ANTICANCER RESEARCH *40*: 1665-1668 (2020)
doi:10.21873/anticanres.14117

Performance Status Is Associated With Survival in Elderly Patients Irradiated for Cerebral Metastases from Prostate Cancer

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Abstract. *Background/Aim: Treatment of elderly patients with cancer has increasing importance. Since many of these patients may not tolerate standard treatments, they might benefit from personalized approaches. This study was performed to identify characteristics that allow estimation of survival in elderly patients with prostate cancer with cerebral metastases. Patients and Methods: Data of 21 elderly patients (≥65 years) receiving whole-brain radiotherapy (WBRT) for cerebral metastases from prostate cancer were retrospectively evaluated. Six characteristics were investigated: WBRT program, age, Karnofsky performance score (KPS), number of brain metastases, extra-cerebral metastases, and interval between diagnosis of prostate cancer and WBRT. Results: On univariate analyses, KPS ≥80% resulted in better survival than KPS ≤70% (log-rank p=0.018). Three-month survival was 60% vs. 36%, and 6-month survival 50% vs. 0%, respectively. In the Cox model, KPS maintained significance (hazard ratio=3.18, p=0.031). Conclusion: KPS is a significant prognostic factor of survival in elderly patients with prostate cancer receiving WBRT for cerebral metastases.*

Ten to 40% of adult patients with cancer develop cerebral metastases during their disease course (1). Since patients with prostate cancer represent only about 1% of this group, there are few data available focusing on these patients. This applies particularly to elderly patients, who have been recognized as a separate group of those with cancer that is growing and requires more attention (2). Elderly patients are also considered a special group because their tolerance of intensive treatments is often limited. Therefore, many of these patients require personalized treatments which take into account the patient's individual situation and limitations (3). One aspect to be considered is the patient's remaining lifespan. If this is (very) limited, the patient should receive a short treatment program that is minimally burdensome (1). If the lifespan is much longer, late sequelae of the treatment and long-term prognoses are important (1). In order to facilitate the inclusion of a patient's remaining lifespan in the decision when designing a personalized treatment, this study aimed to identify prognostic factors for survival specifically for elderly patients with prostate cancer receiving radiotherapy for cerebral metastases.

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Key Words: Prostate cancer, elderly patients, cerebral metastases, radiotherapy, performance status.

Patients and Methods

The data of 21 patients aged ≥65 years [elderly patients (4)] who received whole-brain radiotherapy (WBRT) alone for cerebral metastases from prostate were retrospectively evaluated for survival. The study was approved by the local Ethics Committee (University of Lübeck, 19-011A). Six characteristics were investigated for their potential impact on survival. Some of these patients were previously included in other studies (3, 5). The six characteristics were the following: WBRT regimen (5×4 Gy *vs.* 10×3 Gy *vs.* 14-20×2.0-2.5 Gy), age at the start of WBRT (median 74 years; ≤74 *vs.* ≥75 years), Karnofsky performance score (KPS) (median 70%; ≤70 *vs.* ≥80%), number of brain metastases (1-3 *vs.* >3), extra-cerebral metastases (no *vs.* yes), and the interval between first diagnosis of prostate cancer and WBRT (median 36 months; ≤36 *vs.* >36 months). These six characteristics are summarized in Table I. For univariate analyses of survival following WBRT, we used the Kaplan–Meier method and the log-rank test. Characteristics found significant on univariate analyses ($p<0.05$) were additionally analyzed using the Cox proportional hazards model.

Results

In the cohort of all 21 patients, the median survival time was 2 months, and the 3-month and the 6-month survival rates

were 48% and 24%, respectively. On univariate analyses (Table II), KPS had a significant impact on survival (p=0.018). Patients with a KPS of ≥80% had a better survival than those patients with a KPS of ≤70%. The corresponding 3-month survival rates were 60% and 36%, respectively, and the 6-month survival rates were 50% and 0%, respectively (Figure 1). To evaluate the independence of the impact of the KPS on survival, KPS was subsequently analyzed using the Cox proportional hazards model, where it maintained significance. The corresponding hazard ratio was 3.18, and the 95% confidence interval was 1.11-10.53 (p=0.031).

Table I. I*nvestigated potential prognostic factors*.

	Number of patients	Proportion (%)
Dose-fractionation regimen		
5×4 Gy	10	48
10×3 Gy	7	33
14-20×2.0-2.5 Gy	4	19
Age at the start of WBRT		
≤74 Years	11	52
≥75 Years	10	48
Karnofsky performance score		
≤70%	11	52
≥80%	10	48
Number of brain metastases		
1-3	9	43
>3	12	57
Extra-cerebral metastases		
No	4	19
Yes	17	81
Interval between first diagnosis of prostate cancer and WBRT		
≤36 Months	12	57
>36 Months	9	43

WBRT: Whole-brain radiotherapy.

Discussion

Although considerable research has been performed, many patients with metastatic prostate cancer still have a limited survival prognosis (6-9). This is particularly true for patients with cerebral metastases (10-15). In addition to novel systemic therapies, the concept of treatment personalization may improve outcomes. Elderly patients, who are considered a separate group of patients with cancer, may not tolerate novel systemic drugs, particularly novel immunotherapies that can be associated with new side effects including inflammatory reactions such as encephalitis, hypophysitis, pneumonitis, nephritis, hepatitis and others (16). Therefore, personalization of the cancer treatment is of particular importance for elderly patients.

