	39
N stage		
0–1	5	15
2–3	20	61
Stage		
Very limited disease	14	42
Limited disease	17	52
Extensive disease	2	6
Concurrent chemotherapy		
Yes	30	91
No	3	9
Radiation dose (EQD2), Gy		
<60	26	79
≥60	7	21
Prophylactic cranial irradiation		
Yes	25	76
No	7	21

radiotherapy series (≤6 versus >6 months), Karnofsky performance score (50–70% versus 80–100%, median 80%), extrathoracic disease (yes versus no), radiation dose (EQD2) at reirradiation (Re-RT) (20–40 versus >40 Gy), concurrent chemotherapy (yes versus no), cumulative dose of first radiotherapy plus Re-RT (EQD2) (≤90 versus >90 Gy, median: 90 Gy) and further systemic treatment (yes versus no) (*Table 2*).

Evaluation of outcomes and toxicity

Follow up was conducted until death of the patient or a median follow up time of 20 months. Each patient was examined for hematologic and non-hematologic toxicity graded according to Common Terminology Criteria for Adverse Events (CTCAE version 4.0).

Statistical analysis

Standard descriptive statistics (mean standard deviation and cross tabulation analysis) were used to describe the evaluated data. For the analyses of potential associations with OS, the Kaplan-Meier method, and the log-rank test were used P values <0.05 were considered significant. OS was calculated from the end of Re-RT. Prognostic factors found to be significant in univariate analyses were additionally evaluated in a multivariate analysis using the Cox proportional hazards model.

Results

The median survival after reirradiation was 7 months (range, 1–54 months). The 1- and 2-year survival rates for the entire patient cohort were 33% and 17%, respectively. Patient characteristics at initial irradiation are shown in *Table 1*. The patient characteristics at reirradiation and the results of the analyses of survival are summarized in *Table 2*.

In univariate analysis, OS was positively associated with a Karnofsky performance score of ≥80% (P=0.016, *Figure 1*), absence of extrathoracic disease (P<0.001, *Figure 2*), radiation dose (EQD2) >40 Gy (P=0.019, *Figure 3*) and cumulative EQD2 of >90 Gy (P=0.019, *Figure 4*). On univariate analysis, we found a trend (P<0.10) towards improved survival for administering concurrent chemotherapy (P=0.085), a longer (>6 months) interval between first irradiation and Re-RT (P=0.10).

On multivariate analysis, absence of extrathoracic disease achieved significance (P=0.003, HR: 6.568, 95%CI: 1.911–22.58). The results of multivariate analysis of OS are summarized in *Table 2*.

Acute esophageal toxicity grade 1–2 from reirradiation was found in 5 patients (15%); no grade 3 or 4 acute toxicity was observed. Late esophageal toxicity was not found at all centers. Acute pulmonary grade 1–2 toxicity from reirradiation was reported in 11 patients (33%), grade 3 toxicity in 1 patient (3%). Late pulmonary grade 1–2 toxicity from reirradiation was reported in 4 (12%) patients and no grade 3 or 4 late toxicity was observed. Acute hematological grade 2 toxicity occurred in 2 patients (6%). Late hematological toxicity wasn't found at all centers.

Table 2 Patient characteristics at reirradiation and survival analysis

Variables	Number of patients [%]	Survival at 6 months (%)	Survival at 12 months (%)	P value (univariate analysis)	P value (multivariate analysis)
Age at Re-RT, years					
≤65	18 [55]	50	25		
>65	15 [45]	58	43	0.497	
Gender					
Female	21 [64]	67	48		
Male	12 [36]	45	25	0.2	
Time interval between end of first RT and second RT, months					
≤6	4 [12]	50	0		
>6	29 [88]	54	38	0.104	
KPS at Re-RT					
50–70%	11 [33]	21	21		
80–100%	19 [58]	68	47	0.016	0.091
Extrathoracic disease at Re-RT					
Yes	6 [18]	0	0		
No	27 [82]	66	41	0.001	0.003
Radiation dose (EQD2) of Re-RT, Gy					
20–40	24 [73]	40	25		
>40	9 [27]	89	56	0.019	0.287
Concurrent chemotherapy					
Yes	4 [12]	100	100		
No	29 [88]	45	24	0.085	
Cumulative dose of first RT plus Re-RT (EQD2), Gy					
≤90	17 [52]	41	23		
>90	16 [48]	67	45	0.019	0.729
Chemotherapy after Re-RT					
Yes	7 [21]	100	43		
No	26 [79]	40	27	0.187	

