Prognostic Factors and a Survival Score for Patients with Metastatic Spinal Cord Compression (MSCC) from Renal Cell Carcinoma (RCC)

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ABSTRACT

This study aimed to identify prognostic factors and create a survival score in 142 patients with MSCC from RCC. On multivariate analysis, functional outcome was associated with visceral metastases ($p=0.011$), interval from cancer diagnosis to MSCC ($p<0.001$), and time developing motor deficits ($p<0.001$). Survival was associated with ambulatory status ($p=0.004$), visceral metastases ($p<0.001$), interval from cancer diagnosis to MSCC ($p=0.002$), and time developing motor deficits ($p=0.002$). Based on these prognostic factors, a survival score was developed. 6-months survival rates of four prognostic groups were 5%, 20%, 72% and 97% ($p<0.001$). The prognostic factors and the survival score help personalize treatment.

Key words: *metastatic spinal cord compression; renal cell carcinoma; radiotherapy; prognostic factors*

INTRODUCTION

Renal cell carcinoma accounts for 5-10% of all primary tumors leading to metastatic spinal cord compression (MSCC).[1,2] The vast majority of patients with MSCC are treated with radiotherapy alone. The radiation regimen may vary with respect to total dose, dose per fraction, overall treatment time, and technical approaches. Selected patients may benefit from upfront decompressive surgery in addition to radiotherapy.[3] To allow better personalization of the treatment of MSCC, it is helpful to know as much as possible about prognostic factors associated with treatment outcomes. Because each type of tumor causing MSCC has a different biological behavior, it appears reasonable to identify prognostic factors for each tumor type. In addition to helping the physician tailor the treatment regimen to the individual patient, independent prognostic factors are important for proper stratification in future trials for MSCC from RCC. This international study aimed to identify prognostic factors for treatment outcomes in terms of post-treatment motor function, local control of MSCC, and survival. An additional goal of this study

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was to develop a scoring system predicting survival in these patients.

MATERIAL AND METHODS

The data from 142 patients irradiated for MSCC from RCC were retrospectively evaluated. All were treated in Germany, the Netherlands, or the United Kingdom between 1992 and 2010. All patients had motor deficits of the lower extremities due to MSCC of the thoracic or the lumbar spine. Patients eligible for this analysis had no previous surgery or radiotherapy to the involved spinal sites. The diagnosis of MSCC was confirmed by spinal CT or MRI. The patients were usually presented to a surgeon before radiotherapy to discuss the option of decompressive surgery if indicated. Dexamethasone (12-32 mg/day) was administered from the first day of radiotherapy for at least one week. The data for the analysis were obtained from the patients themselves, their general practitioners, treating oncologists, and from the patient files. The characteristics of the 142 patients included in this study are summarized in Table 1.

Table 1. Patient characteristics.

	N patients	(%)
Age		
< 65 years	76	54
≥ 65 years	66	46
Gender		
Female	39	27
Male	103	73
ECOG Performance status		
2	63	44
3-4	79	56
Number of involved vertebrae		
1-2	66	46
≥ 3	76	54
Ambulatory status prior to RT		
Not ambulatory	54	38
Ambulatory	88	62
Other bone metastases		
No	68	48
Yes	74	52
Visceral metastases		
No	68	48
Yes	74	52
Interval from cancer diagnosis to MSCC	68	48
≥ 15 months	74	52
> 15 months		
Time developing motor deficits		
1–7 days	50	35
8-14 days	30	21
> 14 days	62	44
Radiation schedule		
Short-course RT	50	35
Longer-course RT	92	65

RT: radiotherapy

Each series from the contributing centers represented an unselected group of MSCC patients treated within a specific time period. Irradiation was performed with 6-10 MV photons. Treatment volumes encompassed one normal vertebra above and below the metastatic lesions. Motor function and ambulatory status were evaluated before radiotherapy, and at 1 month, 3 months and 6 months following radiotherapy. Motor function was evaluated with a 5-point scale according to Tomita et al.[4] Grade 0: normal strength; Grade 1: ambulatory without aid, Grade 2: ambulatory with aid, Grade 3: not ambulatory, Grade 4: paraplegia. Improvement or deterioration of motor function was defined as a change of at least one point on this scale.

