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Outcome in patients with small cell lung cancer re-irradiated for brain metastases after prior prophylactic cranial irradiation

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ABSTRACT

Objectives: Patients with brain metastases from small-cell lung cancer (SCLC) who underwent prior prophylactic cranial irradiation (PCI) are often treated with a second course of whole brain radiation therapy (Re-WBRT) or stereotactic radiosurgery (SRS) for purposes of palliation in symptomatic patients, hope for increased life expectancy or even as an alternative to untolerated steroids. Up to date there is only limited data available regarding the effect of this treatment. This study examines outcomes in patients in a single institution who underwent cerebral re-irradiation after prior PCI.
Methods: We examined the medical records of 76 patients with brain metastases who had initially received PCI between 2008 and 2015 and were subsequently irradiated with a second course of cerebral radiotherapy. Patients underwent re-irradiation using either Re-WBRT (88%) or SRS (17%). The outcomes, including symptom palliation, radiation toxicity, and overall survival (OS) following re-irradiation were analyzed. Survival and correlations were calculated using log-rank, univariate, and multivariate Cox proportional hazards-ratio analyses. Treatment-related toxicity was classified according to CTCAE v4.0.
Results: Median OS of all patients was 3 months (range 0–12 months). Median OS after Re-WBRT was 3 months (range 0–12 months). Median OS after SRS was 5 months (range 0–12 months). Karnofsky performance status scale (KPS ≥50%) was significantly associated with improved OS in both univariate (HR 2772; p = 0,009) and multivariate analyses (HR 2613; p = 0,024) for patients receiving Re-WBRT. No unexpected toxicity was observed and the observed toxicity remained consistently low. Symptom palliation was achieved in 40% of symptomatic patients.
Conclusions: In conclusion, cerebral re-irradiation after prior PCI is beneficial for symptom palliation and is associated with minimal side effects in patients with SCLC. Our survival data suggests that it is primarily useful in patients with adequate performance status.

1. Introduction

In approximately 10% of patients with SCLC, brain metastases are found at the time of initial diagnosis and more than 50% of patients are at risk of developing brain metastases at 2 years [1,2]. In 1999, Auperin and colleagues published a meta-analysis of PCI trials in SCLC and showed that PCI leads to a 25% decrease of brain metastases [3]. Since publication of this meta-analysis, PCI has been considered standard of care for limited-stage SCLC patients with a complete remission after chemotherapy. After a phase III

Abbreviations: IMRT, intensity modulated radiotherapy; PCI, prophylactic cranial irradiation; WBRT, whole brain radiotherapy; SRS, stereotactic radiosurgery; SCLC, small-cell lung cancer; MRI, magnetic resonance imaging; CT, computed tomography; KPS, Karnofsky performance status; CTC, common toxicity criteria; CTCAE, Common Terminology Criteria for Adverse Events; GPA, graded prognostic assessment; RPA, recursive partitioning analysis NFS neurological function scale.

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Table 1
Patients' and radiation characteristic of 76 patients with brain metastases of SCLC after prior PCI.

Patient characteristics.	n	[%]	Radiation therapy	n	[%]
Age			WBRT	67	88
			20 in 2 Gy fractions	32	
			24–26 Gy in 2 Gy fractions	10	
			28–30 Gy in 2 Gy fractions	16	
			30 Gy in 3 Gy fractions	1	
			Incompleted RT	8	
44–60	41	53	SRS (80%-isodose)	13	17%
			18–19 Gy single dose	5	
			20 Gy single dose	7	
			24 Gy single dose	1	
61–70	26	47	Both/Salvage treatment	4	<1%
>70	9	12	RPA Class		
Sex			RPA Class I	11	14
female	30	39	RPA Class II	25	32
Male	46	60	RPA Class III	40	52
Stage at initial diagnose			Modified GPA Score		
LD	46	60	0–1.0	45	59
ED	30	39	1.5–2.0	25	32
			2.5–3.0	6	<1

study conducted by Slotman et al., PCI is also offered to patients with extensive disease SCLC [4]. Recurrence and progression of brain metastases after PCI is, however, not uncommon and the survival of patients with recurrent intracranial disease generally remains poor [4,5]. Salvage options in this setting are often limited to re-irradiation or best supportive care, as surgery or systemic treatments have limited efficacy, are impossible to perform due to multiple metastases, or are associated with unnecessary toxicity in a highly palliative stage of disease [6,7]. Especially for patients with good performance status, re-irradiation offers an option for intracranial local control.

