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Clinical Factors Associated with Treatment Outcomes Following Whole-brain Irradiation in Patients with Prostate Cancer

LIESA DZIGGEL[1], STEVEN E. SCHILD[2], THEO VENINGA[3], AMIRA BAJROVIC[4] and DIRK RADES[1]

[1]*Department of Radiation Oncology, University of Lübeck, Lübeck, Germany;*
[2]*Department of Radiation Oncology, Mayo Clinic, Scottsdale, AZ, U.S.A.;*
[3]*Department of Radiotherapy, Dr. Bernard Verbeeten Institute, Tilburg, the Netherlands;*
[4]*Department of Radiotherapy, University Medical Center Eppendorf, Hamburg, Germany*

Abstract. *Background/Aim: Patients with prostate cancer represent a small minority of cancer patients presenting with metastases to the brain. This study investigated the role of whole-brain irradiation (WBI) in this rare group. Patients and Methods: Eighteen such patients were included. Clinical factors including fractionation program of WBI, age at WBI, Karnofsky performance score (KPS), number of metastases to the brain, involvement of extracerebral metastatic sites, time from prostate cancer diagnosis to WBI and recursive-partitioning-analysis (RPA) class were investigated regarding local (intracerebral) control and survival. Results: On multivariate evaluation, longer time from prostate cancer diagnosis to WBI showed a trend towards improved local control (hazard ratio 2.77, p=0.098). Better KPS (hazard ratio 5.64, p=0.021) and longer time from prostate cancer diagnosis to WBI (hazard ratio 5.64, p=0.013) were significantly associated with better survival. Conclusion: Two independent predictors of survival were identified and should be considered when designing for personalized treatment regimens and clinical trials.*

Metastases to the brain represent a palliative situation that occurs in up to 40% of patients with cancer (1-3). The most common primary tumors associated with brain metastases are lung cancer (40-50%) and breast cancer (20-25%). In contrast, patients with prostate cancer account for a minority of less than 1%. Therefore, there is a considerable lack of data regarding this group. Many patients with metastases to the brain from prostate cancer have a short expected survival and are treated with whole-brain irradiation (WBI) alone.

When a patient is assigned to WBI, several options, *i.e.* dose-fractionation programs, are available (2, 3). These options range from 1-week programs with lower total doses and higher doses per fraction to more protracted programs lasting up to 4 weeks with higher total doses but lower doses per fraction. Previous studies of WBI for brain metastases from different tumor types suggested that patients with a short expected survival should be treated with a short WBI program to allow the patients to spend more of their remaining time at home (2, 4). In contrast, longer WBI programs were reported to result in improved local (intracerebral) control and survival in the group of patients with the longest estimated survival time (5).

Thus, it is important to be able to judge a patient's remaining survival time before assigning them to a WBI program. Therefore, this study was performed with the major goal as the identification of possible independent predictors of survival, and additionally of local control in patients with metastases to the brain from prostate cancer. Identification of such predictors would assist the treating physicians when choosing the most appropriate WBI program for such a patient.

Patients and Methods

In this retrospective study, 18 unselected patients with prostate cancer treated with WBI for metastases to the brain were included. The major goal of this study was the evaluation of possible associations between local (intracerebral) control and survival and seven clinical factors. These factors were the WBI fractionation program (4 Gy × 5 *vs.* 3 Gy × 10), age at WBI (<75 *vs.* ≥75 years, median=74.5 years), Karnofsky performance score (KPS) (≤70% *vs.* 80%), number of metastases to the brain (<4 *vs.* ≥4), involvement of extracerebral metastatic sites (none *vs.* bone only *vs.* sites other than bone), time interval from prostate cancer diagnosis to WBI (≤28 *vs.* >28 months), and recursive partitioning analysis (RPA) class (2 *vs.* 3) (6). The distribution of these factors is shown in Table I. Univariate analyses of local control and survival were carried out

Correspondence to: Professor Dirk Rades, MD, Department of Radiation Oncology, University of Lübeck, Lübeck, Ratzeburger Allee 160, 23538 Lübeck, Germany. Tel: +49 4515006661, Fax: +49 4515003324, e-mail: rades.dirk@gmx.net

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with the Kaplan–Meier method and the log-rank test (7). Thereafter, the significant ($p<0.05$) and borderline significant ($p<0.06$) clinical factors were evaluated for independence with the Cox proportional hazards model.