The following potential prognostic factors were evaluated with for functional outcome: age (<65 vs. ≥65 years, median age: 65 years), Eastern Cooperative Oncology Group (ECOG) performance status (2 vs. 3-4), number of involved vertebra (1-2 vs. ≥3), ambulatory status before radiotherapy (not ambulatory vs. ambulatory), other bone metastases at the time of radiotherapy (no vs. yes), visceral metastases at the time of radiotherapy (no vs. yes), interval from first diagnosis of renal cell carcinoma to MSCC (≤15 vs. >15 months), time developing motor deficits before radiotherapy (1-7 vs. 8-14 vs. >14 days), and the radiation schedule (short-course radiotherapy with 1x8 Gy or 5x4 Gy in one week vs. longer-course radiotherapy with 10x3 Gy in two weeks, 15x2.5 Gy in three weeks or 20x2 Gy in four weeks).

These potential prognostic factors were evaluated for functional outcome (improvement vs. no change vs. deterioration of motor function), local control of MSCC (defined as absence of recurrence of MSCC in the irradiated spinal region), and overall survival. The diagnosis of an in-field recurrence of MSCC was

confirmed by spinal CT or MRI. Local control and survival rates were calculated with the Kaplan-Meier-method.[5] The differences between the Kaplan-Meier curves were calculated with the log-rank test. The prognostic factors found to be significant ($p<0.05$) in the univariate analysis were included in a multivariate analysis, performed with the Cox proportion hazards model. Regarding functional outcome, a multivariate analysis including all potential prognostic factors was performed with the ordered-logit model, as the data for functional outcome are ordinal (-1 = deterioration, 0 = no change, 1 = improvement). The patients were followed until death or for median 13 months (range: 6-72 months) in those patients alive at the last follow-up visit.

RESULTS

Of the entire cohort, 30 patients (21%) showed improvement of motor function, 87 patients (61%) no further progression, and 25 patients (18%) deterioration. The impact of the potential prognostic factors on functional outcome is shown in Table 2. On multivariate analysis, improved functional outcome was significantly associated with absence of visceral metastases at the time of radiotherapy (estimate: -1.20; 95%-confidence interval [CI: -1.82 to -0.23; $p=0.011$), an interval from cancer diagnosis to MSCC of >15 months (estimate: +1.68; 95%-CI: +0.76 to +2.59; $p<0.001$), and a slow development (>14 days) of motor deficits prior to radiotherapy (estimate: +2.49; 95%-CI: +1.33 to +3.65; $p<0.001$). Of the 26 patients who had all three positive prognostic factors, 17 patients (65%) showed improvement, 9 patients (35%) no further progression, and no patient (0%) deterioration of motor function.

Table 2. Potential prognostic factors in relation to functional outcome.

	Improvement N (%)	No change N (%)	Deterioration N (%)	P
Age				
< 65 years	19 (25)	37 (49)	20 (26)	
≥ 65 years	11 (17)	50 (76)	5 (8)	0.08
Gender				
Female	12 (31)	18 (46)	9 (23)	
Male	18 (17)	69 (67)	16 (16)	0.90
ECOG Performance status				
2				
3-4	15 (24)	42 (67)	6 (10)	
	15 (19)	45 (57)	19 (24)	0.43
Number of involved vertebrae				
1-2				
≥ 3	14 (21)	44 (67)	8 (12)	
	16 (21)	43 (57)	17 (22)	0.74
Ambulatory status prior to RT				
Not ambulatory	12 (22)	30 (56)	12 (22)	
Ambulatory	18 (20)	57 (65)	13 (15)	0.18
Other bone metastases				
No	16 (24)	43 (63)	9 (13)	
Yes	14 (19)	44 (59)	16 (22)	0.98
Visceral metastases				
No				
Yes	22 (32)	38 (56)	8 (12)	
	8 (11)	49 (66)	17 (23)	0.011
Interval from cancer diagnosis to MSCC				
≤ 15 months	3 (4)	45 (66)	20 (29)	
> 15 months	27 (36)	42 (57)	5 (7)	<0.001
Time developing motor deficits				
1–7 days	1 (2)	32 (64)	17 (34)	
8-14 days	4 (13)	20 (67)	6 (20)	
> 14 days	25 (40)	35 (56)	2 (3)	<0.001
Radiation schedule				
Short-course RT				
Longer-course RT	10 (20)	34 (68)	6 (12)	
	20 (22)	53 (58)	19 (21)	0.50

RT: radiotherapy

On univariate analysis of local control of MSCC, improved local control was associated with absence of visceral metastases at the time of radiotherapy ($p=0.040$). The results of the univariate analysis of local control are summarized in Table 3. The Cox Proportional Hazards Model also revealed improved local control was almost significantly associated with absence of visceral metastases (risk ratio [RR]: 2.48; 95%-CI: 0.99-6.28; $p=0.053$).

