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Prognostic factors associated with survival in patients with symptomatic spinal bone metastases: a retrospective cohort study of 1 043 patients

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Background. Expected survival is a major factor influencing extent of treatment for symptomatic spinal bone metastases (SBM). Predictive models have been developed, but their use can lead to over- or undertreatment.. The study objective was to identify prognostic factors associated with survival in patients with symptomatic SBM and to create a validated risk stratification model.

Methods. All patients who were treated for symptomatic SBM between 2001 and 2010 were included in this single center retrospective study. Medical records were reviewed for type of primary cancer, performance status, presence of visceral, brain and bone metastases, number and location of spinal metastases, and neurological functioning. Performance status was assessed with the Karnofsky performance score and neurological functioning with the Frankel scale. Analysis was performed using Kaplan-Meier curves, univariate log-rank tests, Cox regression models, and Harrell's C statistic.

Results. A total of 1 043 patients were studied. The most prevalent tumors were those of breast ($n = 299$), lung ($n = 250$), and prostate ($n = 215$). Median follow-up duration was 6.6 years, and 6 patients were lost to follow-up. Based on the results of the uni- and multivariate analyses, 4 categories were created. Median survival in category A was 31.2 months (95% CI, 25.2–37.3 months), 15.4 months (95% CI, 11.9–18.2 months) for category B, 4.8 months (95% CI, 4.1–5.4 months) for category C, and 1.6 months (95% CI, 1.4–1.9 months) for category D. Harrell's C statistic was calculated after the model was applied to an external dataset, yielding a result of 0.69.

Conclusion. Assessing patients according to the presented model results in 4 categories with significantly different survival times.

Keywords: spinal metastases, survival, stratification.

Metastases to the spinal column are a frequently observed complication of end-stage malignant disease. Depending on their extent and localization, they cause a variety of clinical symptoms ranging from pain to neurological deficits and even paraplegia. These spinal bone metastases (SBM) most commonly arise from the posterior part of the vertebral body. When they extend into the epidural space and compress the spinal cord, the clinical entity is called malignant epidural spinal cord compression.[1]

Due to improvements in systemic treatment options for the primary tumor, overall survival times for patients suffering from metastatic disease are on the rise. Most likely, this will result in a prolonged palliative phase in which the incidence of patients presenting with symptomatic SBM will increase. It has been well established that treatment with radiotherapy and/or surgery can be beneficial to patients presenting with pain, neurological deficit, or both.[2–6] However, the most optimal treatment algorithm for individual patients has not yet been optimized. In practice, the treating physician will match extent and type of treatment not only to a patient's clinical presentation but also to the expected survival time, thus balancing the increase in morbidity and mortality associated with more extensive treatment against the expected gain in quality of life.

Models to aid in therapy selection based on expected survival time have been developed by Tomita,[7] Tokuhashi,[8,9] Bauer,[10,11] and our own group.[4] These models encompass prognostic factors such as primary tumor type, amount and location of spinal metastases, presence of visceral, brain and extraspinal bone metastases, functional status, and neurological status. However, clinical applicability seems limited due to over- or undertreatment, and the existing models fall short, especially when predicting a brief survival.[12,13]

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The goal of this study was to identify risk factors associated with survival and to develop a validated survival risk stratification model for patients with symptomatic SBM.

Materials and Methods

In this single center retrospective cohort study, all patients treated for metastases in the spinal column between January 2001 and December 2010 at a tertiary referral hospital in the Netherlands were included. Patients were identified through database searches linking treatment and diagnostic codes and database searches based on surgical coding. Information on date of death was obtained from medical records or by contacting the general practitioner.

Local treatment consisted of external beam radiotherapy for pain or minor neurological deficit, surgery for rapidly progressive or severe neurological deficit and instability, or a combination of both treatment modalities. Concomitant systemic anticancer treatments, such as chemotherapy and bisphosphonates, were considered to be secondary to the local treatment. For external validation of the final model, the database of the Dutch Bone Metastasis Study (DBMS) was used.[14]

Due to the retrospective nature of the study, it was exempt from medical ethics review according to the Dutch Central Committee on Research Involving Human Subjects.

