A New Score Predicting Survival Prognosis After Whole-Brain Radiotherapy Alone for Brain Metastases in Elderly Patients

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Abstract. *Background/Aim: Elderly patients represent an important subgroup of patients with brain metastases. A survival score has been developed specifically for these patients. Patients and Methods: A total of 544 elderly patients (aged ≥65 years) receiving whole-brain radiotherapy alone were divided into a test (n=272) and a validation group (n=272). In the multivariate analysis of the test group, survival was significantly associated with gender, performance status, and number of organs involved by extracranial metastases. These factors were included in the score. Total scores representing the sum of the three factor scores were 3-13 points. Four prognostic groups were formed. Results: The 6-month survival rates were 2% for those with 3-6 points, 17% for those with 7-9 points, 56% for those with 10-12 points and 90% for those with 13 points in the test group (p<0.001), and 4%, 21%, 50% and 86%, respectively, in the validation group (p<0.001). Conclusion: This score is reproducible and helps estimate the survival prognosis of elderly patients with brain metastasis.*

Most patients with brain metastases receive whole-brain radiotherapy (WBRT)-alone, particularly those with multiple (more than three) lesions. Elderly patients (aged ≥65 years) are an important sub-group of patients irradiated for brain metastases. Elderly patients account for approximately 40% of all patients receiving WBRT-alone for such an indication (1, 2). In order to select the most appropriate treatment regimen for the individual patient, it is mandatory to be able to predict the patient's survival prognosis as precisely as possible. This can be facilitated with survival scores. Several scores already exist for patients with brain metastases (3-5). However, none of the previous scores focused particularly on elderly patients. A separate survival score for elderly patients appears to be important, since the courses of disease observed in elderly patients are quite different from those observed in younger patients. Therefore, we decided to develop a new survival score tailored particularly to the needs of the group of elderly patients irradiated for brain metastases. In order to reduce the risk of a selection bias, only elderly patients treated with WBRT-alone were included. Patients receiving local treatment, such as neurosurgical resection or radiosurgery, generally have a much better performance status and a very limited number of intra-cerebral lesions. In addition to developing a survival score for elderly patients, this study also aimed to validate the score, since only a reproducible and valid score will be of value for clinical routine.

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Patients and Methods

A total of 544 elderly patients (≥65 years) treated with WBRT-alone for brain metastases were included in this retrospective study. The patients were randomly assigned to a test group (N=272) or a validation group (N=272). In the test group, the following seven pre-treatment factors were analyzed for potential association with survival: age (65-74 years *vs.* ≥75 years), gender, Karnofsky Performance Score (KPS <70 *vs.* 70 *vs.* >70), type of primary tumor (breast cancer *vs.* non-small cell lung cancer *vs.* small cell lung cancer *vs.* other), number of brain metastases (1-3 *vs.* ≥4), number of extracranial organs involved by metastases (0 *vs.* 1 *vs.* ≥2), and the interval between tumor diagnosis and WBRT (≤6 months *vs.* >6 months, median interval=6 months). In addition, the impact of the WBRT regimen (5×4 Gy *vs.* longer course WBRT, namely 10×3 Gy

Table I. *Patient characteristics of the test group (N=272) and in the validation group (N=272). The comparison was performed with the Chi-square test.*

	Test group N (%)	Validation group N (%)	*p*-Value
Age			
65-74 years	197 (72)	191 (70)	0.81
≥75 years	75 (28)	81 (30)	
Gender			
Female	117 (43)	120 (44)	0.89
Male	155 (57)	152 (56)	
Karnofsky performance score			0.84
<70	134 (49)	132 (49)	
70	68 (25)	76 (28)	
>70	70 (26)	64 (24)	
Type of primary tumor			0.77
Breast cancer	38 (14)	51 (19)	
Non-small cell lung cancer	108 (40)	102 (38)	
Small cell lung cancer	38 (14)	37 (14)	
Other tumor types	88 (32)	82 (30)	
No. of brain metastases			0.65
1-3	87 (32)	94 (35)	
≥4	185 (68)	178 (65)	
No. of involved extracranial organs			0.69
0	97 (36)	89 (33)	
1	80 (29)	93 (34)	
≥2	95 (35)	90 (33)	
Interval between tumor diagnosis to WBRT			0.73
≤6 Months	137 (50)	144 (53)	
>6 Months	135 (50)	128 (47)	
WBRT regimen			1.00
5×4 Gy	78 (29)	78 (29)	
10×3 Gy/20×2 Gy	194 (71)	194 (71)	

and 20×2 Gy) on survival was investigated. The potential prognostic factors of both the test group and the validation group are summarized in Table I.

