Predicting Survival after Whole-Brain Irradiation for Cerebral Metastases from Prostate Cancer

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Abstract. *Background/Aim: Prostate cancer patients represent a small minority of those presenting with cerebral metastases. Knowledge about overall survival (OS) contributes to individualization of treatment concepts. In this study an OS score was created for patients receiving whole-brain irradiation (WBI) for cerebral metastases from prostate cancer. Patients and Methods: Of six variables, four were significantly associated with OS: performance status, time from diagnosis of prostate cancer to WBI, number of cerebral lesions, extracranial metastases. Results: Six-month OS rates of the four variables (in %, divided by 10) were added. The addition resulted in scores of 1 to 19 points. Six-month OS rates were 0% for <15 points and 100% for ≥15 points (p<0.001). Conclusion: An OS score was generated specifically for patients with cerebral lesions from prostate cancer. For patients with <15 points, a short WBI regimen (5x4 Gy) should be used, for patients with ≥15 points a longer regimen seems appropriate.*

The vast majority of cancer patients presenting with cerebral metastases receive radiation therapy, most of them as whole-brain irradiation (WBI) (1). When WBI is administered, several options exist regarding the dose-fractionation regimen. Frequently used WBI regimens include 5x4 Gy in one week, 10x3 Gy in two weeks and 20x2 Gy in four weeks. According to the findings of retrospective analyses, overall survival (OS) was similar after 5x4 Gy, 10x3 Gy or higher doses in most patients with cerebral metastases, in particular if the OS prognosis was poor (2, 3). However, in another study of patients with a much more favorable OS prognosis, 20x2 Gy resulted in better intracerebral control rates and OS rates at one year than the 10x3 Gy regimen did (4). Therefore, it is important to know a patient's OS prognosis before choosing the individual therapeutic concept. Estimation of the OS time can be made easier with prognostic scores. Several OS scores are already in use for patients with cerebral metastases (5-8). However, most of those scores were designed from patient cohorts including many different primary tumors that have led to cerebral metastasis. Taking into account the variation in biology of the different primary tumors, a specific OS score for each primary tumor type would be desirable in order to optimally tailor the treatment to each patient's individual situation. This study focuses particularly on the OS of patients with cerebral metastases from prostate cancer. Its major goal is generating an OS score for this group of patients.

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Patients and Methods

Patients. In this study, a total of 18 patients were included who received WBI alone for cerebral metastases from prostate cancer. Initially, six variables were retrospectively analyzed for potential associations with OS. These variables were age (<75 *vs.* ≥75 years), the Karnofsky performance score (KPS; ≤70 *vs.* >70), the interval from the diagnosis of prostate cancer until WBI (≤36 *vs.* >36 months), the number of cerebral lesions (1-2 *vs.* ≥3 lesions), presence of extracranial metastases (no *vs.* bone metastases *vs.* other metastases) and the WBI regimen (5×4 Gy *vs.* 10×3 Gy). The distribution of these variables is given in Table I.

Statistical analysis. OS was evaluated by using the Kaplan-Meier-method (9) and the log-rank test. Those variables being significantly associated with OS ($p<0.05$) were included in the predictive score. The score of each of the significant variables was determined by dividing the 6-month OS rate (given in %) by 10. The total score for each patient was obtained from the addition of the scores of the significant variables.

Results

OS was significantly associated with the KPS ($p<0.001$), the interval from the diagnosis of prostate cancer until WBI ($p<0.001$), the number of cerebral lesions ($p=0.016$) and

Table I. *Patients' characteristics*.

	Patients N	Proportion %
Age		
<75 years	10	56
≥75 years	8	44
Karnofsky performance score		
≤70	12	67
>70	6	33
Time from cancer diagnosis to WBI		
≤36 months	10	56
>36 months	8	44
Number of cerebral metastases		
1-2	7	39
≥3	11	61
Extracranial metastases		
No metastases	4	22
Bone metastases	9	50
Other metastases	5	28
WBI regimen		
5×4 Gy	12	67
10×3 Gy	6	33

Table II. *OS rates at 6 months*.

	OS at 6 months (%)	*p*-Value
Age		
<75 years	20	
≥75 years	25	0.75
Karnofsky performance score		
≤70	0	
>70	67	<0.001
Time from cancer diagnosis to WBI		
≤36 months	0	
>36 months	50	<0.001
Number of cerebral metastases		
1-2	43	
≥3	9	0.016
Extracranial metastases		
No metastases	25	
Bone metastases	22	
Other metastases	0	0.044
WBI regimen		
5×4 Gy	25	
10×3 Gy	17	0.90

extracranial metastases (p=0.044). The results of the analysis of OS are summarized in Table II. The 6-month OS rates of the four significant variables and the corresponding scores are shown in Table III.

The addition of the scores of the four significant variables for each patient resulted in total scores ranging between 1 and 19 points. The relation between the scoring points and the 6-month OS rates are shown in Figure 1. The 6-month OS rates were 0% for 1-15 points and 100% for 15-19 points, respectively (p<0.001, log rank test). These OS rates led to the formation of two prognostic groups, <15 points and ≥15 points.