The primary data sources were the patient's' clinical files, radiology reports, and admission forms. Baseline variables obtained before start of treatment were sex, age, primary tumor, location and number of SBM, the presence of visceral and/or brain metastases, the presence of extraspinal bone metastases, pretreatment functioning according to the KPS,[15,16] and neurological functioning according to the Frankel classification.[17]

The primary tumors were categorized based on the Tomita classification.[7] The original classification used growth speed alone to assign a primary tumor into 1 of 3 groups. However, as growth speed is not the only factor determining survival, we renamed the classification "clinical profile" to encompass other contributing factors such as availability of effective systemic treatment options for the primary tumor. The clinical profile of a primary tumor was considered to be favorable, moderate, or unfavorable.

Performance status was dichotomized into normal functioning (KPS 100%–80%) and impaired functioning (KPS 70%–10%). Neurological functioning was inferred from clinical exams and divided into 3 groups: no deficit present (Frankel E), minor motor or sensory deficit (Frankel D), and major motor or sensory deficit (Frankel A, B, C). The number of spinal and extraspinal bone metastases was obtained from radiology reports and further subdivided in 3 categories according to Tokuhashi.[9]

Statistical Analysis

Survival time was calculated as the difference between start of treatment for the spinal metastasis and date of death or the last follow-up recorded. Survival curves were estimated using the Kaplan-Meier method. Follow-up was assessed by employing the reverse Kaplan-Meier method.[18] Cox proportional hazard models were fitted using Collett's method (a univariate analysis followed by multivariate backward and multivariate forward selection).[19] Harrell's C statistic was used for external validation of the predictive accuracy of the presented model.[20] It estimates the probability of concordance between predicted and observed responses. Survival curves were compared using log-rank tests. A P value of $<.05$ was considered statistically significant. All analyses were performed using SPSS 20.0 (SPSS Inc.)

Results

A total of 1 301 patients were treated for symptomatic spinal metastases during the study period. After excluding patients with direct ingrowth of a primary tumor into the vertebra ($n = 23$), patients with bone metastases in the sacral or sacroiliac region ($n = 105$), leptomeningeal metastases ($n = 24$), intradural metastases ($n = 14$), metastases deriving from primary tumors of hematological or of unknown origin ($n = 44$), and metastases deriving from rare primary tumors ($n = 42$), 1 049 patients remained eligible for analysis. Primary tumors classified as adenocarcinoma of unknown primary were not excluded. Six patients moved abroad shortly after finishing treatment and were lost to follow-up (Fig. 1).

Table 1 summarizes the characteristics of the 1 043 patients studied, of whom 542 (52%) were male and 501 (48%) were female. The mean age at start of treatment was 64.8 years (SD ± 12.5 years). At presentation, the majority of patients had no ($n = 518$; 50%) or only minor ($n = 403$; 39%) neurological complaints.

Median follow-up was 6.6 years. The overall median survival was 4.8 months (95% CI, 4.3–5.4 months). In total 984 patients (94%) died during follow-up with a median survival of 4.3 months (95% CI, 3.8–4.9 months). Two-hundred-and-forty-three (23%) patients died within 6 weeks after starting treatment, whereas 179 (17%) patients survived for more than 2 years.

The most prevalent primary tumors were breast cancer ($n = 299$), lung cancer ($n = 255$), prostate cancer ($n = 215$), kidney cancer ($n = 60$), and colon cancer ($n = 55$) (Table 2). Thirty percent of all patients were classified as having a favorable clinical profile with a median survival of 18.6 months (95% CI, 15.1–22.1 months), followed by 29% with a moderate profile and a median survival of 5.9 months (95% CI, 4.8–7.0 months), and 41% with an unfavorable profile and a median survival of 2.2 months (95% CI, 1.9–2.6 months) (Fig. 2).

