

A Tool to Estimate Survival of Elderly Patients Presenting with Metastatic Epidural Spinal Cord Compression (MESCC) from Cancer of Unknown Primary

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Abstract. *Aim: Cancers of unknown primary (CUP) account for about 10% in elderly patients with MESCC. Immediate treatment is indicated. Personalizing treatment for MESCC requires for clear understanding of the patients' survival prognosis. In this case, a tool for estimating survival would be valuable. Patients and Methods: In 104 elderly CUP patients, nine factors were investigated: age, gender, performance score, number of affected vertebrae, ability to walk at presentation for radiotherapy, additional bone metastases, visceral metastases, time developing motor weakness, radiotherapy program. Results: In multivariate analysis, the ability to walk ($p=0.011$) and visceral metastases ($p<0.001$) were associated with survival. The following scores were assigned: unable to walk=0, able to walk=1, visceral metastases=0, no visceral metastases=1. Three groups were formed (0, 1 and 2 points) with 6-month survival rates of 7%, 18% and 73% ($p<0.001$). Conclusion: This specific tool assists the physician to estimate survival and select for the most suitable radiotherapy program in elderly CUP patients with MESCC.*

Metastatic epidural spinal cord compression (MESCC) is in an oncologic emergency generally requiring for immediate treatment that most often includes radiotherapy alone (1). Elderly cancer patients are often considered separately, since they suffer more complications from therapy (2-6). Personalized anticancer treatment has recently gained

importance and elderly patients are also likely to benefit from individualized care. It is crucial to possess a predictive tool that can accurately estimate patient's survival time to optimize personalized treatment.

Patients with cancer of unknown primary (CUP) account for about 10% of the elderly presenting with MESCC (1). These patients have a less favorable prognosis than patients with MESCC from other cancer types such as breast and prostate cancer and must, therefore, be considered as a distinct group. Since CUP has a different clinical behavior than other tumors, it is helpful to create a tool predicting survival specially designed for this group of patients (elderly patients with MESCC from CUP). Therefore, the present study was designed to provide such a tool in order to facilitate personalized treatment for this specific group of cancer patients.

Patients and Methods

In this retrospective analysis, 104 elderly patients (65 years or older) who received radiotherapy alone for MESCC from CUP were analyzed with respect to survival following radiation treatment. The radiotherapy program (short-course: 1×8 Gy or 5×4 Gy vs. long-course: 10×3 Gy, $14-15\times 2.5$ Gy or 20×2 Gy) and eight additional factors were evaluated including age (≤ 72 vs. ≥ 73 years, median age=72.5 years), gender, Eastern Cooperative Oncology Group (ECOG) performance score (2 vs. 3-4), number of affected vertebrae (1-2 vs. 3-4 vs. ≥ 5), ability to walk at presentation for radiotherapy (unable to walk vs. able to walk), additional bone metastases at presentation (no vs. yes), visceral metastases at presentation (no vs. yes) and time developing motor weakness at presentation for radiotherapy (1-7 vs. >7 days).

Those factors achieving significance ($p<0.05$) or showing a trend ($p\leq 0.1$) for associations with survival in the univariate analyses (Kaplan-Meier analysis, log-rank test) were subsequently included evaluated in an additional multivariate analysis (Cox proportional hazards model). Factors significant in both univariate and multivariate analyses were included in the survival tool.

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Table I. Univariate survival analysis; *p*-values were obtained from log-rank test.

	At 3 months (%)	At 6 months (%)	<i>p</i> -Value
Age			
≤72 years (n=52)	48	23	
≥73 years (n=52)	42	23	0.89
Gender			
Females (n=37)	43	24	
Males (n=67)	46	22	0.78
ECOG performance score			
2 (n=21)	71	43	
3-4 (n=83)	39	18	0.003
Number of affected vertebrae			
1-2 (n=27)	67	33	
≥3 (n=77)	38	19	0.10
Ability to walk			
Unable to walk (n=59)	37	14	
Able to walk (n=45)	56	36	0.003
Additional bone metastases			
No (n=32)	63	38	
Yes (n=72)	38	17	0.016
Visceral metastases			
No (n=46)	54	37	
Yes (n=58)	38	12	<0.001
Time developing motor weakness			
1-7 days (n=56)	30	14	
>7 days (n=48)	63	33	<0.001
Radiotherapy program			
Short-course radiotherapy (n=62)	44	19	
Long-course radiotherapy (n=42)	48	29	0.17

ECOG, Eastern Cooperative Oncology Group. Bold *p*-values are significant.

Results

On univariate analysis, better survival was associated with absence of visceral metastases ($p < 0.001$), absence of additional bone metastases ($p = 0.016$), time developing motor weakness of >7 days ($p < 0.001$), ability to walk ($p = 0.003$) and an ECOG performance score of 2 ($p = 0.003$). In addition, affection by only 1-2 vertebrae showed a trend ($p = 0.10$). The complete results of the univariate analysis are given in Table I. In the subsequent multivariate analysis, visceral metastases ($p < 0.001$) and ability to walk ($p = 0.011$) were the only factors that maintained significance. The complete results of the multivariate analysis are given in Table II.

