

Prognostic Factors and a Survival Score in Patients Irradiated for Metastatic Epidural Spinal Cord Compression from Urothelial Carcinoma Cancer of the Bladder

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Abstract. *Background/Aim: Prognoses of patients with metastatic epidural spinal cord compression (MESCC) from urothelial carcinoma of the bladder are generally poor. This study aimed to identify prognostic factors that can facilitate personalized care of these patients. Patients and Methods: In 46 patients, 10 factors were evaluated for overall response (OR), post-radiotherapy (RT) ambulatory status, local control of MESCC and overall survival (OS). Independent predictors of OS were incorporated in a scoring system. Results: Being ambulatory post-RT was associated with pre-RT ambulatory status ($p<0.001$) and better performance score ($p<0.001$). No factor was significantly associated with OR and local control. On multivariate analyses, lack of visceral metastases ($p=0.002$), being ambulatory pre-RT ($p=0.001$) and performance score 1-2 ($p=0.004$) were associated with improved OS. Based on these factors, there were three distinct prognostic groups with 0, 1-2 and 3 points and median OS times of 2, 4 and 11.5 months, respectively. Conclusion: Prognostic factors were identified and a new survival score was created that will help physicians aiming to personalize treatment for patients with MESCC from urothelial carcinoma of the bladder.*

Since metastatic epidural spinal cord compression (MESCC) is a palliative situation, personalized treatments for patients

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are very important (1, 2). Tailoring the treatment to a patient's specific situation should include the attempt to avoid over- and under-treatment. This means that patients with a very poor overall survival (OS) should preferably receive a less aggressive treatment that will not significantly impair quality of life during their short remaining lifespan. Moreover, treatment should be kept as short as reasonably possible to give the patients as many days as possible without receiving anticancer treatment (3, 4). Late treatment-related morbidity plays only a minor role for patients with a limited OS prognosis, who likely will die before they would have experienced such morbidity. On the contrary, in patients with longer survival, durable local control of MESCC and late morbidity due to anticancer treatment become an issue, and the focus of treatment changes from short overall treatment time to persistent local control with fewer and less severe late sequelae (5-7). In addition to OS, other endpoints are important, including response to treatment, post-treatment ambulatory status and local control of MESCC (1-7). Selection of a personalized treatment approach should take into account all these endpoints and it would be important to identify prognostic factors for each.

In order to provide an optimal personalized treatment, it would be desirable to have a detailed understanding of prognostic factors for the different primary tumour types that show a considerable variety with respect to their biological behaviour and prognoses (1, 2, 8). The present study focused on patients irradiated for MESCC from urothelial carcinoma of the bladder, which are quite rare and account for only about 2% of patients receiving radiotherapy (RT) for MESCC (9). In addition to the investigation of potential associations between 10 clinical factors and response, post-RT ambulatory status, local control of MESCC and OS, this study aimed to create a new OS score specifically for this cohort of patients

Table I. Overall response to radiotherapy (RT) according to patient characteristics.

Characteristic	Overall response, N (%)	p-Value
Age		
≤65 Years (N=23)	21 (91)	0.52
≥66 Years (N=23)	17 (74)	
Interval from diagnosis of UC to RT of MESCC		
≤15 Months (N=21)	16 (76)	0.67
>15 Months (N=25)	22 (88)	
Visceral metastases		
No (N=22)	16 (73)	0.47
Yes (N=24)	22 (92)	
Additional bone metastases		
No (N=12)	8 (67)	0.48
Yes (N=34)	30 (88)	
Gender		
Female (N=5)	4 (80)	0.96
Male (N=41)	34 (83)	
Time developing motor dysfunction		
≤7 Days (N=20)	15 (75)	0.62
>7 Days (N=26)	23 (88)	
Pre-RT ambulatory status		
Not ambulatory (N=26)	20 (77)	0.62
Ambulatory (N=20)	18 (90)	
Number of involved vertebrae		
1-2 (N=14)	11 (79)	0.83
≥3 (N=32)	27 (84)	
ECOG-PS		
1-2 (N=16)	16 (100)	0.34
3-4 (N=30)	22 (73)	
Total dose of RT (EQD2)		
<25 Gy (N=22)	18 (82)	0.95
>30 Gy (N=24)	20 (83)	
Entire cohort	38 (83)	

MESCC: Metastatic spinal cord compression; ECOG-PS: Eastern Cooperative Oncology Group performance score; EQD2: equivalent dose in 2-Gy fractions; UC: urothelial carcinoma.

