Estimating the Survival of Elderly Patients with Renal Cell Carcinoma Presenting with Malignant Spinal Cord Compression

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Abstract. *Aim: To develop a tool for predicting survival of elderly patients with malignant spinal cord compression (MSCC) from renal cell carcinoma. Patients and Methods: In 71 elderly patients, 10 factors were analyzed. Predictive scores were generated based on 6-month survival rates. Results: Longer interval from renal cell carcinoma diagnosis to MSCC (p=0.019), lack of visceral metastases (p<0.001), slower progression of motor deficits (p<0.001), ambulation (p<0.001) and better performance status (p=0.002) were positive predictors. On multivariate analysis, interval from renal cell carcinoma diagnosis to MSCC (p=0.022), visceral metastases (p<0.001), time to developing motor dysfunction (p=0.041), gait function (p=0.002) and performance status (p=0.017) remained significant. Predictive scores were 17 to 36 points. Four groups were created: 17-23, 24-26, 27-29 and 30-36 points. Six-month survival rates were 8%, 30%, 69% and 100%, respectively (p<0.001). Conclusion: This tool improves estimation of survival and personalized treatment options in elderly patients with MSCC from renal cell carcinoma.*

Malignant spinal cord compression (MSCC) is an oncological emergency that occurs in up to 10% of adult patients with cancer (1, 2). Renal cell carcinoma is one of the more common cancer types associated with MSCC and accounts for about 10% of these patients. Radiotherapy is the most common treatment modality for MSCC, either alone or proceeded by spinal surgery. The combined approach of surgery plus radiotherapy is generally limited to patients with a good performance status, a relatively favorable survival prognosis and involvement of the spinal cord by MSCC limited to one consecutive segment (3). Therefore, most patients with MSCC receive radiotherapy alone, even for a less radiosensitive tumor such as renal cell carcinoma.

If radiotherapy alone is selected as the treatment of choice, a variety of radiotherapy schedules are utilized, including single-fraction schedules, multi-fraction short-course schedules lasting one week, and long-course schedules lasting from 2 to 4 weeks (2, 4). In order to select the optimal schedule in the context of personalized cancer treatment, it is of fundamental importance to determine a patient's remaining lifetime as precisely as possible. In patients with a very poor prognosis, one should avoid long-lasting schedules, whereas patients with a better prognosis can benefit from long-course schedules in terms of better local control of MSCC and survival (4-7). The forecast of an individual patient's survival time can be facilitated by predictive tools. Ideally, separate tools should be available for the most common cancer types associated with MSCC, such as renal cell carcinoma, because cancer types have different patterns of metastatic spread and tumor biologies (1, 2).

The proportion of elderly patients with cancer is growing worldwide and requires particular consideration regarding personalized treatment approaches (8, 9). Elderly patients with cancer should be regarded as a separate group because many of these patients are not as robust as younger patients when receiving anticancer treatment. The life expectancy of elderly people is increasing because of improved treatment of diseases other than cancer. Because the risk of

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developing distant metastases increases with the duration of life, more elderly patients will likely present with metastatic problems such as MSCC in the future. All these points support the need for a tool particularly designed to predict the survival time of elderly patients with MSCC from renal cell carcinoma. This was the rationale for conducting the present study.

Patients and Methods

Seventy-one elderly patients, who were not candidates for spinal surgery and received radiotherapy alone for MSCC from renal cell carcinoma, were included in the study. Elderly patients were defined as 65 years or older (10, 11). Radiotherapy was performed with modern linear accelerators using 6- to 18-MeV photon beams. It was delivered to the vertebrae involved by MSCC plus additional one vertebra above and below. The following potential prognostic factors were retrospectively analyzed for association with survival: Age (≤74 *vs.* ≥75 years, median: 74 years), interval from diagnosis of renal cell carcinoma to MSCC (≤15 *vs.* >15 months), visceral metastases at the time of radiotherapy (no *vs.* yes), additional bone metastases at the time of radiotherapy (no *vs.* yes), gender, time developing motor deficits before radiotherapy was started (1-7 *vs.* 8-14 *vs.* <14 days), gait function at the time of radiotherapy (ambulatory *vs.* not ambulatory), number of vertebrae affected by MSCC (1-3 *vs.* ≥3), Eastern Cooperative Oncology Group (ECOG) performance score (1,2 *vs.* 3,4), and the radiotherapy schedule (short-course radiotherapy with 1×8 Gy in one day or 5×4 Gy in 1 week *vs.* long-course radiotherapy with 10×3 Gy, 15×2.5 Gy or 20×2 Gy in 2 to 4 weeks). Comorbidity was not separately considered as a potential prognostic factor since its addition would have introduced confounding variables (12, 13).