In the present analysis, we evaluated a group of patients with recurrent brain metastases after PCI treated with Re-WBRT or SRS with the objective to assess symptom palliation, radiation toxicity, and survival data following re-irradiation. This group represents the largest number of patients published to date and the only study exclusively examining the effect of cerebral re-irradiation after prior PCI.

2. Material and methods

2.1. Patients and brain metastases

According to our cancer center database 420 patients had received PCI in our department between 2008 and 2015. We identified 76 (18%) patients with SCLC that had received WBRT or SRS after prior treatment with PCI. No patients were excluded from the analysis. Detailed patient characteristics are shown in Table 1. All reviews were performed following institutional guidelines and the Declaration of Helsinki of 1975 in its most recent version. Ethics approval for the study was requested from the local ethics committee at the Heidelberg University Hospital.

The following data were retrieved from the clinical record of each patient: age, stage, extracranial disease status, first diagnosis and number of brain metastases, dose and fractionation of radiotherapy, symptoms before and after irradiation, response to re-irradiation, additional treatment, and side effects of irradiation. Karnofsky performance status (KPS) was taken from patient records. If no KPS was indicated in the records, the value was estimated based on the description of the patient's clinical status at the relevant time points. In our institution, PCI was generally offered to all patients with a partial or complete response to initial chemotherapy. If the patient was at high risk for neurocognitive deterioration due to comorbidities, PCI was usually not administered.

All patients were assigned a recursive partitioning analysis (RPA) class [8] based on KPS, local control, extracranial status and age. We assigned a modified graded prognostic assessment (GPA) score [9] based on KPS, age, extracranial disease (progressive or stable/complete remission) and number of brain metastasis. Furthermore, we estimated neurologic function status [10] at the start of Re-RT based on the description of the patient's clinical status. Patients were classified by neurologic function status as follows: asymptomatic (0), minor neurological symptoms (1), moderate neurological symptoms (2), neurologically seriously limited, requiring hospitalization (3) and requiring hospitalization and constant nursing care (4). Date of death was obtained from medical and official records.

2.2. Planning and treatment features

2.2.1. Radiosurgical procedures

For radiation, an individual mask was manufactured for each patient, and treatment planning was performed using 3 mm CT and/or Gadolinium enhanced MRI-imaging. For SRS the target included the macroscopic tumor with a 2-mm margin expansion. Doses were prescribed to the 80% isodose line in SRS patients, while in WBRT, doses were prescribed as mean doses with $D_{2\%} \leq 107\%$. For WBRT the portals included the whole brain. For low infratentorial lesions, the treatment volume included the whole brain down to the second cervical vertebra. RT was applied with two portals using a 6 MeV photon linear accelerator. In our institution, the decision to treat with Re-WBRT or SRS is made depending on the overall performance status of the patients, the underlying disease, and the number of brain metastases (BM). SRS was limited to a maximum number of 4 BM. All patients received a prior PCI dose of 30 Gy in 15 fractions, except for one patient who had received 30,6 Gy in 17 fractions at another institution.

2.3. Outcome evaluation

Statistical analysis was conducted using Graphpad Prism 5 (GraphPad Software, La Jolla, USA). Kaplan–Meier survival analysis was performed for overall-survival analyses. For comparison of survival curves Log-rank (Mantel-Cox) test was used. A statistical analysis was carried out using SigmaPlot™ (Systat Software GmbH, Germany). Univariate and multivariate Cox proportional-hazards ratios (HRs) were used to assess the influence of cofactors on overall survival. Living patients were censored from survival analysis at last known contact. A p value of <0.05 was considered statistically