Results

The median follow-up was 4 months (range=1-13 months) for the whole series and 12 months (range=10-13 months) in patients still alive at their last follow-up. The local control rates at 3 and 6 months were 48% and 35%. On univariate evaluation, a longer time interval from prostate cancer diagnosis to WBI showed a strong trend towards improved local control ($p=0.057$, Table II). On the Cox proportional hazards analysis, this trend was confirmed (hazard ratio=2.77, 95% confidence interval=0.83-10.75, $p=0.098$).

The survival rates recorded at 3 and 6 months were 67% and 22%. On univariate evaluation, a better KPS ($p=0.027$) and a longer time interval from prostate cancer diagnosis to WBI ($p=0.009$) were significantly correlated with better survival (Table III). On Cox proportional hazards analysis, both KPS (hazard ratio=5.64, 95% confidence interval=1.27-43.48, $p=0.021$) and the interval from prostate cancer diagnosis to WBI (hazard ratio=5.64, 95% confidence interval=1.39-24.39, $p=0.013$) remained significant predictors. The 6-month survival rate for the seven patients with a KPS of ≤70% and an interval from prostate cancer diagnosis to WBI of ≤28 months was 0%. In contrast, the 6-month survival rate of the three patients with a KPS of 80% and an interval from prostate cancer diagnosis to WBI of >28 months was 100%.

Table I. *Clinical factors and their distribution.*

Factor	Number of patients (N)	Proportion (%)
Fractionation program of WBI		
4 Gy × 5 fractions	11	61
3 Gy × 10 fractions	7	39
Age at WBI		
<75 years	9	50
≥75 years	9	50
Karnofsky performance score		
≤70%	13	72
80%	5	28
Number of metastases to the brain		
<4	8	44
≥4	10	56
Involvement of extra-cerebral metastatic sites		
None	3	17
Bone metastasis only	10	56
Sites other than bone	5	28
Time from prostate cancer diagnosis to WBI		
≤28 months	9	50
>28 months	9	50
Recursive partitioning analysis class		
Class 2	12	67
Class 3	6	33

WBI: Whole-brain irradiation.

Discussion

Since prostate cancer is the most common type of cancer in men, considerable research is performed in order to improve the outcomes of these patients, including preclinical studies and clinical investigations of new systemic treatments, surgical approaches and radiation techniques (8-13). In contrast to metastatic spread to the bone, metastases to the brain are very rare. Although prostate cancer is one of the most common types of cancer, patients with brain metastases from this tumor entity account for fewer than 1% of patients presenting with metastases to the brain (1-3). Therefore, little is known about this particular patent group in this regard. In order to provide additional information, the present study was carried out. It investigated potential associations between clinical factors and outcomes in terms of local control and survival in order to identify independent prognostic factors.

According to the results of this study, the time interval from prostate cancer diagnosis to WBI was an important prognostic factor. On multivariate analysis, an interval of more than 28 months showed a trend towards association with improved local control and a significant association with improved survival. In addition, a KPS of 80% (when compared to ≤70%) was an independent predictor of better survival. The performance status has been identified as an independent predictor of survival in previous studies including patients with brain metastases from different tumor entities (6, 14-16). The most widely used tool for estimating the survival of patients with metastases to the brain is the RPA classification, published in 1997 (6). This classification includes three prognostic groups with median survival times of 7.1 months (RPA class 1), 4.2 months (RPA class 2) and 2.3 moths (RPA class 3), respectively. It was mainly based on the KPS (<70% *vs.* ≥70%) but additionally on age (<65 *vs.* ≥65 years) and extracranial disease. The prognostic value of the RPA classification for patients with brain metastases from prostate cancer was investigated in the present study. However, the RPA classification did not achieve significance on univariate analysis. This may be explained by the fact that the vast majority of patients with prostate cancer are 65 years or older, which means that discrimination by age will not be important for these patients. Furthermore, the RPA classification does not consider the time interval from prostate cancer diagnosis to WBI, which proved to be an important prognostic factor in the present study particularly focusing on prostate cancer (6). Similar limitations could be expected for the graded prognostic assessment tool, another