Both visceral metastases and ability to walk were included in the survival score. The following scores were assigned: unable to walk=0, able to walk=1, visceral metastases=0 and no visceral metastases=1. Considering these scores, three survival groups were formed: 0, 1 and 2 points. The corresponding 3-month survival rates of these groups were

Table II. Multivariate survival analysis; *p*-values were obtained from Cox proportional hazards model.

	Risk ratio	95%CI	<i>p</i> -Value
ECOG performance score	1.29	0.62-2.80	0.50
Number of affected vertebrae	1.26	0.87-1.88	0.22
Ability to walk	2.03	1.17-3.61	0.011
Additional bone metastases	1.07	0.49-2.30	0.87
Visceral metastases	2.57	1.60-4.18	<0.001
Time developing motor weakness	1.18	0.92-1.52	0.20

Bold *p*-values are significant.

32%, 43% and 80%, respectively, and the 6-month survival rates were 7%, 20% and 73%, respectively ($p < 0.001$).

Discussion

Most patients with metastatic CUP still have a poor survival prognosis despite considerable scientific research on the field (7-10). Bone metastases are quite common in patients with CUP and may lead to MESCC. MESCC is a serious complication generally associated with severe bone pain and neurologic deficits such as motor weakness (1). If motor dysfunction develops, the situation must be considered an emergency. Urgent treatment, usually radiotherapy alone, is necessary. In order to provide the most suitable radiation program, each patient's individual situation including expected survival time must be considered. Since a quick treatment decision is required putting the physicians under certain pressure, a predictive tool would be helpful in this situation. One important tool would be an instrument that allows the estimation of a patient's survival prognosis. Several of such instruments are already available (11-13). It has been well-recognized that separate tools are required for the different tumor entities that vary considerably regarding biology, prognoses and predominant metastatic sites. Furthermore, elderly cancer patients require particular attention. Therefore, it is reasonable to enable the treating physicians to access particular survival scores for different tumor types as well as for elderly patients. The present analysis was performed to account for this individualized approach. A new tool was developed in particular for elderly patients with MESCC from CUP. In the multivariate analysis of this study, two factors, visceral metastases and ability to walk at presentation for radiotherapy, were significantly associated with survival and, therefore, included in the tool. Both factors had also been significant for survival in a previous study of 182 patients of any age who had MESCC from CUP (14). In that study, the performance status and the time developing motor weakness before radiotherapy were

additionally significant in the multivariate analysis, which supports the concept that elderly patients are a separate group of cancer patients.

The tool developed in the current study allows the differentiation of three prognostic groups with different survival rates. Out of patients who had 0 points, only 7% survived 6 months or longer. To keep the overall treatment time as short as possible, these patients should receive a single fraction of 8 Gy. According to a previous study with 1,304 patients irradiated for MESCC, 1x8 Gy was similarly effective with respect to motor weakness and ambulatory function as multi-fraction radiotherapy programs (15). The patients with a score of 1 point in this tool had a moderately better survival prognosis with a 6-month survival rate of 18%, respectively. These patients appear to be good candidates for short-course multi-fraction radiotherapy such as 5x4Gy in 1 week (15).

The patients with a score of 2 points had more favorable prognoses. In this group, 73% of patients survived 6 months or longer. These patients benefited from long-course radiotherapy programs such as 10x3 Gy over 2 weeks. Previous studies have shown that long-course radiotherapy programs lead to better local control of MESCC when compared to single-fraction or short-course multi-fraction programs (15-18). One may even consider to deliver total radiation doses of >30 Gy (for example 14-15x2.5 Gy over 3 weeks or 20x2 Gy over 4 weeks), since a retrospective study suggested that such programs result in better local control and survival in patients with MESCC and very favorable survival prognoses (19). Patients achieving 2 points in this tool may also be considered for addition of decompressive spinal surgery prior to radiotherapy if they qualify by meeting the criteria established by Patchell *et al.* (20). A retrospective study suggested better functional outcome with the combined treatment compared to radiotherapy alone for patients with MESCC from unfavorable tumors such as CUP (20).

In summary, this new tool allows for estimation of the survival prognoses of elderly patients with MESCC from CUP and can assist treating physicians when selecting the most suitable treatment option for these patients.