Radiotherapy was the most commonly used primary treatment in a total of 997 patients (95%). Only 46 patients (5%) underwent surgery. See Table 3 for the radiotherapy regimens and surgical techniques used.

The DBMS database consisted of 342 SBM cases treated with radiotherapy. Median follow-up was 2.2 years, and overall median survival was 8.9 months (95% CI, 7.4–10.3 months). In total, 258

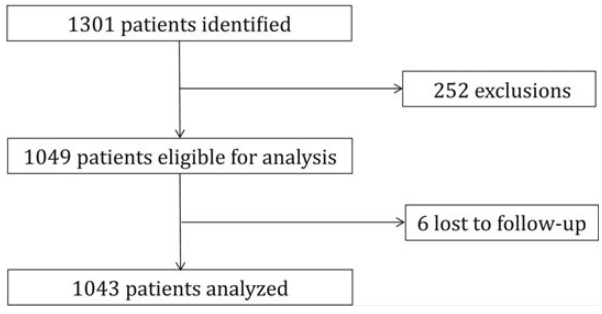

Fig. 1. Patient flow diagram.

Table 1. Population characteristics

Characteristic	*n* (%)
Sex	
Male	542 (52)
Female	501 (48)
Age (mean, years ± SD)	64.8 ± 12.5
Clinical profile	
Favorable	312 (30)
Moderate	296 (28)
Unfavorable	435 (42)
Location treated spinal metastases	
Cervical only	40 (4)
Cervicothoracic	121 (12)
Thoracic only	256 (24)
Thoracolumbar	275 (27)
Lumbar only	309 (30)
Diffuse	42 (3)
Number spinal metastases	
1	326 (31)
2	191 (19)
3 or more	526 (50)
Number extraspinal bone metastases	
None	370 (35)
1 or 2	287 (28)
3 or more	386 (37)
Visceral metastases	
Present	380 (36)
Not present	663 (64)
Brain metastases	
Present	71 (7)
Not present	972 (93)
Karnofsky performance status	
Normal (100%–80%)	387 (37)
Impaired (70%–10%)	607 (58)
Missing	49 (5)
Frankel classification	
No deficit (E)	518 (50)
Minor motor or sensory deficit (D)	403 (39)
Major motor or sensory deficit (A, B, C)	112 (10)
Missing	10 (1)

Abbreviation: SD, standard deviation.

patients (76%) died during follow-up. Further details of the patient population are published elsewhere.[4]

Analysis of the Entire Cohort

Results of the univariate and multivariate analyses are detailed in Table 4. The 3 clinical profiles (moderate HR 1.6; 95% CI, 1.3–2.1; $P < .001$) (unfavorable HR 3.5; 95% CI, 2.9–4.4; $P < .001$), the KPS (HR 1.9; 95% CI, 1.6–2.2; $P < .001$), and the presence of visceral metastases (HR 1.5; 95% CI, 1.3–1.7; $P < .001$) were shown to be of influence on survival. The Frankel classification, the number and location of the spinal metastases, and the presence of brain and extraspinal bone metastases did not influence survival.