Table II. *Local control rates at 3 and 6 months.*

Factor	At 3 months (%)	At 6 months (%)	*p*-Value
Fractionation program of WBI			
4 Gy × 5 fractions	42	42	
3 Gy × 10 fractions	57	29	0.94
Age at WBI			
<75 years	33	n.a.	
≥75 years	65	65	0.07
Karnofsky performance score			
≤70%	34	26	
80%	80	60	0.24
Number of metastases to the brain			
<4	50	38	
≥4	47	35	0.75
Involvement of extra-cerebral metastatic sites			
None	33	33	
Bone metastasis only	60	38	
Sites other than bone	27	n.a.	0.96
Time from prostate cancer diagnosis to WBI			
≤28 months	27	0	
>28 months	67	56	0.057
Recursive partitioning analysis class			
Class 2	50	40	
Class 3	44	n.a.	0.41

WBI: Whole-brain irradiation, n.a.: not available.

Table III. *Survival rates at 3 and 6 months.*

Factor	At 3 months (%)	At 6 months (%)	*p*-Value
Fractionation program of WBI			
4 Gy × 5 fractions	55	18	
3 Gy × 10 fractions	86	29	0.22
Age at WBI			
<75 years	67	0	
≥75 years	67	44	0.18
Karnofsky performance score			
≤70%	62	8	
80%	80	60	**0.027**
Number of metastases to the brain			
<4	75	38	
≥4	60	10	0.18
Involvement of extra-cerebral metastatic sites			
None	67	33	
Bone metastasis only	70	30	
Sites other than bone	60	0	0.42
Time from prostate cancer diagnosis to WBI			
≤28 months	56	0	
>28 months	78	44	**0.009**
Recursive partitioning analysis class			
Class 2	75	33	
Class 3	50	0	0.11

WBI: Whole-brain irradiation, bold values represent significant *p*-values.

commonly used survival score for patients with brain metastases (16). This tool was based on four factors, including age (>60 *vs*. 50-59 *vs*. <50 years), but not on the interval from prostate cancer diagnosis to WBI. These considerations demonstrate the importance of looking separately at different tumor entities, as performed in the current study. Bearing in mind its limitations due to the retrospective design and the small number of patients included, one may suggest choosing a WBI program for an individual patient based on the two independent predictors of survival identified in this study. Patients with an interval from prostate cancer diagnosis to WBI of ≤28 months and a KPS of ≤70% have a very poor prognosis and might be considered for a short WBI program, or even best supportive care alone. A previous study suggested that 4 Gy × 5 was not inferior to 3 Gy × 10 in a large cohort of patients with metastases to the brain from different tumor entities (4). The survival rates at 6 months were 24% and 27%, respectively (p=0.29). In contrast, those patients with an interval from prostate cancer diagnosis to WBI of >28 months and a KPS of >70%, who have a more favorable prognosis, would likely benefit from WBI with higher total doses and lower doses per fraction such as 2.5 Gy ×14 or 2 Gy × 20. A previous study of long-term surviving patients with brain metastases from various tumor entities suggested that WBI with 2 Gy × 20 led to significantly better local control and survival than 3 Gy × 10 (5); the survival rates at 12 months were 61% and 50%, respectively (p=0.008).

In conclusion, this study identified two independent predictors of survival. These two clinical factors should be considered when assigning personalized treatment regimens for individual patients and when designing prospective clinical trials.

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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