Conflicts of Interest

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

References

- 1 Rades D and Abrahm JL: The role of radiotherapy for metastatic epidural spinal cord compression. *Nat Rev Clin Oncol* 7: 590-598, 2010.
- 2 De Iuliis F, Salerno G, Taglieri L, Vicinanza R, Lanza R and Scarpa S: Elderly woman with triple-negative metastatic breast cancer successfully treated with metronomic capecitabine. *Anticancer Res* 34: 4287-4291, 2014.
- 3 Darlin L, Borgfeldt C, Widén E and Kannisto P: Elderly women above screening age diagnosed with cervical cancer have a worse prognosis. *Anticancer Res* 34: 5147-5151, 2014.
- 4 Evers JN, Schild SE, Segedin B, Nagy V, Khoa MT, Trang NT and Rades D: A new score predicting survival prognosis after whole-brain radiotherapy alone for brain metastases in elderly patients. *Anticancer Res* 34: 2455-2458, 2014.
- 5 Chokshi S, Ghobadi A, Athar M, Shah S and Dowell J: Impact of comorbidity on initial treatment and overall survival in elderly head and neck cancer patients. *Anticancer Res* 34: 5543-5546, 2014.
- 6 Pasqualetti F, Ferrazza P, Cocuzza P, Fatigante L, Pasqualetti G, Fabbrini MG and Monzani F: Radio-chemotherapy with temozolomide in elderly patients with glioblastoma. A mono-institutional experience. *Anticancer Res* 34: 4281-4285, 2014.
- 7 Douglas S, Huttenlocher S, Bajrovic A, Rudat V, Schild SE and Rades D: Prognostic factors for different outcomes in patients with metastatic spinal cord compression from cancer of unknown primary. *BMC Cancer* 12: 261, 2012.
- 8 Pavlidis N, Peccatori F, Lofts F and Greco AF: Cancer of Unknown Primary During Pregnancy: An Exceptionally Rare Coexistence. *Anticancer Res* 35: 575-579, 2015.
- 9 Rades D, Kühnel G, Wildfang I, Börner AR, Schmol HJ and Knapp W: Localised disease in cancer of unknown primary (CUP): the value of positron emission tomography (PET) for individual therapeutic management. *Ann Oncol* 12: 1605-1609, 2001.
- 10 Komine K, Inoue M, Otsuka K, Fukuda K, Nanjo H and Shibata H: Utility of Measuring Circulating Tumor Cell Counts to Assess the Efficacy of Treatment for Carcinomas of Unknown Primary Origin. *Anticancer Res* 2014 34: 3165-3168, 2014.
- 11 Rades D, Douglas S and Schild SE: A validated survival score for breast cancer patients with metastatic spinal cord compression. *Strahlenther Onkol* 189: 41-46, 2013.
- 12 Rades D, Douglas S, Veninga T and Schild SE: A validated survival score for patients with metastatic spinal cord compression from non-small cell lung cancer. *BMC Cancer* 12: 302, 2012.
- 13 Rades D, Douglas S, Veninga T, Bajrovic A, Stalpers LJ, Hoskin PJ, Rudat V and Schild SE: A survival score for patients with metastatic spinal cord compression from prostate cancer. *Strahlenther Onkol* 188: 802-806, 2012.
- 14 Douglas S, Schild SE and Rades D: Metastatic spinal cord compression in patients with cancer of unknown primary. Estimating the survival prognosis with a validated score. *Strahlenther Onkol* 188: 1048-1051, 2012.
- 15 Rades D, Stalpers LJA, Veninga T, Schulte R, Hoskin PJ, Obralic N, Bajrovic A, Rudat V, Schwarz R, Hulshof MC, Poortmans P and Schild SE: Evaluation of five radiation schedules and prognostic factors for metastatic spinal cord compression in a series of 1304 patients. *J Clin Oncol* 23: 3366-3375, 2005.
- 16 Rades D, Lange M, Veninga T, Rudat V, Bajrovic A, Stalpers LJ, Dunst J and Schild SE: Preliminary results of spinal cord compression recurrence evaluation (score-1) study comparing short-course *versus* long-course radiotherapy for local control of malignant epidural spinal cord compression. *Int J Radiat Oncol Biol Phys* 73: 228-234, 2009.

- 17 Rades D, Lange M, Veninga T, Stalpers LJ, Bajrovic A, Adamietz IA, Rudat V and Schild SE: Final results of a prospective study comparing the local control of short-course and long-course radiotherapy for metastatic spinal cord compression. *Int J Radiat Oncol Biol Phys* 79: 524-530, 2011.
- 18 Rades D, Fehlauer F, Schulte R, Veninga T, Stalpers LJ, Basic H, Bajrovic A, Hoskin PJ, Tribius S, Wildfang I, Rudat V, Engenhart-Cabilic R, Karstens JH, Alberti W, Dunst J and Schild SE: Prognostic factors for local control and survival after radiotherapy of metastatic spinal cord compression. *J Clin Oncol* 24: 3388-3393, 2006.
- 19 Rades D, Panzner A, Rudat V, Karstens JH and Schild SE: Dose escalation of radiotherapy for metastatic spinal cord compression (MSCC) in patients with relatively favorable survival prognosis. *Strahlenther Onkol* 187: 729-735, 2011.
- 20 Rades D, Huttenlocher S, Bajrovic A, Karstens JH, Adamietz IA, Kazic N, Rudat V and Schild SE: Surgery followed by radiotherapy *versus* radiotherapy alone for metastatic spinal cord compression from unfavorable tumors. *Int J Radiat Oncol Biol Phys* 81: e861-868, 2011.

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