Table 2. Primary tumor, related survival, and clinical profile

Primary tumor	Number (%)	Median Survival months (95% CI)	Profile
Breast	299 (29)	18.6 (14.9–22.2)	Favorable
Thyroid	13 (1)	4.8 (0.0–24.9)	Favorable
Prostate	215 (21)	6.6 (5.2–8.1)	Moderate
Kidney	60 (6)	4.5 (2.6–6.4)	Moderate
Ovary	8 (1)	4.9 (2.3–7.6)	Moderate
Osteosarcoma	9 (1)	6.3 (0.0–12.6)	Moderate
Uterine sarcoma	4 (< 1)	4.6 (0.0–10.0)	Moderate
Lung	250 (24)	1.9 (1.5–2.4)	Unfavorable
Colon	55 (5)	3.2 (1.8–4.5)	Unfavorable
UCC	27 (3)	1.7 (0.9–2.6)	Unfavorable
ACUP	22 (2)	2.4 (0.9–3.8)	Unfavorable
Esophagus	20 (2)	1.7 (0.1–3.3)	Unfavorable
Melanoma	17 (2)	1.2 (0.5–1.8)	Unfavorable
Pancreaticobiliary	11 (1)	1.7 (1.2–2.2)	Unfavorable
Ewing's sarcoma	10 (1)	1.9 (0.3–3.5)	Unfavorable
Cervix	7 (1)	2.3 (0.0–5.7)	Unfavorable
Endometrium	5 (1)	1.9 (0.9–3.0)	Unfavorable
Stomach	4 (<1)	1.2 (0.2–2.3)	Unfavorable
Liver	4 (<1)	7.5 (0.0–15.8)	Unfavorable
Tongue	3 (<1)	0.8 (0.7–0.8)	Unfavorable

Abbreviations: ACUP, adenocarcinoma of unknown primary; CI, confidence interval; UCC, urothelial cell carcinoma.

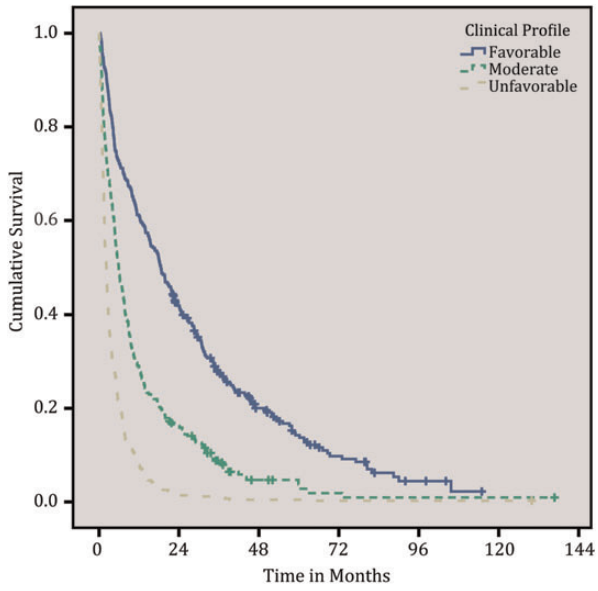

Fig. 2. Survival curves of clinical profiles.

Analysis Stratified for Clinical Profile

Results of the univariate and multivariate analyses for the 3 clinical profiles are illustrated in Table 5. A poor KPS (HR 1.7; 95% CI, 1.3–2.2; $P < .001$), the presence of visceral metastases (HR 2.0; 95% CI, 1.5–2.7; $P < .001$), and the presence of brain metastases

(HR 1.8; 95% CI, 1.1–3.0; $P = .016$) were shown to have an association with survival in the favorable profile. In the moderate and unfavorable profiles, only the KPS affected survival (HR 2.3; 95% CI, 1.7–3.0; $P < .001$ and HR 1.9; 95% CI, 1.5–2.3; $P < .001$, respectively).

Training Data Set and Validation Data Set

Based on the results of the 3 multivariate analyses, the cohort was divided into 8 groups (Fig 3A). By comparing the median survival of the groups, 4 final categories (A, B, C, and D) were created (Table 6). Patients in category A had a median overall survival of 31.2 months (95% CI, 25.2–37.3 months), compared with 15.4 months (95% CI, 11.9–18.2 months) for patients in category B, 4.8 months (95% CI, 4.1–5.4 months) for patients in category C, and 1.6 months (95% CI, 1.4–1.9 months) for patients in category D (Fig. 3B and Table 7). Harrell's C statistic was 0.71 when calculated based on the training data set.

