Forecasting Survival Probabilities After Radiotherapy of Metastatic Epidural Spinal Cord Compression from Colorectal Cancer in the Elderly

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Abstract. *Aim: To develop a tool forecasting survival of elderly patients with metastatic epidural spinal cord compression (MESCC) from colorectal cancer (CRC). Patients and Methods: Fifty-seven patients were retrospectively evaluated. Eleven characteristics were investigated for survival. Independent characteristics were used for the tool. Scores were obtained from dividing 6-month survival rates by 10. From summing these points, patient scores were obtained. Results: On survival analysis (Cox regression model), organ metastases (p=0.006), performance status (p<0.001), pre-radiotherapy walking ability (p<0.001) and the dynamic of developing motor weakness (p=0.033) were significant factors affecting survival and were incorporated into the tool. Possible patient scores were 5, 9, 10, 13, 14, 16, 20 or 24 points. Three groups were created with scores of 5-10, 13-16 and 20-24 points, with 6-month survival rates of 4%, 23% and 79%, respectively (p<0.001). Conclusion: By applying this tool, it is possible to forecast the survival of elderly patients experiencing MESCC from CRC, which is important for optimal treatment personalization.*

Due to improved treatment of primary tumors and lymph node metastases, the number of patients with cancer presenting with organ metastasis is growing. This also applies to patients with malignant epidural spinal cord compression (MESCC). Today, 5% to 10% of adult patients with cancer experience MESCC (1, 2). Patients with colorectal cancer (CRC) represent more than 5% of all patients presenting with MESCC. MESCC from CRC has a worse prognosis than MESCC from several other solid tumor types such as breast and prostate cancer, and spinal cord compression from hematological malignancies such as lymphomas and myelomas (3-5). Therefore, patients with MESCC from CRC deserve particular attention. The outcomes of these patients may be improved with the administration of personalized programs. Personalization of treatment optimally includes the patient's wishes, needs, living conditions and their survival prognosis. If a palliative treatment is indicated, less-standardized approaches are available when compared to a curative situation. For palliative situations, such as in cases with brain metastases, bone metastases and MESCC, several prognostic tools are available for forecasting a patient's survival prognosis in order to achieve optimal treatment personalization (6-9). It is widely agreed that separate tools should be available for different tumor entities because tumor entities vary considerably regarding patterns and dynamic of metastatic spread and disease progression. Therefore, separate tools have been presented for MESCC from particular tumor entities, including CRC.

However, in order to further optimize the individualization of MESCC treatment, additional tools should be available for the growing group of elderly patients with CRC. Many elderly patients are less robust and impaired by a greater number and more severe concomitant diseases compared to young and middle-aged patients with cancer. The present study was initiated to take into account these demands and to develop a tool that allows forecasting of the survival of elderly patients with MESCC from CRC.

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Table I. *Univariate analysis: Associations between investigated characteristics and survival.*

Characteristic	At 3 months (%)	At 6 months (%)	At 12 months (%)	*p*-Value
Age				
≤72 years (n=29)	52	28	21	
≥73 years (n=28)	75	39	28	0.14
Gender				
Female (n=24)	58	21	14	
Male (n=33)	67	42	32	0.25
Cancer type				
Colon cancer (n=30)	63	40	27	
Rectal cancer (n=27)	63	26	26	0.42
Interval from diagnosis of CRC to MESCC				
≤15 months (n=22)	68	32	16	
>15 months (n=35)	60	34	29	0.62
Organ metastases at start of RT				
No (n=17)	82	59	29	
Yes (n=40)	55	23	19	0.005
Additional bone metastases at start of RT				
No (n=30)	70	37	18	
Yes (n=27)	56	30	25	0.29
Number of vertebrae affected by MESCC				
1-2 (n=28)	75	39	31	
>2 (n=29)	52	28	19	0.046
ECOG PS				
1, 2 (n=21)	95	71	56	
3, 4 (n=36)	44	11	6	<0.001
Pre-RT walking ability				
No (n=27)	44	7	7	
Yes (n=30)	80	57	40	<0.001
Dynamic of developing motor weakness				
Faster: 1-7 days (n=22)	45	14	14	
Slower: >7 days (n=35)	74	46	32	0.030
Fractionation of RT				
1×8 Gy/5×4 Gy (n=16)	56	44	35	
10×3 Gy (n=20)	78	33	25	
15×2.5 Gy/20×2 Gy (n=23)	57	26	17	0.78

CRC: Colorectal cancer; MESCC: metastatic epidural spinal cord compression; ECOG PS: Eastern Cooperative Oncology Group performance status.