Discussion

Despite an increasing incidence of lung cancer worldwide during the last 30 years, the treatment of SCLC and its high mortality rates of more than 75% have remained almost unchanged the last 30 years (4-8,19-21). The prognosis of patients with recurrent SCLC remains dismal with 6-month and 1-year OS rates of <40% and <10%, respectively, with established second-line treatment with topotecan (8). Moreover, several cytotoxic or targeted agents have been investigated also providing suboptimal outcomes (6).

In NSCLC, the introduction of immune checkpoint inhibition has been a great success and changed the prognosis of patients with advanced stage dramatically (22,23). Based on the result of the CheckMate 032 trial, PD-1 inhibition appears effective and well tolerated for recurrent SCLC. However, the 1-year OS rate of these patients was reported

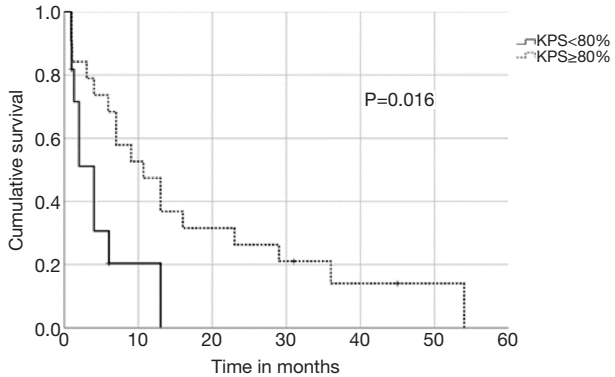

Figure 1 Kaplan-Meier curves according to Karnofsky performance status.

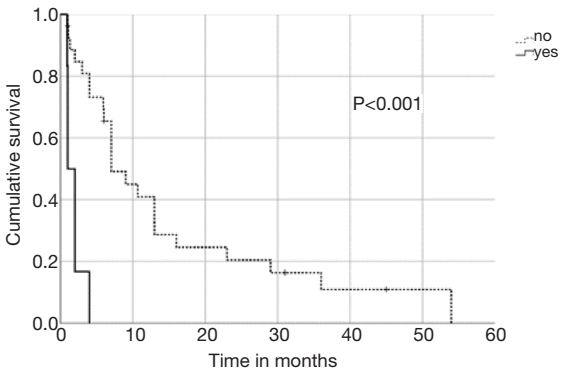

Figure 2 Kaplan-Meier curves according to extrathoracic disease.

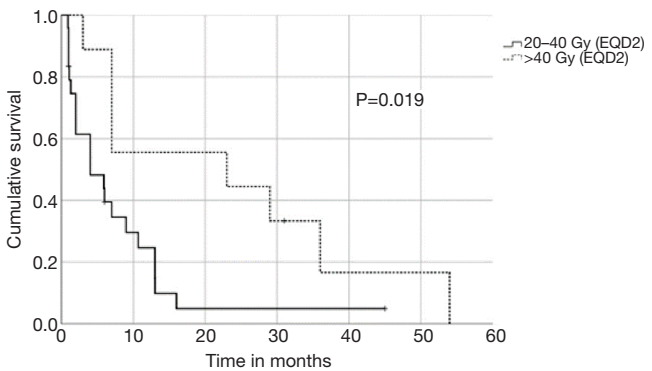

Figure 3 Kaplan-Meier curves according to the reirradiation dose (EQD2).

to be <30% (24), suggesting a modest effect of these therapies as salvage therapy for progressive disease.

After definitive chemoradiotherapy, recurrences often occur at the site of the original primary tumor or the initially affected lymph nodes (25). Therefore, reirradiation as a loco-regional treatment offers the chance of disease control as well as symptomatic relief in these patients.