Table 3. Treatment details

Treatment	*n* (%)
Overall	
Radiotherapy only	997 (95)
Surgery and radiotherapy	39 (4)
Surgery only	7 (1)
Radiotherapy regimens	
1 × 8 Gy	445 (43)
2 × 8 Gy	169 (16)
6 × 4 Gy or 5 × 4 Gy	322 (31)
Other – Total dose >24 Gy	100 (10)
Surgery	
Minimal invasive	10 (22)
Limited decompression and fixation	23 (50)
Extended decompression and fixation	13 (28)

Table 5. Results of the uni- and multivariate analyses stratified for clinical profile

Univariate Analysis	Favorable ($n = 312$)	Moderate ($n = 296$)	Unfavorable ($n = 435$)
Performance status	<0.001	<0.001	<0.001
Visceral metastases	<0.001	0.086	0.165
Brain metastases	0.009	0.482	0.528
Frankel classification	0.043	0.757	0.248
Number spinal metastases	0.054	0.469	0.243
Bone metastases	0.078	0.120	0.943
Location spinal metastases	0.657	0.196	0.867
Cox regression models	HR	95% CI	*P* value
Model 1: Favorable profile			
Performance status ≤70%	1.7	1.3–2.2	<.001
Visceral metastases present	2.0	1.5–2.7	<.001
Brain metastases present	1.8	1.1–3.0	0.016
Model 2: Moderate profile			
Performance status ≤70%	2.3	1.7–2.9	<.001
Model 3: Unfavorable profile			
Performance status ≤70%	1.9	1.5–2.3	<.001

Abbreviations: CI, confidence internal; HR, hazard ratio.

Table 4. Results of the uni- and multivariate analyses

Univariate Log-Rank Test			*P* value
Clinical profile (Favorable/Moderate/Unfavorable)			<.001
Karnofsky (100%-80%/70%-10%)			<.001
Frankel classification (ABC/D/E)			<.001
Visceral metastases (Yes/No)			<.001
Brain metastases (Yes/No)			.012
Number spinal metastases (1/2/≥3)			.983
Bone metastases (0/1/≥2)			.093
Location spinal metastases (C/CT/T/TL/L/D)			.836
Multivariate Cox Regression Model	HR	95% CI	*P* value
Clinical profile			
Favorable	–	–	<.001
Moderate	1.6	1.3–2.1	<.001
Unfavorable	3.5	2.9–4.4	<.001
Karnofsky performance status			
Normal (100%-80%)	–	–	<.001
Impaired (70%-10%)	1.9	1.6–2.2	<.001
Visceral metastases			
Not present	–	–	<.001
Present	1.5	1.3–1.7	<.001

Abbreviations: C, cervical; CI, confidence interval; CT, cervicothoracic; D, diffuse; HR , hazard ratio; L, lumbar; T, thoracic; TL, thoracolumbar.