Table II. Ambulatory rates following radiotherapy (RT) of metastatic spinal cord compression (MESCC) according to patient characteristics.

Characteristic	Ambulatory, N (%)	p-Value
Age		
≤65 Years (N=23)	14 (61)	0.20
≥66 Years (N=23)	8 (35)	
Interval from diagnosis of UC to RT of MESCC		
≤15 Months (N=21)	7 (33)	0.20
>15 Months (N=25)	15 (60)	
Visceral metastases		
No (N=22)	12 (55)	0.52
Yes (N=24)	10 (42)	
Additional bone metastases		
No (N=12)	6 (50)	0.88
Yes (N=34)	16 (47)	
Gender		
Female (N=5)	2 (40)	0.78
Male (N=41)	20 (49)	
Time developing motor dysfunction		
≤7 Days (N=20)	6 (30)	0.12
>7 Days (N=26)	16 (62)	
Pre-RT ambulatory status		
Not ambulatory (N=26)	3 (12)	<0.001
Ambulatory (N=20)	19 (95)	
Number of involved vertebrae		
1-2 (N=14)	9 (64)	0.29
≥3 (N=32)	13 (41)	
ECOG-PS		
1-2 (N=16)	15 (94)	<0.001
3-4 (N=30)	7 (23)	
Total dose of RT (EQD2)		
<25 Gy (N=22)	10 (45)	0.83
>30 Gy (N=24)	12 (50)	
Entire cohort	22 (48)	

ECOG-PS: Eastern Cooperative Oncology Group performance score; EQD2: equivalent dose in 2-Gy fractions; UC: urothelial carcinoma. Bold indicates significant p-Values.

Patients and Methods

Forty-six patients (32 previously reported and 14 new patients) were included in this retrospective study and had received palliative RT for MESCC from urothelial carcinoma of the bladder associated with motor dysfunction of the lower extremities (9). Investigated endpoints included overall response (OR) to RT (defined as improvement or no further progression of motor dysfunction), post-RT ambulatory status, local control of MESCC (defined as no in-field recurrence of MESCC following RT) and OS. In order to determine OR, the best response during the follow-up period of up to 6 months was considered. Time to in-field recurrence and time to death were counted from the last day of RT. The analyses of local control of MESCC were limited to those patients who responded to RT.

In addition to the outcomes of the entire cohort, associations of 10 potential prognostic factors with these endpoints were investigated. The 10 factors were age (≤65 vs. ≥66 years, median 65.5 years),

interval between diagnosis of urothelial carcinoma and RT of MESCC (≤15 vs. >15 months), presence of visceral metastases at the start of RT (no vs. yes), additional bone metastases (no vs. yes), gender, time of developing motor dysfunction prior to RT (≤7 vs. >7 days), pre-RT ambulatory status (no vs. yes), number of vertebrae involved by MESCC, (1-2 vs. ≥3), Eastern Cooperative Oncology Group performance score (ECOG-PS) (1-2 vs. 3-4) and the total RT dose given as equivalent dose in 2 Gy fractions (EQD2) using an α/β -ratio of 10 Gy for tumour cell kill (<25 vs. >30 Gy) (10).

The statistical analyses regarding OR and post-RT ambulatory status were performed with the Chi-square test. For the analyses of local control of MESCC and OS, the Kaplan–Meier method (11) and the Wilcoxon test were used (=univariate analyses). For all endpoints, p-values of less than 0.05 were regarded as significant. Those factors achieving significance on the univariate analyses of local control of MESCC and OS were additionally analysed in a multivariate manner using the Cox proportional hazards model.

Table III. Local control of metastatic spinal cord compression (MESCC) at 3, 6, 9 and 12 months following radiotherapy (RT) according to patient characteristics. These analyses were performed in those 38 patients who responded to RT.