Initially, all factors were evaluated for survival in a univariate analysis (Kaplan–Meier analysis) (14). The Kaplan–Meier curves were compared with the log-rank test. Factors achieving significance ($p<0.05$) were additionally evaluated with the Cox regression model (multivariate analysis). Those factors that had a significant impact on survival in both the univariate and the multivariate analyses were included in the tool designed for estimating survival. The scoring for each of the significant factors (factor scores) was generated by dividing the 6-month survival rate by 10. The total predictive score for each individual patient was generated by summing the scores for individual factor.

Results

The univariate analysis revealed significant positive associations between survival and a longer interval from diagnosis of renal cell carcinoma to MSCC of >15 months ($p=0.019$), lack of visceral metastases at the time of radiotherapy ($p<0.001$), slower development of motor deficits before radiotherapy was initiated ($p<0.001$), being ambulatory at the time of radiotherapy ($p<0.001$), and a better ECOG performance score ($p=0.002$). The data of the entire univariate analyses are shown in Table I. In the additional multivariate analysis, the interval from diagnosis of renal cell carcinoma to MSCC ($p=0.022$), visceral metastases at the time of radiotherapy ($p<0.001$), the time to developing motor deficits before radiotherapy ($p=0.041$), gait function at the time of radiotherapy ($p=0.002$) and the ECOG performance score ($p=0.017$) remained significant (see Table II). These five independent prognostic factors of survival were included in the predictive tool (Table III).

The total predictive scores for each individual patient ranged between 17 and 36 points (Figure 1). Based on the survival rates at 6 months by total predictive scores, the following four survival groups were created: 17-23, 24-26, 27-29 and 30-36 points. The survival rates at 6 months of the four groups were 8%, 30%, 69% and 100%, respectively ($p<0.001$) and the survival rates at 1 year were 0%, 15%, 35% and 75%, respectively ($p<0.001$).

Table I. *Influence of the potential prognostic factors on survival (Kaplan–Meier analysis, log-rank test).*

Factor	At 6 months	At 1 year	*p*-Value
Age			
≤74 Years (N=37)	62	39	
≥75 Years (N=34)	38	22	0.16
Interval from diagnosis of RCC to MSCC			
≤15 Months (N=31)	39	17	
>15 Months (N=40)	60	40	0.019
Visceral metastases at radiotherapy			
No (N=28)	89	60	
Yes (N=43)	26	13	<0.001
Additional bone metastases at radiotherapy			
No (N=28)	61	31	
Yes (N=43)	44	30	0.17
Gender			
Female (N=16)	38	38	
Male (N=55)	55	30	0.84
Time to developing motor deficits before radiotherapy			
1-7 days (N=24)	25	6	
8-14 days (N=19)	53	34	
>14 days (N=28)	71	51	<0.001
Gait function at radiotherapy			
Ambulatory (N=43)	67	45	
Not ambulatory (N=28)	25	11	0.001
Number of vertebrae affected by MSCC			
1, 2 (N=31)	58	32	
≥3 (N=40)	51	31	0.19
ECOG performance score			
1, 2 (N=27)	70	60	
3, 4 (N=44)	39	14	0.002
Radiotherapy schedule			
Short-course (N=30)	50	43	
Long-course (N=41)	51	22	0.38

RCC: Renal cell carcinoma, MSCC: malignant spinal cord compression, ECOG: Eastern Cooperative Oncology Group.