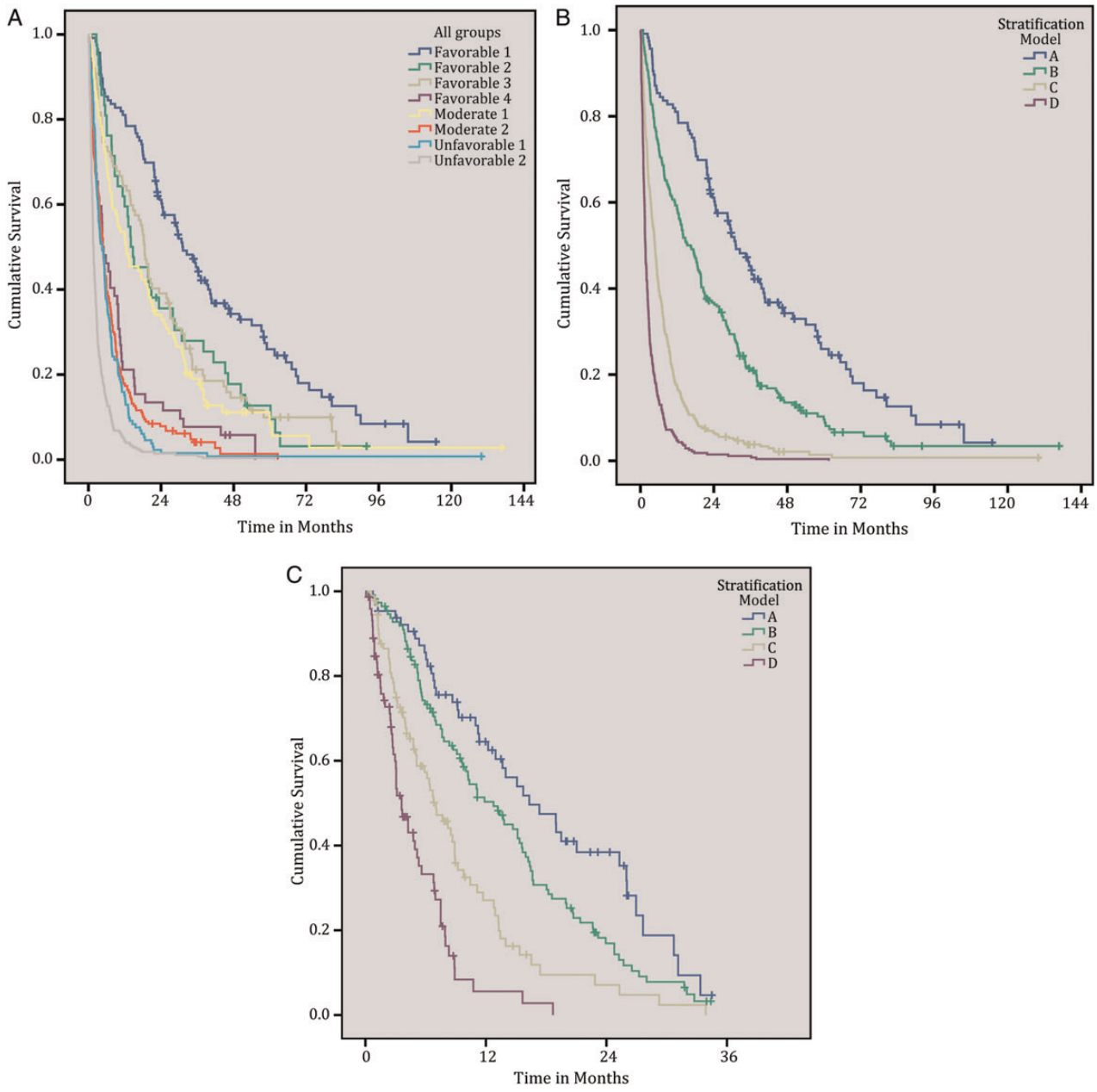

Fig. 3. (A) Eight categories prior to merging. (B) Stratification model after merging. (C) Stratification model applied to Dutch Bone Metastasis Study database.

Patients in category A of the validation data set had a median survival of 16.3 months (95% CI, 11.1–21.6 months), compared with 12.8 months (95% CI, 9.5–16.0 month) for category B, 7.0 months (95% CI, 5.1–9.0 months) for category C, and 3.6 months (95% CI, 2.6–4.6 months) for category D (Fig. 3C and Table 7). The C statistic based on the validation data set was 0.69.

Discussion

In this retrospective study of 1 043 patients treated for symptomatic SBM, it has been shown that the clinical profile of the primary tumor, performance status and—in the subgroup of a favorable clinical profile only—the presence of visceral and brain metastases is associated with survival. Other prognostic factors, such as the presence of extraspinal bone metastases, number and location of spinal metastases, and neurological functioning, did not show a significant effect on survival.