Characteristic	3 Months (%)	6 Months (%)	9 Months (%)	12 Months (%)	<i>p</i> -Value
Age					
≤65 Years (N=21)	93	93	78	n.a.	0.88
≥66 Years (N=17)	93	92	92	92	
Interval from diagnosis of UC to RT of MESCC					
≤15 Months (N=16)	92	92	92	92	0.92
>15 Months (N=22)	94	94	80	0	
Visceral metastases					
No (N=16)	93	93	82	41	0.96
Yes (N=22)	92	92	92	n.a.	
Additional bone metastases					
No (N=8)	83	83	42	n.a.	0.16
Yes (N=30)	95	95	95	48	
Gender					
Female (N=4)	67	67	67	n.a.	0.09
Male (N=34)	96	96	84	42	
Time developing motor dysfunction					
≤7 Days (N=15)	89	89	89	0	0.55
>7 Days (N=23)	95	95	83	55	
Pre-RT ambulatory status					
Not ambulatory (N=20)	100	100	100	n.a.	0.17
Ambulatory (N=18)	88	88	77	26	
Number of involved vertebrae					
1-2 (N=11)	89	89	59	59	0.46
≥3 (N=27)	95	95	95	n.a.	
ECOG-PS					
1-2 (N=16)	87	87	74	25	0.13
3-4 (N=22)	100	100	100	n.a.	
Total dose of RT (EQD2)					
<25 Gy (N=18)	86	86	64	64	0.12
>30 Gy (N=20)	100	100	100	n.a.	
Entire cohort	93	93	83	41	

ECOG-PS: Eastern Cooperative Oncology Group performance score; EQD2: equivalent dose in 2 Gy fractions; UC: urothelial carcinoma; n.a.: not available. Bold indicates significant *p*-Values.

Subsequently, the factors that proved to be independently associated with OS were incorporated in a scoring system that allows estimating the OS probability of individual patients.

Results

Patients were followed-up until death, or for a median of 10 months in patients alive at the last follow-up. Considering the entire cohort, the OR rate was 83% (11% with improvement and 72% with no further progression of motor dysfunction). None of the 10 investigated factors were significantly associated with OR (Table I). Post-RT, 48% of the entire cohort were ambulatory, and this was significantly associated with being ambulatory pre-RT ($p<0.001$) and with an ECOG-PS of 1-2 ($p<0.001$). Three out of 26 non-ambulatory patients (12%) regained the ability to walk after RT, and 19 out of 20 ambulatory patients (95%) maintained ambulation. The ambulatory rates post-RT according to all

investigated factors are given in Table II. Considering the entire cohort, the local control rates at 3, 6, 9 and 12 months following RT were 93%, 93%, 83% and 41%, respectively. On univariate analyses of local control of MESCC, no factor proved to be significantly associated with outcomes. The local control rates are summarized in Table III.

Median OS time was 3.5 months considering the entire cohort, and OS rates at 3, 6, 9 and 12 months following RT were 50%, 26%, 18% and 16%, respectively. On univariate analyses of OS, significant associations with improved outcomes were found for absence of visceral metastases ($p=0.017$), a time of developing motor dysfunction of >7 days (representing a slower development of motor deficits) ($p=0.026$), ambulatory status pre-RT ($p<0.001$) and an ECOG-PS of 1-2 ($p<0.001$). The results of the univariate analyses of OS are summarized in Table IV. On subsequent multivariate analyses of OS, lack of visceral metastases

Table IV. Overall survival of patients (MESCC) at 3, 6, 9 and 12 months following radiotherapy (RT) for metastatic spinal cord compression according to patient characteristics.

