Number of Involved Extracranial Organs Predicts Survival in Patients with Brain Metastasis from Small Cell Lung Cancer

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Abstract. *Background/Aim: To investigate the prognostic role of the number of involved extracranial organs in patients with brain metastasis from small-cell lung cancer (SCLC). Patients and Methods: Data of 155 patients receiving whole-brain radiotherapy (WBRT) alone for brain metastasis from SCLC were retrospectively evaluated. In addition to the number of involved extracranial organs, six potential prognostic factors were analyzed including WBRT regimen, age, gender, Karnofsky performance score (KPS), number of brain metastases, and interval from diagnosis of SCLC to WBRT. Results: Six-month survival rates of patients with involvement of 0, 1, 2, and ≥3 extracranial organs were 52%, 29%, 9%, and 0%, respectively (p<0.001). On multivariate analysis, the number of involved extracranial organs remained significant (p=0.003). Older age (p=0.005), lower KPS (p<0.001), and greater number of brain metastases (p=0.005) were also significantly associated with poorer survival. Conclusion: The number of involved extracranial organs is an independent prognostic factor of survival in SCLC patients with brain metastasis.*

Brain metastases occur in 10-30% of adult patients with cancer during their lifetime. Lung cancer accounts for approximately one half of all patients with brain metastases. Additionally, one-third of all patients with lung cancer have small-cell lung cancer (SCLC) (1, 2). When compared to patients with brain metastasis from other primaries, patients with SCLC have an unfavorable survival prognosis. In order to improve treatment outcomes in these patients, a personalized treatment approach may be important. The selection of an individual approach can be facilitated by a clear understanding of prognostic factors regarding the patient's survival.

Some prognostic factors have been reported to be positively associated with survival in patients with brain metastases from SCLC including younger age, a better performance status, a limited number of brain metastases, and absence of extracranial metastases (3).

However, the factor "extracranial metastases" was classified as either the presence or absence of extracranial metastases, and the number of organs involved by the extracranial metastases has not been evaluated. We hypothesized that the number of involved extracranial organs may also be associated with survival in patients with brain metastasis from SCLC. To our knowledge, this is the first study to evaluate this potential prognostic factor in patients with SCLC treated with whole-brain radiotherapy (WBRT) alone.

Patients and Methods

The data of 155 patients treated with WBRT alone for brain metastases from SCLC were included in this retrospective study. WBRT was performed with either 5×4 Gy in one week or 10×3 Gy in two weeks. The primary goal of the present study was to evaluate whether the number of involved extracranial organs (0 *vs.* 1 *vs.* 2 *vs.* ≥3) may be prognostic for survival. In addition to the number of involved extracranial organs, six further potential prognostic factors were investigated including the WBRT regimen (5×4 Gy *vs.* 10X3 Gy), age (<65 *vs.* ≥65 years), gender, Karnofsky performance score (KPS <70 *vs.* ≥70), number of brain metastases (1-3 *vs.* ≥4), and the interval between the first diagnosis of SCLC and WBRT (≤6 *vs.* >6 months). The patient characteristics are shown in Table I.

Univariate analyses were performed with the Kaplan-Meier method and the log-rank test (4). Prognostic factors found to be significant in the univariate analysis ($p<0.05$) were included in a multivariate analysis performed with the Cox hazards proportional model.

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Table I. *Patients' characteristics*.

	N patients (%)
WBRT regimen	
20 Gy in 5 fractions	47 (30)
30 Gy in 10 fractions	108 (70)
Age	
<65 years	90 (58)
≥65 years	65 (42)
Gender	
Female	54 (35)
Male	101 (65)
Karnofsky performance score	
<70	71 (46)
≥70	84 (54)
Number of brain metastases	
1-3	42 (27)
≥4	113 (73)
Interval from cancer diagnosis to WBRT	
≤6 Months	86 (55)
>6 Months	69 (45)
Number of involved extracranial organs	
0	58 (37)
1	41 (26)
2	44 (28)
≥3	12 (8)

WBRT: Whole-brain radiotherapy.

In addition to the analysis of the entire cohort of 155 patients, separate analyses were performed for the 97 patients with extracranial metastases to assure that a significant result regarding the impact of the number of involved extracranial organs on survival was not due to the comparison of those with to those without extracranial disease.

Results

In the univariate analysis of the entire cohort, survival was associated with younger age (p=0.016), better KPS (p<0.001), fewer brain metastases (p<0.001), and fewer involved extracranial organs (p<0.001; Figure 1). The results of the univariate analysis are given in Table II. In the multivariate analysis of survival, age [risk ratio (RR)=1.68, 95% confidence interval (CI)=1.17-2.40; p=0.005), KPS (RR=3.07, 95% CI=2.06-4.59; p<0.001), the number of brain metastases (RR=1.87, 95% CI=1.21-2.97; p=0.005), and the number of involved extracranial organs (RR=1.34, 95% CI=1.11-1.62; p=0.003) maintained significance.