On univariate analysis, improved survival was associated with ECOG-PS 1-2 ($p<0.001$), ambulatory status prior to radiotherapy ($p<0.001$), absence of visceral metastases at the time of radiotherapy

Table 3. Univariate analysis of local control of MSCC.

	At 6 months (%)	At 12 months (%)	P
Age			
< 65 years	98	71	
≥ 65 years	85	70	0.82
Gender			
Female	100	77	
Male	89	68	0.27
ECOG Performance status			
2	90	68	
3-4	95	75	0.70
Number of involved vertebrae			
1-2	95	73	
≥ 3	89	67	0.28
Ambulatory status prior to RT			
Not ambulatory	96	65	
Ambulatory	91	72	0.93
Other bone metastases			
No	94	70	
Yes	90	70	0.46
Visceral metastases			
No	93	77	
Yes	91	57	0.040
Interval from cancer diagnosis to MSCC			
≤ 15 months	95	71	
> 15 months	91	71	0.88
Time developing motor deficits			
1–7 days	95	66	
8-14 days	93	62	
> 14 days	91	70	0.57
Radiation schedule			
Short-course RT	91	66	
Longer-course RT	93	74	0.61

RT: radiotherapy

Table 4. Univariate analysis of survival.

	At 6 months (%)	At 12 months (%)	P
Age			
< 65 years	51	37	
≥ 65 years	50	32	0.65
Gender			
Female	49	43	
Male	51	32	0.69
ECOG Performance status			
2	71	56	
3-4	34	17	<0.001
Number of involved vertebrae			
1-2	58	36	
≥ 3	45	33	0.14
Ambulatory status prior to RT			
Not ambulatory	26	16	
Ambulatory	66	47	<0.001
Other bone metastases			
No	57	37	
Yes	45	32	0.06
Visceral metastases			
No	76	55	
Yes	27	17	<0.001
Interval from cancer diagnosis to MSCC			
≤ 15 months	35	23	
> 15 months	65	45	<0.001
Time developing motor deficits			
1–7 days	24	11	
8-14 days	47	28	
> 14 days	74	57	<0.001
Radiation schedule			
Short-course RT	56	41	
Longer-course RT	48	31	0.42

RT: radiotherapy

(p<0.001), an interval from cancer diagnosis to MSCC >15 months (p<0.001), and a slower development (>14 days) of motor deficits before radiotherapy (p<0.001). On multivariate analysis, improved survival was significantly associated with ambulatory status (RR: 2.04; 95%-CI: 1.25-3.38; p=0.004), absence of visceral metastases (RR: 3.31; 95%-CI: 2.15-5.21; p<0.001), an interval from cancer diagnosis to MSCC >15 months (RR: 1.40; 95%-CI: 1.14-1.73 ; p=0.002), and time developing motor deficits >14 days (RR: 1.45; 95%-CI: 1.15-1.83; p=0.002). The ECOG-PS (RR: 1.32; 95%-CI: 0.78-2.22; p=0.31) was not significant in the

multivariate analysis.

A survival score was developed based on the four prognostic factors significantly associated with survival in the multivariate analysis. For each of the four significant prognostic factors, a separate score was calculated representing the 6-months survival rate (given in %) divided by 10. The 6-month survival rates and the separate scores for each of the four prognostic factors are summarized in Table 5. The total score included in this scoring system was the sum of the scores from all four prognostic factors. Total scores ranged between 12 and 29 points, and four groups were formed: ≤15 points (n=20, group A), 16 to 20 points (n=46, group B), 21 to 25 points (n=47, group C), and ≥26 points (n=29, group D). The 6-months survival rates of the four groups were 5%, 20%, 72% and 97%, respectively (Figure 1, p<0.0001).

Table 5. Actuarial overall survival rates 6 months after radiotherapy and the corresponding score.

	Survival at 6 months (%)	Score
Ambulatory status prior to RT		
Not ambulatory	26	3
Ambulatory	66	7
Visceral metastases		
Yes	76	8
No	27	3
Interval from cancer diagnosis to MSCC		
≤ 15 months	35	4
> 15 months	65	7
Time of developing motor deficits		
1-7 days	24	2
8-14 days	47	5
> 14 days	74	7

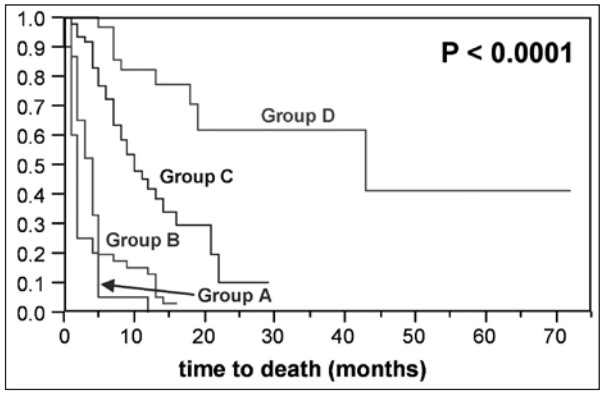

Figure 1. Survival Score: The Kaplan-Meier curves of the four groups with respect to survival (A: ≤15 points, B: 16-20 points, C: 21-25 points, D: ≥26 points).