Despite an emerging role of radiosurgery and fractionated stereotactic radiotherapy for the treatment of cerebral metastases, many elderly patients receive WBRT alone, preferably in case of multiple cerebral lesions or because they have a reduced performance status and significant co-morbidities (17-19). When using WBRT for elderly patients, several dose-fractionation programs are available (1). The most common programs include short-course WBRT with 5×4 Gy over 1 week and longer-course programs ranging from 10×3 Gy over 2 weeks to 14-20×2.0-2.5 Gy over 3-4 weeks. Short-course WBRT is considered a good option for patients with poor estimated survival, mainly to ensure they spend as little as necessary of their limited lifespan receiving radiotherapy. WBRT with 5×4 Gy was shown to be as effective as 10×3 Gy with respect to cerebral control and survival in patients with limited prognoses and multiple cerebral lesions (20). Patients with more favorable prognoses, however, can benefit from treatment with a longer-course WBRT program. In these patients, WBRT with higher total doses can lead to improved cerebral control and survival rates (21). Moreover, the use of lower doses per fraction can reduce the risk of neurocognitive deficits (22).

These considerations illustrate that it is important to be able to estimate a patient's survival prognosis prior to their treatment, in order to choose the optimal individual WBRT program. This can be facilitated by using prognostic factors. As stated above, treatment personalization is particularly important for elderly patients, who are different from younger patients with respect to organ function and tolerability of cancer treatments. Therefore, it is important to identify predictors of survival for this particular group. Moreover, for optimal personalization, specific prognostic factors are required for each tumor entity potentially spreading to the brain.

In this study, one prognostic factor, namely KPS, was identified for elderly patients with cerebral metastases from prostate cancer. In a previous study of patients of any age with prostate cancer who received WBRT for cerebral metastases, KPS was also significantly associated with survival (5). However, in that study, survival was additionally affected by the number of brain metastases, extra-cerebral metastases and the interval between first diagnosis of prostate cancer and WBRT (5). This difference in comparison to the findings of the present study supports the need for separate studies focusing on elderly patients.

In the current study, 50% of the patients with a KPS ≥80% survived for 6 months or longer, whereas all patients with a KPS of ≤70% died within 5 months (Figure 1). Thus, patients with a KPS ≥80% appear to be good candidates for a longer-course WBRT program, whereas those with a KPS of ≤70% would be better treated with 5×4 Gy (20, 22). However, when following these suggestions, the limitations

Table II. *Survival rates at 3 and 6 months following whole-brain radiotherapy.*

	Survival rate (%)		
	At 3 months	At 6 months	*p*-Value
Dose-fractionation regimen			
5×4 Gy	50	20	0.513
10×3 Gy	57	29	
14-20×2.0-2.5 Gy	25	25	
Age at the start of WBRT			
≤74 Years	45	18	0.252
≥75 Years	50	30	
Karnofsky performance score			
≤70%	36	0	**0.018**
≥80%	60	50	
Number of brain metastases			
1-3	67	33	0.202
>3	33	17	
Extra-cerebral metastases			
No	50	25	0.672
Yes	47	24	
Interval between diagnosis of prostate cancer and WBRT			
≤36 Months	50	17	0.626
>36 Months	44	33	

WBRT: Whole-brain radiotherapy, bold: significant *p*-values.

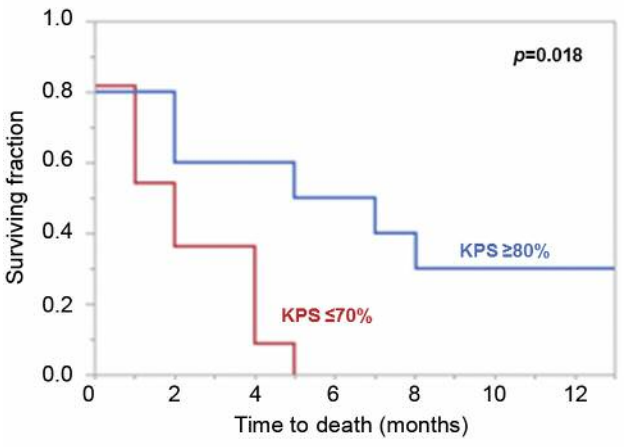

Figure 1. *Kaplan–Meier curves for survival comparing patients with a Karnofsky performance score (KPS) of ≥80% (n=10) to those with a KPS of ≤70% (n=11). The p-value was obtained from calculations using the log-rank test.*

of this study, namely its retrospective nature and its relatively small sample size, should be taken into account.

In conclusion, KPS proved to be an important prognostic factor of survival in elderly patients with prostate cancer treated with WBRT alone for cerebral metastases. Thus, the KPS can be helpful when aiming to choose an optimally personalized WBRT program for an individual patient of this group.

Conflicts of Interest

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

Authors' Contributions

T.N., T.B., S.E.S and D.R. participated in the design of the study. T.N. and D.R. provided the data that were analyzed by S.E.S. and D.R. S.E.S and D.R. drafted the article reviewed and approved by all Authors.

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Received February 1, 2020
Revised February 11, 2020
Accepted February 12, 2020