In the test group, the univariate analyses of survival were performed with the Kaplan–Meier method (6) and the log-rank test (Table II). The prognostic factors that were significant in the univariate analysis ($p<0.05$) were re-evaluated in a multivariate analysis, which was performed with the Cox proportional hazards model.

Those prognostic factors significant in the multivariate analysis were included in the score. The total prognostic scores were obtained from the sum of the scores from each factor. Prognostic groups were designed based on the total prognostic scores. To test the reproducibility of the score, each of the prognostic groups of the test group was compared to each corresponding prognostic group of the validation group using the Chi-square test.

Table II. *Univariate analysis of survival at six months. The 6-months survival rates are given in %.*

	Survival rate at 6 months (%)	*p*-Value
Age		<0.001
65-74 years	30	
≥75 years	15	
Gender		0.002
Female	33	
Male	20	
Karnofsky performance score		<0.001
<70	3	
70	35	
>70	60	
Type of primary tumor		0.08
Breast cancer	42	
Non-small cell lung cancer	26	
Small cell lung cancer	29	
Other tumor types	17	
No. of brain metastases		0.032
1-3	37	
≥4	21	
No. of involved extracranial organs		0.003
0	36	
1	28	
≥2	14	
Interval between tumor diagnosis to WBRT		0.16
≤6 Months	25	
>6 Months	27	
WBRT regimen		0.23
5×4 Gy	28	
10×3 Gy/20×2 Gy	25	

Results

In the multivariate analysis of the test group, gender, KPS, and the number of involved extracranial organs were significantly associated with survival (Table III), and included in the survival score. A score for each of these three factors was obtained from the 6-month survival rate (in %) divided by 10 (Table IV). The total prognostic scores representing the sum of the scores from each factor ranged between 3 and 13 points (Figure 1). Four prognostic groups were designed according to the total prognostic scores: group A, 3-6 points; group B, 7-9 points; group C, 10 to 12 points; and group D, 13 points. In the test group, the 6-month survival rates were 2% in group A, 17% in group B, 56% in group C, and 90% in group C, respectively ($p<0.001$). In the validation group the 6-month survival rates were 4% in group A, 21% in group B, 50% in group C, and 86% in group C, respectively ($p<0.001$).

The comparisons between each of the prognostic groups A, B, C and D of the test group and the corresponding

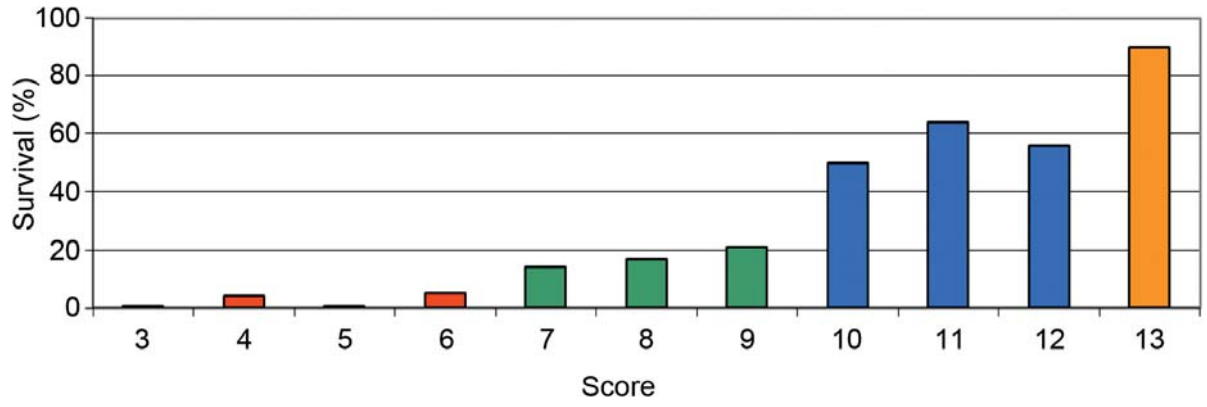

Figure 1. *The 6-month survival rate by prognostic score.*

Table III. *Results of the multivariate analysis of survival.*

	Risk ratio	95% Confidence interval	*p*-Value
Age			
65-74 *vs.* ≥75 years	1.21	0.90-1.62	0.21
Gender			
Female *vs.* male	1.42	1.09-1.87	0.010
Karnofsky Performance Score			
>70 *vs.* 70 *vs.* <70	1.91	1.58-2.34	<0.001
No. of brain metastases			
1-3 *vs.* ≥4	1.03	0.77-1.39	0.87
No. of involved extracranial organs			
0 *vs.* 1 *vs.* ≥2	1.20	1.02-1.41	0.025