Patients and Methods

Fifty-seven elderly patients receiving radiotherapy (RT) alone for MSCC from CRC were included and retrospectively evaluated. 'Elderly' was defined in accordance with the homepage of the World Health Organisation as ≥65 years (10). Potential associations between survival and 11 characteristics were investigated: age (≤72 *vs.* ≥73 years, median 72 years), gender, cancer type (colon cancer *vs.* rectal cancer), interval from initial diagnosis of CRC to MSCC (≤15 *vs.* >15 months), organ metastases at start of RT (no *vs.* yes), additional bone metastases at start of RT (no *vs.* yes), number of vertebrae affected by MSCC (1 or 2 *vs.* >2), Eastern Cooperative Oncology Group performance status (1, 2 *vs.* 3, 4), pre-RT walking ability (no *vs.* yes), dynamic of developing motor weakness of the legs (faster: 1-7 days *vs.* slower: >7 days), and fractionation of RT (1×8 Gy/5×4 Gy *vs.* 10×3 Gy *vs.* 15×2.5 Gy/20×2 Gy). The Charlson Comorbidity Index was not included as a potential prognostic factor to avoid confounding variables and redundancy because metastatic cancer, the major criterion for inclusion in this study, receives the highest score in the Charlson index (11).

For univariate analyses, the Kaplan–Meier method (12) was applied and supplemented by the log-rank test. Significant characteristics ($p<0.05$) were subsequently analyzed using a Cox regression model to assure independent association with survival. All independent characteristics were used for the tool that allows forecasting the survival of elderly patients with MSCC from CRC. Scores for the independent characteristics were obtained by dividing the survival rates at 6 months by 10. After summation of the points for each independent characteristic, the scores for individual patients were obtained.

Results

Five characteristics had a significant impact on survival in the univariate analysis: organ metastases at RT ($p=0.005$), number of vertebrae affected by RT ($p=0.046$), performance status

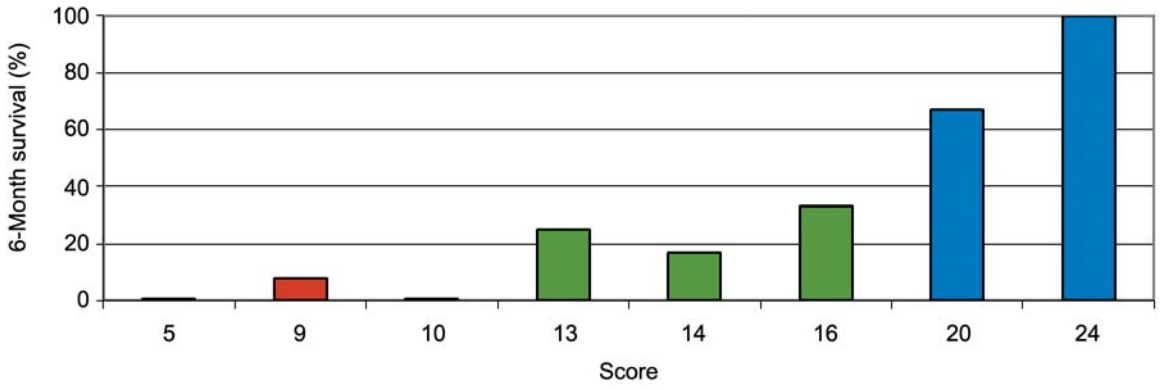

Figure 1. *Scores for individual patients and the survival rates at 6 months following radiotherapy (RT).*

(p<0.001), pre-RT walking ability (p<0.001), and the dynamic of developing motor weakness (p=0.030). Findings of the entire analysis are presented in Table I. In the analysis with the Cox regression model, organ metastases [risk ratio (RR)=2.64, 95% confidence interval (CI)=1.30-5.93; p=0.006], performance status (RR=4.67, 95% CI=2.25-10.69; p<0.001), pre-RT walking ability (RR=3-04, 95% CI=1.61-5.88; p<0.001), and the dynamic of developing motor weakness (RR=1.44, 95% CI=1.03-2.00; p=0.033) were again significant in contrast to the number of affected vertebrae (RR=1.26, 95% CI=0.93-1.72; p=0.13). The four characteristics achieving significance in both the univariate and the Cox regression analyses were incorporated into the instrument developed for forecasting survival. The scoring points assigned to these characteristics are shown in Table II. Possible individual patient scores were 5, 9, 10, 13, 14, 16, 20 or 24 points. Corresponding survival rates at 6 months are given in Figure 1. Three survival groups were created based on these survival rates, 5-10 points, 13-16 points and 20-24 points, with 6-month survival rates of 4%, 23% and 79%, respectively (p<0.001, Figure 2).