Characteristic	3 Months (%)	6 Months (%)	9 Months (%)	12 Months (%)	p-Value
Age					
≤65 Years (N=23)	57	30	21	21	0.51
≥66 Years (N=23)	43	22	16	11	
Interval from diagnosis of UC to RT of MESCC					
≤15 Months (N=21)	48	19	19	19	0.57
>15 Months (N=25)	52	32	20	16	
Visceral metastases					
No (N=22)	68	50	34	28	0.017
Yes (N=24)	33	4	4	n.a.	
Additional bone metastases					
No (N=12)	42	25	17	8	0.67
Yes (N=34)	53	26	19	19	
Gender					
Female (N=5)	60	40	20	0	0.92
Male (N=41)	49	24	19	19	
Time developing motor dysfunction					
≤7 Days (N=20)	35	15	15	8	0.026
>7 Days (N=26)	62	35	22	22	
Pre-RT ambulatory status					
Not ambulatory (N=26)	23	8	8	n.a.	<0.001
Ambulatory (N=20)	85	50	34	28	
Number of involved vertebrae					
1-2 (N=14)	50	29	21	14	0.75
≥3 (N=32)	50	25	17	17	
ECOG-PS					
1-2 (N=16)	88	50	38	31	<0.001
3-4 (N=30)	30	13	7	n.a.	
Total dose of RT (EQD2)					
<25 Gy (N=22)	59	27	22	16	0.39
>30 Gy (N=24)	42	25	15	15	
Entire cohort		50	26	18	16

ECOG-PS: Eastern Cooperative Oncology Group performance score; EQD2: equivalent dose in 2 Gy fractions; UC: urothelial carcinoma; n.a.: not available. Bold indicates significant p-Values.

Table V. Overall survival according to total prognostic score (0, 1, 2 and 3 points) and the three prognostic groups.

	Points	3 Months (%)	6 Months (%)	9 Months (%)	12 Months (%)	p-Value
Prognostic score	0 (N=13)	8	0	0	0	<0.001
	1 (N=16)	38	13	13	n.a.	
	2 (N=9)	89	33	17	n.a.	
	3 (N=8)	100	88	63	50	
Prognostic group	0 (N=13)	8	0	0	0	0.001
	1-2 (N=25)	56	20	13	n.a.	
	3 (N=8)	100	88	63	50	

n.a.: Not available. Bold indicates significant p-Values.

[hazard ratio (HR)=3.24, 95% confidence interval (CI)=1.54-7.12, $p=0.002$], ambulatory status pre-RT (HR=3.58, 95% CI=1.67-8.00, $p=0.001$) and ECOG-PS of 1-2 (HR=3.34, 95% CI=1.48-7.95, $p=0.004$) maintained significance, whereas the

time of developing motor dysfunction >7 days was no longer significant (HR=1.66, 95%-CI=0.84-3.27, $p=0.14$).

These three independent predictors of OS, visceral metastases, pre-RT ambulatory status and ECOG-PS, were

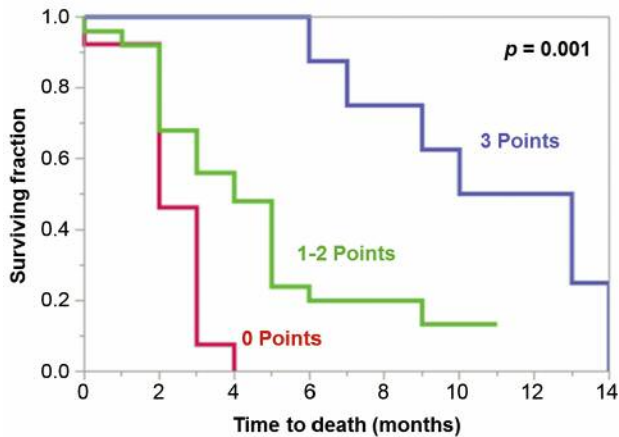


Figure 1. Kaplan–Meier curves of survival according to the three prognostic groups with 0 points, 1-2 points and 3 points.

used to create the scoring system for estimating OS. The following scoring points were assigned (factor scores): visceral metastases=0 points, no visceral metastases=1 point; not ambulatory=0 points, ambulatory=1 point; ECOG-PS of 3-4=0 points and ECOG-PS of 1-2=1 point. To obtain the total score for an individual patient, the three factor scores were summed. Thus, patient scores were 0, 1, 2 and 3 points. The corresponding OS rates at 3, 6, 9 and 12 months are shown in Table V. Based on the OS rates according to patient scores, three prognostic groups (0 points, 1-2 points, 3 points) with significantly different OS rates were designated (Table V, Figure 1, $p=0.001$). The median OS times of these groups were 2 months, 4 months and 11.5 months, respectively.