DISCUSSION

The incidence of cancer patients developing metastatic disease such as MSCC is constantly increasing. The life expectancy of patients with MSCC varies between a few months and several years.[2] In order to better tailor the treatment regimen to the individual patient, identification of prognostic factors predicting treatment outcomes is important and likely to have a relevant impact on the treatment selection.

One important question is whether a patient might benefit from upfront decompressive surgery in addition to radiotherapy? A randomized trial of 101 patients revealed a benefit for decompressive surgery followed by radiotherapy when compared to radiotherapy alone in terms of improved functional outcome and survival.[3] Patients included in that trial were highly selected with a good performance status, a relatively favorable survival prognosis, involvement of only one spinal segment, and paraplegia for less than 48 hours. In contrast, a retrospective matched-pair study of 324 less highly selected patients did not find such a benefit.[6] However, another retrospective matched-pair (1:2) study of 201 patients with MSCC from an unfavorable tumor including 27 patients with renal cell carcinoma suggested that these patients may benefit from additional "state-of-the-art surgery" prior to radiotherapy in terms of improved motor function.[7] "State-of-the-art surgery" was defined as direct decompressive surgery plus stabilization.

Summarizing the available data, it appears difficult to give general recommendations either for or against upfront surgery. Thus, it is important to understand the independent prognostic factors for functional outcome. Because every primary tumor type has its own biological behavior, it appears reasonable trying to identify prognostic factors separately for each tumor type. The present study aimed to identify independent prognostic factors for patients with MSCC from renal cell carcinoma. Motor function following radiotherapy was positively associated with absence of visceral metastases, a longer interval from first diagnosis of renal cell carcinoma

to the radiotherapy of MSCC, and a slow (>14 days) development of motor deficits prior to radiotherapy. Patients who have all three positive prognostic factors may be considered candidates for radiotherapy alone, because 65% of these patients showed improvement of motor function in the present study. With radiotherapy alone, surgery related complications such as wound infections, extensive bleeding, postoperative pneumonia, and pulmonary embolism can be avoided. The frequency of such complications is 11-13%.[3,6,7] Those patients with less than three positive factors may be candidates for additional decompressive surgery.

Local control is another important endpoint in the treatment of MSCC. The risk of developing a recurrence of MSCC within the treated area of the spine increases with the length of survival. Therefore, it is important to be able to predict the individual patient's survival prognosis. This can be achieved with the help of significant prognostic factors. In this study, visceral metastases, ambulatory status, a longer interval from diagnosis of renal cell carcinoma to radiotherapy of MSCC, and the time developing motor deficits prior to radiotherapy were identified as independent prognostic factors for survival. Based on these four prognostic factors, a survival score was developed including four prognostic groups. Group A patients may be considered candidates for short-course radiotherapy or best supportive care, because their 6-months survival rate was only 5%. Group B patients (6-months survival rate of 20%) may be candidates for short-course radiotherapy such as 5x4 Gy in one week or 1x8 Gy in one day taking into account the short estimated life time. Patients of groups C and D (6-months survival rates of 72% and 97%, respectively) may be candidates for longer-course radiotherapy with 10x3 Gy in two weeks or 20x2 Gy in four weeks, since the risk of a local recurrence of MSCC increases with survival time. According to a recent prospective study, longer-course radiotherapy resulted in better local control of MSCC than short-course programs.[8]

CONCLUSIONS

This study identified several independent prognostic factors for post-treatment motor function and survival in patients irradiated for MSCC from renal cell carcinoma. Improved functional outcome was significantly associated with absence of visceral metastases, a longer interval from cancer diagnosis to MSCC, and a slower development of motor deficits prior to radiotherapy. Improved survival was significantly associated with ambulatory status prior to radiotherapy, absence of visceral metastases, a longer interval from cancer diagnosis to MSCC, and a slower development of motor deficits. These prognostic factors and the survival score can help tailor treatment to the individual patient.

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