In the additional analysis of the 97 patients with extracranial metastases, the number of involved extracranial organs was also significantly associated with survival in both univariate (p=0.003) and multivariate analyses (RR=1.47, 95% CI=1.06-2.02; p=0.021).

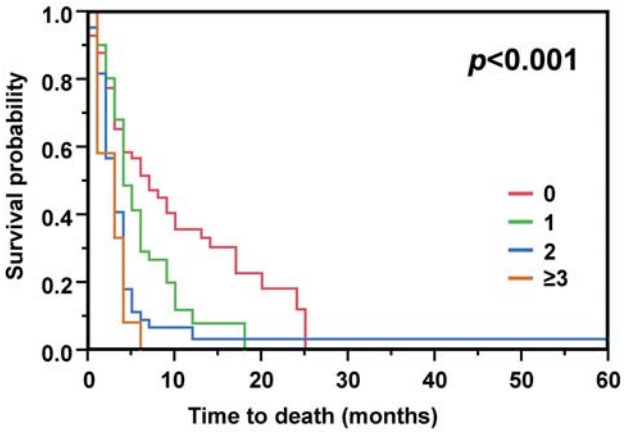

Figure 1. *Entire cohort (N=155): Impact of the number of involved extracranial organs (0 vs. 1 vs. 2 vs. ≥3) on survival.*

Table II. *Univariate analysis of survival*.

	Survival at 6 months (%)	Survival at 12 months (%)	p-Value
WBRT regimen			
20 Gy in 5 fractions	30	14	
30 Gy in 10 fractions	30	17	0.96
Age			
<65 years	34	19	
≥65 years	23	13	0.016
Gender			
Female	33	22	
Male	28	14	0.40
Karnofsky performance score			
<70	4	1	
≥70	51	30	<0.001
Number of brain metastases			
1-3	60	41	
≥4	19	7	<0.001
Interval from cancer diagnosis to WBRT			
≤6 Months	36	19	
>6 Months	22	13	0.54
Number of involved extracranial organs			
0	52	36	
1	29	8	
2	9	3	
≥3	0	0	<0.001

WBRT: Whole-brain radiotherapy.

Discussion

The majority of patients with metastasis to the brain from SCLC have a poor survival prognosis when compared to patients with brain metastasis from other primary tumors (1-

3). These patients would benefit from a short course of WBRT to avoid having to spend as much of their short remaining life receiving anticancer treatment. However, some patients live considerably longer and may be candidates for longer WBRT programs with lower doses per fraction, or for local treatments such as neurosurgical resection and radiosurgery (5-9). Longer course WBRT programs with doses per fraction lower than 3 Gy result in fewer chronic neurocognitive deficits which generally only become manifest in patients living six months or longer following WBRT (10). Therefore, it is important to be able to estimate the patient's survival prognosis in order to select the most appropriate individual treatment approach. The estimation of survival is facilitated with a clear understanding of prognostic factors. Since different primary tumors exhibit a great variability with respect to their biological and clinical behavior, separate prognostic factors should be defined for each type of primary tumor frequently associated with brain metastasis, such as SCLC (1, 2).

Specific independent prognostic factors have already been identified for patients with brain metastasis from SCLC. These include the age, KPS, number of brain metastases, and extracranial metastases (3). Regarding extracranial metastases, only presence or absence of such lesions has been evaluated. However, in the present study, we hypothesized that the number of involved extracranial organs may also be relevant. Indeed, patients without extracranial metastases had a significantly better survival prognosis than other patients, and patients with involvement of only one extracranial organ did significantly better than patients with two or more extracranial organs involved. The results were significant in both univariate and multivariate analyses. Therefore, the number of involved extracranial organs is a new independent prognostic factor of survival in patients with brain metastasis from SCLC.

In addition to the number of involved extracranial organs, survival was significantly associated with age, KPS, and the number of brain metastases, which agrees well with previously reported data (3). However, this was a retrospective study and, therefore, bears the risk of a hidden selection bias. In order to reduce the risk of a selection bias introduced by the administration of different treatment approaches, only patients treated with WBRT alone were included. Furthermore, WBRT regimens with doses greater than the worldwide most common standard regimen of 30 Gy in 10 fractions were excluded from this study because a recent study suggested that increasing the dose beyond 30 Gy in 10 fractions may improve treatment outcomes in selected patients with a favorable survival prognosis (10). In contrast patients, treated with 20 Gy in five fractions were not excluded from our study because it has been previously reported for patients with brain metastasis from SCLC that 20 Gy in five fractions provided similar survival rates as 30 Gy in 10 fractions (3). The rationale for including both regimens of 20 Gy in five fractions provided similar survival rates as 30 Gy in 10 fractions is supported by the fact that in the present study, the WBRT regimen had no impact on survival (p=0.96).

In conclusion, this study revealed the number of involved extracranial organs to be an independent prognostic factor in patients with brain metastasis from SCLC. This new prognostic factor can help personalize the treatment of these patients and should be considered in future trials of brain metastasis from SCLC.

Conflicts of Interest

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

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