Discussion

MESCC has been reported to occur in up to 10% of adult patients with cancer (1, 2). About 2% of these patients have urothelial carcinoma of the bladder. In a previous retrospective study of 32 patients treated with RT alone, the median OS time was only 4 months (9). However, 16% of patients survived for 1 year or longer following RT. There is general agreement that patients with MESCC and a short remaining survival time should preferably be treated with single-fraction or short-course multi-fraction RT, *e.g.* 1×8 Gy or 5×4 Gy in 1 week (1-4). These RT programs were found to be similarly effective with respect to improving or maintaining motor function than longer-course RT programs such as 10×3 Gy in 2 weeks, 15×2.5 Gy in 3 weeks or 20×2 Gy in 4 weeks (3, 4). However, longer-course programs were reported to provide better local control of MESCC than single-fraction or short-course RT (5, 6, 12). Moreover, patients with a favourable OS prognosis may even benefit from doses higher than 10×3 Gy

(EQD2=32.5 Gy). In a retrospective matched-pair study of patients with favourable survival prognoses, 191 patients receiving 10×3 Gy in 2 weeks were matched 1:1 to 191 patients receiving 15×2.5 Gy in 3 weeks (EQD2=39.1 Gy) or 20×2 Gy in 4 weeks (EQD2=40 Gy) for 10 clinical factors (7). In the higher-dose groups, both local control of MESCC ($p=0.012$) and OS ($p=0.013$) were significantly better. These data show that it is very important to be able to estimate an individual patient's OS prognosis prior to the start of treatment, in order to prescribe the most appropriate RT program. Therefore, prognostic factors were identified and survival scores were developed for patients with MESCC in general and additionally for MESCC from specific primary tumour types such as breast, prostate and lung cancer, as well as several others (8, 13-17).

In the present study, the first OS score was created particularly for patients irradiated for MESCC from urothelial carcinoma of the bladder and is, therefore, much more specific than a previous score developed for metastatic bladder cancer in general, including patients with metastases to the brain and other sites (18). Based on the three independent prognostic factors, visceral metastases, pre-RT ambulatory status and ECOG-PS, a tool was designed including three prognostic groups. Patients achieving 0 points had a median OS time of only 2 months and none of these patients survived longer than 4 months. Therefore, such patients appear to be good candidates for short-course RT with 5×4Gy or even single-fraction RT with 1×8 Gy. In the group of patients achieving 1-2 points, the median OS time was 4 months, and only 20% of the patients survived 6 months or longer. Thus, short-course RT with 5×4 Gy appears appropriate, 10×3 Gy in 2 weeks may also be considered. Those patients achieving 3 points had the most favourable OS prognosis, with a median OS time of 11.5 months; 88% of the patients survived 6 months or longer. Therefore, these patients should receive longer-course RT, preferentially with an EQD2 doses higher than the EQD2 of 10×3 Gy (7).

This study also investigated response to RT and ambulatory status post-RT. RT was able to improve, or at least avoid further progression of motor dysfunction in 83% of the patients. However, improvement of motor deficits was achieved only in 11% of patients. Of those patients who were not ambulatory prior to RT, only 12% regained the ability to walk after treatment, whereas 95% of ambulatory patients maintained this status. Since the proportion of patients showing improvement of motor function is small, upfront decompressive surgery plus stabilization in addition to RT appears to be indicated for many patients with MESCC from urothelial carcinoma of the bladder. A previous randomized trial of 101 patients demonstrated that upfront surgery significantly increased the rate of ambulation for patients who met certain criteria, including a relatively good PS, involvement of only one spinal segment by MESCC and an

expected OS of at least 3 months (19). Therefore, patients with MESCC from urothelial carcinoma of the bladder who meet these criteria should strongly be considered for upfront decompressive surgery plus stabilization, particularly those patients who are not ambulatory for a short period. When following these recommendations, the retrospective design of the present study should be considered, since retrospective studies bear a risk of hidden selection biases.

In summary, a new score system was developed for patients with MESCC from urothelial carcinoma of the bladder that can help radiation oncologists choose the best RT program for an individual patient. Furthermore, the rate of improvement of motor dysfunction following RT was low; so was the rate of non-ambulatory patients who regained the ability to walk. Thus, upfront decompressive surgery plus stabilization should be strongly considered for patients who meet the criteria used in a previous randomized trial (19).

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