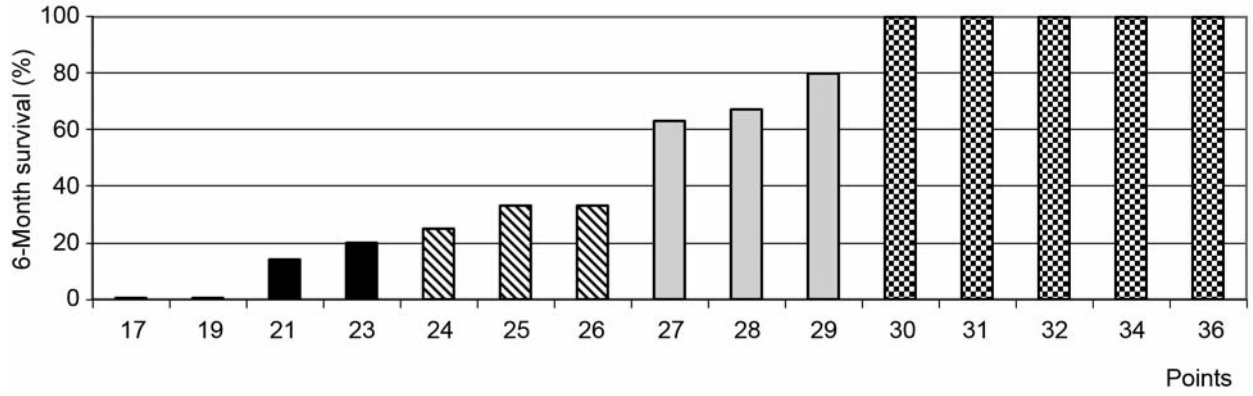

Figure 1. *Six-month survival rate by total predictive score.*

Table II. *Multivariate analysis (Cox regression model) of factors associated with survival in the univariate analysis.*

Factor	Risk ratio	95% Confidence interval	*p*-Value
Interval from diagnosis of RCC to MSCC			
≤15 Months *vs*. >15 months	1.43	1.05-1.95	0.022
Visceral metastases at radiotherapy			
No *vs*. Yes	5.02	2.50-11.00	<0.001
Time to developing motor deficits before radiotherapy			
>14 Days *vs*. 8-14 days *vs*. 1-7 days	1.42	1.01-2.02	0.041
Gait function at radiotherapy			
Ambulatory *vs*. not ambulatory	2.54	1.41-4.61	0.002
ECOG performance score			
1, 2 *vs*. 3, 4	2.10	1.14-4.10	0.017

RCC: Renal cell carcinoma, MSCC: malignant spinal cord compression, ECOG: Eastern Cooperative Oncology Group.

Discussion

Many patients with metastatic renal cell carcinoma have a poor survival prognosis (1, 2). A great amount of clinical research has been carried out to improve the outcome of these patients. Novel systemic treatments such as targeted therapies have been investigated and subsequently introduced into clinical routine (15-18). In patients with oligometastatic disease or symptomatic metastases, novel targeted therapies may be supplemented by local treatments (19).

In addition to new approaches of local and systemic treatment for metastatic renal cell carcinoma, patient outcomes can be improved with personalized approaches tailored to the individual patient's situation. For optimization of such personalized approaches in patients with metastatic renal cell carcinoma, one should take into account the patient's survival prognosis. To achieve this goal, prognostic factors and predictive tools allowing for precise estimation of individual survival times are of great help.

Due to demographic changes, the number of elderly patients with cancer is growing and increasingly gaining attention as a clinically distinctive group. When compared to younger patients, elderly patients generally have a worse performance status, more concomitant diseases, and a less competent immune system. Therefore, prognostic factors need to be identified and predictive tools created separately for this particular group. This applies particularly to the metastatic situation, such as MSCC. Therefore, this study was initiated aiming to create a predictive tool for survival particularly for elderly patients with MSCC from renal cell carcinoma. When interpreting its results, the retrospective design should be kept in mind.