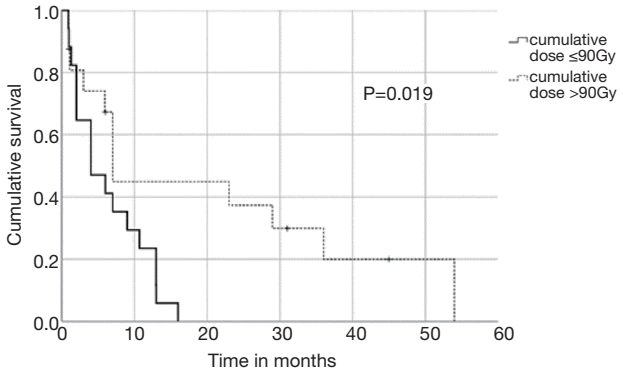

Figure 4 Kaplan-Meier curves according to cumulative radiation dose (EQD2).

In the treatment of NSCLC, reirradiation is a frequently utilized treatment option for palliative treatment and in patients with limited locoregionally recurrent disease. Studies examine Re-RT in NSCLC suggest that its utilization can result in improved OS with the chance of even long-term survival (9-15). Previous evidence regarding a role of reirradiation in recurrent SCLC is still limited, (3,11-16). Therefore, we performed a multi-institutional study to evaluate the outcome of reirradiation for recurrent SCLC, identify prognostic factors and assess treatment-related toxicity.

Our study revealed a median overall survival after reirradiation of 7 months (range, 1–54 months). For patients with a good performance status and a re-irradiation dose (EQD2) of >40 Gy resulted in a favourable 1- and 2-year overall survival rates of 89% and 56%, respectively. These results appear consistent with the reported outcomes of reirradiation in previous studies of patients with localized NSCLC (9,11,26,27). On the other hand, in the present study those patients with extrathoracic disease had an OS of only <6 months and extrathoracic disease was found to be an independent prognostic factor for patients with recurrent SCLC. As a result, reirradiation should be considered only as palliative treatment in order to provide symptomatic relief, and short fractionation schedules may be most appropriate.

However, many cancer centers are quite hesitant to administer reirradiation for recurrent thoracic malignancies. This could be explained by the potential damage to organs at risk. Potential side effects of reirradiation may include radiation-induced pneumonitis, lung fibrosis, pericarditis,

myelopathy, esophagitis and fistula. In our study, we found grade 3 acute pulmonary toxicity only in 1 patient (3%). An earlier study of Ren *et al.* found that the mean lung dose (MLD) of the initial RT plan, V5 of the composite plans and overlap-V5/re-V5 were independent predictors for grade ≥3 radiation-induced pneumonitis and should be considered during planning of reirradiation (28).

Despite the relevance of the reirradiation dose, recovery of organs at risk is of importance for reirradiation. However, knowledge about recovery and tolerance of organs at risk such as lung and spinal cord for thoracic reirradiation is limited. Future studies are required to establish dose constraints in reirradiation setting to avoid high acute and late toxicity.

In order to identify patients benefiting from reirradiation, prognostic factors are essential and guide physicians for treatment decision-making. We demonstrated that a Karnofsky performance score of ≥80%, absence of extrathoracic disease, administered radiation dose (EQD2) >40 Gy at reirradiation and a cumulative radiation dose (EQD2) of >90 Gy were associated with improved OS. Based on our findings, it appears one may reasonably consider Re-RT with doses of >40 Gy in patients with good performance status. In contrast, reirradiation in patients with poor performance status or with extrathoracic disease should be limited to carefully selected symptomatic patients. The main limitation of this multicenter study is the retrospective design, which may have uncontrolled biases, and a relatively small sample size. Therefore, the recommendations must be considered with caution. However, the study represents the largest patient cohort reirradiated for recurrent SCLC.

Conclusions

Reirradiation for locoregionally recurrent SCLC appears safe and feasible if administered with modern radiation delivery techniques (3D-RT, IMRT). Patients reirradiated with doses >40Gy experienced favourable survival rates. In patients with poor performance status and extrathoracic disease, Re-RT may be considered only for selected symptomatic patients.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tlcr.2020.01.19). HH reports personal fees from Astrazeneca, outside the submitted work. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by institutional ethics committee of the University of Luebeck (No. 15-352A) and written informed consent was obtained from all patients.

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