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Predicting Survival After Irradiation of Metastases from Transitional Carcinoma of the Bladder

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Abstract. *Aim: For patients with metastatic bladder cancer, radiotherapy is a good option to control symptoms and improve outcomes. Potential prognostic factors for survival including the radiation dose were investigated. Patients and Methods: Ten factors were evaluated in 63 patients for association with survival after irradiation namely age, gender, performance status, initial T-category, initial N-category, metastases at initial diagnosis, number of metastases, metastatic sites, radiation dose and time from diagnosis of metastases to irradiation. Results: On univariate analysis, survival was negatively associated with Karnofsky performance score (KPS) ≤70 (p=0.033), initial N-category ≥1 (p=0.026) and radiation doses given as equivalent dose in 2-Gy fractions (EQD2) <20 Gy. Doses >30 Gy were slightly superior to 20-30 Gy. On multivariate analysis, EQD2 (p=0.015) maintained its significance; a trend was found for N-category (p=0.063) and KPS (p=0.073). Conclusion: Predictors for survival after irradiation of metastases from bladder cancer were identified. Radiation doses ≥20 Gy should be used.*

Patients with urinary bladder cancer represent approximately 2% of all patients with cancer (1-3). Distant metastases occur in 10-29% of patients with bladder cancer during the course of their disease (4). Since the median age of patients with bladder cancer is over 70 years, this type of cancer as considered an age-associated malignancy (5). Patients with metastatic bladder cancer have been reported to have an average life expectancy of 14 months (5). Polychemotherapy regimens such as methotrexate, vinblastine and adriamycin combined with cisplatin (M-VAC) result in prolongation of life. However, not all patients can tolerate such an intensive treatment. Radiotherapy has several roles in the management of metastatic bladder cancer, including pain control especially in case of bone metastases, control of progressive visceral metastases and palliation of brain metastases (2, 3, 6).

The optimal radiation approach for individual patients with metastatic bladder cancer should always take into account the patient's remaining life time. This study aimed to identify prognostic factors that can facilitate the administration of more personalized radiotherapy treatment approaches in patients with metastatic bladder cancer. Furthermore, the study compared different radiation doses in order to define an appropriate dose range for this group.

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Patients and Methods

Sixty-three patients irradiated for symptomatic metastases from transitional carcinoma of the bladder were included in this retrospective study. The median age at start of radiotherapy was 70 years (range= 50-87 years). The radiation dose was given as equivalent dose in 2 Gy fractions (EQD2). Three EQD2 levels (<20 Gy *vs.* 20-30 Gy *vs.* >30 Gy) and nine additional factors were evaluated for potential associations with survival. These nine characteristics were gender, Karnofsky performance score (KPS) (≤70 *vs.* >70), initial tumor (T)-category (1-2 *vs.* 3-4), initial lymph node (N)-category (0 *vs.* ≥1), distant metastases at initial diagnosis (no *vs.* yes), number of metastases (1 *vs.* 2 *vs.* ≥3), metastases sites (bone *vs.* other *vs.* both), time between diagnosis of metastases and irradiation (≤2 *vs.* >2 months, median 2 months). At the end of radiotherapy, symptom control was assessed and rated as complete symptom control (complete palliation), partial symptom relief/stable symptoms or progressive symptoms.

Univariate analysis of these factors was performed using the Kaplan–Meier method and the log-rank test at 6 and 12 months (7). The characteristics that showed a significant association with survival ($p<0.05$) were additionally included in a multivariate (Cox regression) analysis.

Results

Results of the survival analysis are summarized in Table I. Median survival after irradiation was 6 months. On univariate analysis, negative prognostic factors for survival were KPS

Table I. *Univariate analysis for survival at 6 and 12 months.*

	At 6 months (%)	At 12 months (%)	*p*-Value
Age			
≤70 Years (n=29)	48	7	
>70 Years (n=34)	18	6	0.095
Gender			
Female (n=17)	18	6	
Male (n=46)	37	4	0.409
Karnofsky performance score			
≤70 (n=32)	16	3	
>70 (n=31)	39	10	0.033
Initial tumor category			
T1-2 (n=37)	30	8	
T3-4 (n=26)	23	4	0.927
Initial lymph node category			
N0 (n=42)	36	7	
N≥1 (n=17)	12	0	0.026
Distant metastases at initial diagnosis			
No (n=40)	30	8	
Yes (n=43)	22	4	0.61
Number of metastases			
1 (n=23)	39	9	
2 (n=17)	16	6	
>2 (n=23)	22	4	0.245
Metastatic sites			
Bone (n=22)	41	9	
Other (n=18)	29	6	
Both (n=23)	17	4	0.244
Equivalent dose in 2 Gy fractions			
<20 Gy (n=3)	0	0	
20-30 Gy (n=12)	25	0	
>30 Gy (n=47)	30	9	0.001
Time between diagnosis of metastases and irradiation			
0-2 months (n=33)	30	6	
>2 months (n=30)	23	7	0.480

<70 (p=0.033), initial N-category ≥1 (p=0.026) and radiation dose (EQD2) <20 Gy (p=0-0.01). Results of the univariate analysis of the EQD2 levels are displayed in Figure 1.

On multivariate analysis, EQD2 <20Gy [hazard ratio (HR)=0.549, 95% confidence interval (CI)=0.339-0.889; p=0.015) was negatively associated with survival. A negative trend for survival was seen for initial N-category ≥1 (HR=1.738, 95% Cl=0.970-3.117; p=0.063) and KPS ≤70 (HR=0.609, 95% Cl=0.354-1.048; p=0.073).