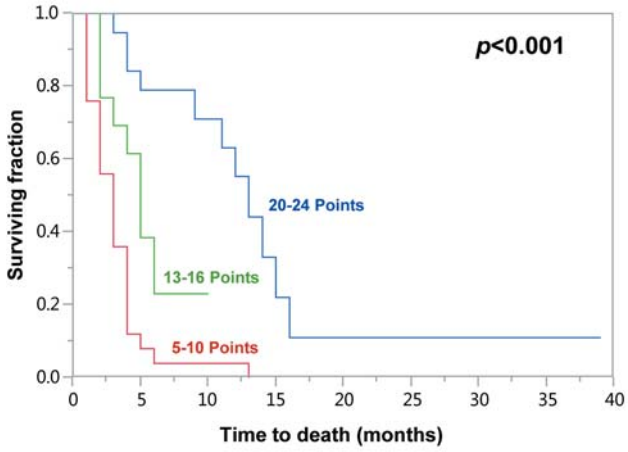

Figure 2. *Kaplan–Meier curves of the three survival groups with 5-10 points, 13-16 points and 20-24 points.*

Discussion

To provide the best possible individual treatment for patients with CRC, prognostic factors allowing forecasting of a patient's survival time are important (13-16). Patients with CRC developing MESCC have a very poor prognosis, and the treatment results of these patients need to be considerably improved. Systemic agents are not effective for the treatment of MESCC in patients with solid tumors such as CRC. Local treatments, most of all RT, are much more important in these situations. When RT is administered, the question arises: What is the most appropriate fractionation regimen of RT? The selection of the most appropriate fractionation regimen is primarily influenced by the patient's expected survival. Patients with a short remaining survival time should receive a RT regimen that is as short as possible to avoid these patients

Table II. *Six-month survival rates of the four independent characteristics and related scores.*

	6-Month survival rate (%)	Score
Organ metastases at RT		
No (n=17)	59	6
Yes (n=40)	23	2
ECOG PS		
1, 2 (n=21)	71	7
3, 4 (n=36)	11	1
Pre-RT walking ability		
No (n=27)	7	1
Yes (n=30)	57	6
Dynamic of developing motor weakness		
Faster: 1-7 days (n=22)	14	1
Slower: >7 days (n=35)	46	5

RT: Radiotherapy; ECOG PS: Eastern Cooperative Oncology Group performance status.

spending too much of their remaining time undergoing treatment. The use of a short RT regimen (1×8 Gy or 5×4 Gy) is justified because several studies have shown that such a regimen has a similar impact on pain relief and improvement of motor weakness as RT regimens to longer overall treatment times (17, 18). In contrast, patients with a longer expected survival time are more optimally treated with a RT regimen including a longer overall treatment time and a higher total dose (10×3 Gy, 15×2.5 Gy or 20×2 Gy). These regimens lead to significantly better local control of MESCC than 1×8 Gy or 5×4 Gy (19). Because the risk of a local recurrence of MESCC increases with the duration of the patient's lifespan, an RT regimen with a longer overall treatment time and a higher dose would be the regimen of choice for this subgroup. In a study of patients with a very favorable survival prognosis, 15×2.5 Gy and 20×2 Gy resulted in significantly better local control of MESCC than 10×3 Gy and should, therefore, be used for long-term survivors (20).

The treatment of patients with MESCC needs individual consideration based on a patient's survival prognosis, which is also important for elderly patients with MESCC from CRC. Therefore, a tool was created in this study that enables the treating physicians to forecast the prognosis of an individual patient. According to the results of this study, three groups were identified with 6-month survival rates of 4% (patients with 5-10 points), 23% (patients with 13-16 points) and 79% (patients with 20-24 points), respectively. Because of their very short survival time, patients with 5-10 points should receive RT with 1×8 Gy or 5×4 Gy. Those patients who achieved 13-16 points (the intermediate group) should be considered for 10×3 Gy, since the survival rate of these patients at 10 months was 23%. Twelve-month data were not available. Of the patients with 20-24 points, 55% survived for 12 months or longer. Therefore, these patients could benefit from a fractionation regimen with a dose >30 Gy such as 15×2.5 Gy and 20×2 Gy in terms of better local control rates of MESCC. For selected patients of this group, stereotactic body RT may also be an option, preferably in a clinical trial (21).

In addition, since a previous matched-pair study that compared RT alone to surgery plus RT in patients with MESCC from unfavorable tumors suggested that decompressive surgery plus stabilization had a better effect on improvement of motor weakness than RT alone (28% *vs.* 19%, p=0.024), surgery should be considered for those patients with 13-16 points and 20-24 points (22). However, particularly in elderly patients, the potential benefits and risks of spinal surgery must be carefully weighed.

In conclusion, the new tool designed in this study for elderly patients with MESCC from CRC is effective in forecasting the survival of these patients. Furthermore, it is an important tool for helping avoid under-treatment of long-term survivors and overtreatment of patients with extremely short survival times.

Conflicts of interest

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

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