Table IV. *Survival rates at six months after WBRT (given in %) and the corresponding scores.*

	Survival rate at 6 months (%)	Score
Gender		
Female	33	3
Male	20	2
Karnofsky Performance Score		
<70	3	0
70	35	4
>70	60	6
No. of involved extracranial organs		
0	36	4
1	28	3
≥2	14	1

prognostic groups of the validation group did not reveal a significant difference. The *p*-values were $p=0.93$ for the comparison of both groups A, $p=0.91$ for both groups B, $p=0.65$ for both groups C, and $p=0.98$ for both groups D, respectively.

Discussion

Most patients with brain metastases receive WBRT-alone. The most commonly used WBRT regimen worldwide is 10×3 Gy over two weeks. Another option would be short-course WBRT with 5×4 Gy in two weeks for patients with a poor estimated survival. According to a retrospective study, 5×4 Gy results in similar survival and intra-cerebral control rates without increased acute toxicity when compared to 10×3 Gy in two weeks (7). On the other hand, patients with a very favorable survival prognosis may benefit from doses beyond 30 Gy such as 20×2 Gy in four weeks in terms of improved survival and intra-cerebral control, which has been suggested by another retrospective study (8). Furthermore, doses per fraction of less than 3 Gy have been reported to result in lower rates of neurocognitive deficits than of 3 Gy and higher (9-10). Late sequelae such as neurocognitive deficits become more important in long-term surviving patients. Patients with a favorable survival prognosis and a very limited number of brain metastases should also be considered for local treatments such as resection, radiosurgery and fractionated stereotactic radiation therapy (11-13). All these considerations demonstrate that it is very important to be able to estimate the individual patient's survival prognosis in order to choose for the best treatment option.

For the clinical routine, physicians need an instrument that allows them to quickly and easily estimate the patient's survival prognosis. Several survival scores already exist (3-5). However,

those scores were developed for patients of any age and may, therefore, not be optimal for elderly patients. In the present study, a new survival score was developed specifically for patients of 65 years or older. The current score included three independent predictors of survival, namely gender, KPS, and the number of extracranial organs involved by metastatic disease. The latter prognostic factor has only recently been identified and is for the first time included in a survival score in the present study (1-2). This aspect also makes the current score somewhat unique. Gender has been included in only one previous score, which demonstrates the need for a separate score for elderly patients (14).

Based on scores for each of the three independent prognostic factors, four prognostic groups were created that significantly differed with respect to their 6-month survival rates. Low-scoring, group A patients had a very poor survival prognosis. Only 2% and 4% of the group A patients of the test group and the validation group, respectively, survived for at least six months. These patients obviously did not really benefit from WBRT and may be considered candidates for best supportive care and treatment with corticosteroids instead of irradiation. Patients of group B had survival rates of 17% and 21%, respectively. They should be considered for short-course WBRT such as 5×4 Gy in one week. The patients of group C had an intermediate survival prognosis, with 6-month survival rates of 56% and 50%, respectively. For these patients, 10×3 Gy in two weeks, the most common WBRT regimen, may be appropriate. The patients of group D, who had the most favorable survival prognosis with 6-month survival rates of 90% and 86%, respectively, should be considered for long-course WBRT with doses per fraction of <3 Gy such as 20×2 Gy in four weeks. For group C and D patients, with a very few brain metastases, radiosurgery or neurosurgery, either alone or in addition to WBRT, should be considered (11-13).

The 6-month survival rates of the four prognostic groups of the validation group were quite similar to the 6-month survival rates of the corresponding groups of the test group, which shows that this score is reproducible. One has to be aware that the data this score are based on were retrospective in nature. However, a prospective validation of this score cannot be expected in the near future.

In conclusion, since the 6-month survival rates of the validation and the test groups were quite similar, this score can be considered reproducible. This new score allows for estimation of the survival of elderly patients with brain metastases and, therefore, can assist treating physicians in choosing the best treatment for each of these patients.

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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