Table III. *6-months OS rates and the corresponding scores*.

	OS at 6 months (%)	Score
Karnofsky performance score		
≤70	0	0
>70	67	7
Time from cancer diagnosis to WBI		
≤36 months	0	0
>36 months	50	5
Number brain metastases		
1-2	43	4
≥3	9	1
Extracranial metastases		
No metastases	25	3
Bone metastases	22	2
Other metastases	0	0

Discussion

Prognostic scores that help estimating a patient's OS time are very important for the selection of the best available treatment approach for the individual patient. Our present study aimed to generate an OS score particularly for patients with cerebral lesions from prostate cancer. In this study, improved OS was associated with a KPS >70, an interval from the diagnosis of prostate cancer until WBI of >36 months, only one or two cerebral lesions and with either no extracranial metastases or bone metastases alone. These four factors allowed generation of an OS score particularly for patients with cerebral lesions from prostate cancer. Two prognostic groups, <15 points and ≥15 points were formed. The 6-month OS rates of these two groups were 0% and 100%, respectively.

These findings help choose the most appropriate WBI regimen for each patient. In a retrospective study of 442 patients who were treated with WBI alone for more than three cerebral metastases from different primary tumor types, the 6-month OS rates were 24% after 5×4 Gy and 27% after 10×3 Gy, respectively (p=0.29) (3). In that study, the acute toxicity rates were similar. Patients receiving 5×4 Gy needed higher median doses of dexamethasone (24 mg *vs*. 20 mg per day). Since data exist suggesting that the risk of radiation-related neurocognitive dysfunction increases with the dose

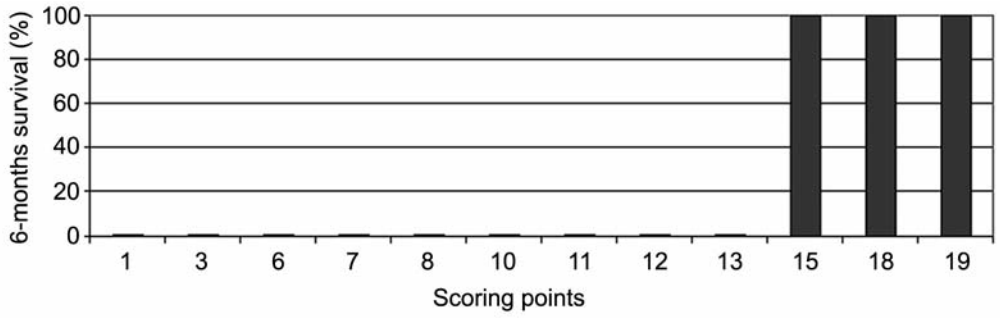

Figure 1. *Six-month OS rates in relation to the prognostic scores ranging between 1 and 19 points.*

per fraction, 5×4 Gy appears the preferable WBI regimen for patients with a short OS (10, 11). These patients will not likely live long enough to experience neurocognitive problems. Thus, those patients with cerebral metastases from prostate cancer who do not achieve 15 points in our new OS score should receive a short course of WBI such as 5×4 Gy. In contrast, those patients who achieve 15 or more points are considered candidates for a longer WBI program such as 10×3 Gy or even 20×2 Gy. The risk of experiencing radiation-related neurocognitive deficits increases with the patient's life span. Moreover, a retrospective study has found that in patients with cerebral metastases and a more favorable OS prognosis, 20×2 Gy was associated with better intracerebral control and better OS when compared to 10×3 Gy (4). The intracerebral control rates at one year were 44% after 20×2 Gy and 28% after 10×3 Gy, respectively (p=0.064). The OS rates at one year were 61% and 50%, respectively (p=0.007). However, when applying the new OS score that resulted from this study, one has to be aware of the small sample size and the retrospective nature of the data used for developing the score.

The KPS and extracranial metastases were previously recognized as significant predictors of OS in patients with cerebral metastases in four OS scores generated in very large cohorts of patients with brain metastases from different primary tumors (5-8). The number of cerebral lesions was included in two of these four scoring systems (7, 8). The interval from the diagnosis of cancer until WBI was included in one of the four scoring systems, which was validated about one year ago (12).

Specific OS scores for single tumor entities leading to cerebral metastases have already been designed for non-small cell lung cancer, small-cell lung cancer, breast cancer, malignant melanoma and kidney cancer (13-16). The prognostic factors associated with OS varied between the primary tumor types. This finding supports the development of further specific OS scores for other tumor entities, as done in the study presented here.

In conclusion, a new OS score was generated specificlly for patients with cerebral metastases from prostate cancer. The patient's OS must be considered when choosing the individual treatment concept. For patients with a score of <15 points, a short WBI regimen such as 5×4 Gy should be used. For those patients with ≥15 points, a longer WBI regimen with a higher total dose and a lower dose per fraction is preferable.

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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