In the present study, five independent prognostic factors were identified, namely the interval from renal cell carcinoma diagnosis to MSCC, visceral metastases at the time of radiotherapy, time to developing motor deficits prior to initiation of radiotherapy, pre-radiotherapy gait function and the performance score. In a previous score for elderly

Table III. *Survival rates by independent prognostic factors at 6 months and scoring points.*

Factor	Survival rate at 6 months (%)	Points
Interval from diagnosis of RCC to MSCC		
≤15 Months	39	4
>15 Months	60	6
Visceral metastases at radiotherapy		
No	89	9
Yes	26	3
Time to developing motor deficits before radiotherapy		
1-7 Days	25	3
8-14 Days	53	5
>14 Days	71	7
Gait function at radiotherapy		
Ambulatory	67	7
Not ambulatory	25	3
ECOG performance score		
1, 2	70	7
3, 4	39	4

RCC: Renal cell carcinoma, MSCC: malignant spinal cord compression, ECOG: Eastern Cooperative Oncology Group.

patients with MSCC from different tumor types, age, performance score, primary tumor type, pre-radiotherapy gait function, additional bone metastases, visceral metastases, interval from cancer diagnosis to MSCC, and time to developing motor deficits before the start of radiotherapy were significantly associated with survival (20). The differences with respect to significant and independent factors between the previous study of many different tumor types and the current study focusing on renal cell carcinoma supports the idea of developing separate tools for the more common types of cancer.

In the current study, four survival groups were designed based on the 6-month survival rates using the total predictive scores for individual patients: 17-23, 24-26, 27-29 and 30-36 points. Of those patients with 17-23 points, only 8% survived for 6 months, and no patient was alive at 1 year following radiotherapy for MSCC. To keep the overall treatment time as short as possible in light of the extraordinarily short survival time, these patients should receive single-fraction radiotherapy such as 1×8 Gy or 1×10 Gy. Previous studies have shown that single-fraction radiotherapy is as effective as fractionated schedules with respect to pain relief and improvement of motor function in patients with poor prognosis (4, 6, 21). Out of the patients achieving 24-26 points, 30% survived 6 months and 15% 1 year following radiotherapy of MSCC. These patients may be treated with short-course multi-fraction radiotherapy such as 5×4 Gy or 6×4 Gy in about 1 week or single-fraction radiotherapy, since according to a recent matched-pair analysis including many different types of cancer, both schedules are similarly effective with respect to functional outcome, survival and local control (22). However, since renal cell carcinoma is less radiosensitive than many other solid tumor types, the total dose of single-fraction radiotherapy may not be sufficient. Therefore, patients of the present study with 24-26 points would appear to be better-treated with 5×4 Gy or 6×4 Gy. Patients achieving 27-29 points have an intermediate survival prognosis (69% at 6 months, 35% at 1 year) and can, therefore, be considered candidates for 10×3 Gy in 2 weeks, the most common radiotherapy schedule used worldwide for MSCC. The schedule 10×3 Gy results in better local control of MSCC than single-fraction and short-course multi-fraction radiotherapy schedules. Since the risk of developing a local recurrence increases with life time, single-fraction and short-course multi-fraction radiotherapy schedules cannot be recommended for patients with 27-29 points. Patients with 30-36 points were found to have a relatively favorable survival prognosis (100% at 6 months, 75% at 1 year). Since a previous study showed that patients with such favorable prognosis benefit from long-course radiotherapy schedules, with total doses greater than 30 Gy (*e.g.* 15×2.5 Gy in 3 weeks or 20×2 Gy in 4 weeks), patients of this group should be treated with such a schedule (7). Selected patients of the latter group may also be considered for stereotactic body radiation therapy, preferably within a clinical trial (21). Since renal cell carcinoma is a less radiosensitive tumor, properly selected favorable patients should be presented to a neurosurgeon or orthopedic surgeon before the start of radiotherapy to timely identify candidates for decompressive surgery (3).

In conclusion, the present study identified five independent predictors of survival for elderly patients with MSCC from renal cell carcinoma that formed the basis of a predictive tool specifically for these patients. This new tool contributes to optimization of personalized treatment in this particular group.

Conflicts of Interest

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

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