Complete palliation at end of radiotherapy was achieved in 56% of all patients (N=35). Progression of symptoms was stopped in another 27% of the patients (N=17). Disease progression was seen in 17% of patients (N=11), who were subsequently treated with best supportive care.

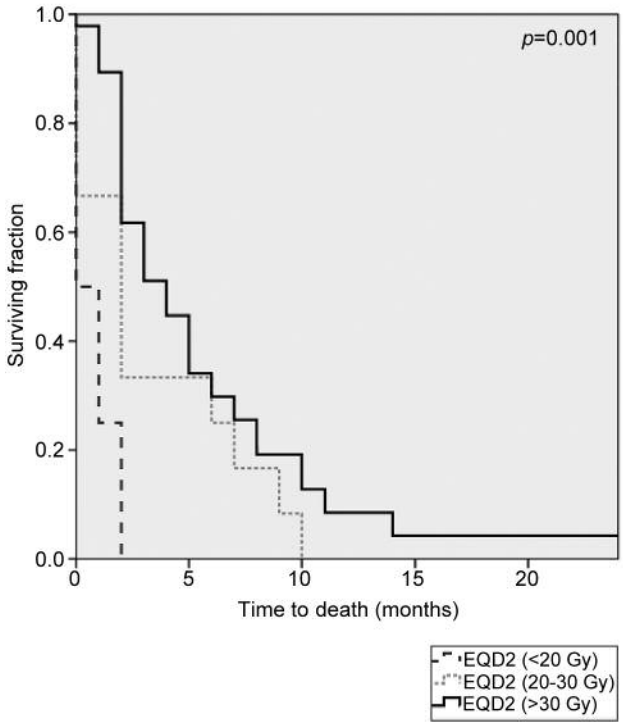

Figure 1. *Kaplan–Meier curves of overall survival according to the administered radiation doses given as equivalent doses in 2-Gy fractions (EQD2) comparing <20 Gy, 20-30 Gy and >30 Gy.*

Discussion

Urinary bladder cancer accounts for approximately 2% of all cancer types in adult patients (1-3). Up to 29% of these patients will experience metastatic spread to organs such as bone and brain (4, 6). Platinum-based chemotherapy represents the standard of care for metastatic bladder cancer. However, bladder cancer is an age-associated malignancy, and many patients are not candidates for conventional chemotherapy regimens such as M-VAC (5). New targeted therapies such as angiogenic inhibitors and drugs affecting the phosphatidylinositol 3 kinase –protein kinase B pathway have shown promising outcomes (8). However, there is a lack of evidence and a need for better understanding of tumor biology. Several biomarkers were found to have a prognostic impact on survival. A recent study demonstrated that copper transporter (CTR1) expression is correlated with pathological response and suggested that its expression is useful as a biomarker for platinum-based chemotherapy (9).

Radiotherapy can contribute to the palliative management of patients with metastatic bladder cancer in the form of pain control, particularly for patients with bone metastases, for

control of advancing visceral metastases and palliation for brain metastases (2, 3, 6). Prognostic factors for patients irradiated for metastases from bladder cancer have not yet been properly defined. One goal of this study was to identify independent prognostic factor and, therefore, to contribute to personalization of radiotherapy treatment in patients with metastatic bladder cancer.

Several studies have investigated the use of radiotherapy for bone metastases. In a large study of 765 patients, different radiotherapy regimens (8 Gy single-fraction radiotherapy *vs*. 20 Gy in five fractions or 30 Gy in 10 fractions) for painful bone metastases were compared (10). Single-fraction radiotherapy resulted in a higher re-treatment rate, but no difference in time to response or to first increase in pain at any time up to 12 months was observed. In another study, 8 Gy single-fraction radiotherapy was compared to 24 Gy in six fractions in 1,171 patients with bone metastases (11). No statistical difference was observed between the two treatment regimens regarding treatment response, change in pain medication requirement, quality of life and side-effects. Retreatment rates were significantly higher in the single fraction arm.

Bellmunt *et al*. investigated prognostic factors in metastatic bladder cancer and identified three factors associated with significantly improved survival, namely KPS >80, pretreatment hemoglobin level >10 g/dl and absence of liver metastases (12). Bajorin *et al*. suggested that a baseline KPS <80 and visceral metastases had a negative impact on survival (13).

In the present study, KPS <70 and N-category ≥1 were significantly associated with poorer survival following irradiation on univariate analysis and showed a trend on multivariate analysis. Summarizing the data of the three studies including the present one, KPS can be considered the most important prognostic factor of survival in patients with metastatic bladder cancer and should be taken into account when selecting the treatment for such a patient.

In the present study, three different dose ranges were compared, <20 Gy, 20-30 Gy and >30 Gy. Doses <20 Gy were associated with a significantly worse survival than doses ≥20 Gy, and doses >30 Gy appeared slightly superior to doses of 20-30 Gy. The radiation dose was also significantly associated with survival on multivariate analysis, which demonstrates the independence of its impact on survival.

In conclusion, predictors for survival after irradiation of metastases from bladder cancer were identified. Radiation doses (EQD2) of ≥20 Gy resulted in significantly better survival rates than lower doses and should, therefore, be used for these patients. Further studies are required to reveal whether doses of >30 Gy are superior to doses of 20-30 Gy.

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