The most important limitation of this study is its retrospective design. Due to the fact that all patients were treated in a single institution, clinical information was readily available, including radiology reports. However, this does not rule out the possibility of inaccuracy of the source data. Furthermore, no SBM-specific treatment protocols existed, exemplified by the fact that the

Table 6. Groups based on multivariate analysis

Clinical Profile	KPS	VM/BRM	MOS (95% CI)	*n* (%)	Category
Favorable	100%–80%	No	31.2 (25.2–37.3)	116 (12)	A
Favorable	100%–80%	Yes	14.0 (6.8–21.1)	42 (4)	B
Favorable	70%–10%	No	18.6 (16.0–21.1)	87 (9)	B
Favorable	70%–10%	Yes	4.8 (2.3–7.3)	52 (5)	C
Moderate	100%–80%	N/A	12.5 (6.5–18.5)	97 (10)	B
Moderate	70%–10%	N/A	4.8 (4.0–5.6)	190 (19)	C
Unfavorable	100%–80%	N/A	4.5 (3.1–5.8)	132 (13)	C
Unfavorable	70%–10%	N/A	1.6 (1.4–1.9)	278 (28)	D

Abbreviations: CI, confidence interval; MOS, median overall survival; VM/BRM, visceral and/or brain metastases.

Table 7. Survival times by training and validation data sets

Category	MOS (95% CI)	*n* (%)	HR	95% CI	*P* value
Training data set					
A	31.2 (25.2–37.3)	116 (12)	–	–	<.001
B	15.4 (11.9–18.2)	226 (23)	1.8	1.4–2.3	<.001
C	4.8 (4.1–5.4)	374 (37)	4.4	3.5–5.6	<.001
D	1.6 (1.4–1.9)	278 (28)	9.3	7.2–12.1	<.001
Validation data set					
A	16.3 (11.1–21.6)	64 (19)	–	–	<.001
B	12.8 (9.5–16.0)	111 (33)	1.5	1.0–2.2	.029
C	7.0 (5.1–9.0)	91 (27)	2.8	1.9–4.1	<.001
D	3.6 (2.6–4.6)	73 (21)	6	3.9–9.2	<.001

Abbreviations: CI, confidence interval; HR , hazard ratio; MOS, median overall survival.

landmark study by Patchell et al.[2] resulted in more surgical interventions being performed in the period after publication. However, as this study analyzes survival only and therapy for SBM is not directly aimed at prolonging survival, it is unlikely that our results are influenced by this change in therapeutic approach. It is possible that the presence of brain metastases is underrepresented in this study population because whole-brain scans were not routinely performed, contrary to thoracic and abdominal scans. As a result, most of the patients with brain metastases had symptomatic lesions. It is unclear whether asymptomatic brain metastases have the same predictive value in this specific patient population. Lastly, treatment for SBM in our institution only takes place in symptomatic patients, and only patients treated locally for their SBM by means of surgery or radiotherapy were included. As a consequence, patients with symptomatic SBM that received only supportive care no were not represented in this study.

In contrast to the previous study by our group, which was based on a prospective database with only radiotherapy patients, patients with a cervical SBM were not excluded, nor were patients with renal cell carcinoma, leading to better generalizability of the data. Because the prospective DBMS database was closed after an inclusion period of 2.5 years, median follow-up times were distinctly different. Survival times in category A are therefore limited. Since the DBMS inclusion criteria were stricter and contained more patients with a favorable clinical profile and fewer with an unfavorable profile, median survival times were better than in the current database. However, as a nearly identical C score shows, the presented model is still capable of stratification based on the identified risk factors.

As has been established in the literature, primary tumor type (represented by clinical profile in this study) was shown to be the factor of greatest influence on survival in patients with symptomatic SBM.[21] This means that an accurate and up-to-date tumor classification is essential for prognostication. The positive effect of new treatments, such as anti-VEGF therapy, will mean that survival with symptomatic SBM may increase considerably for certain tumors in the near future.[22] Also, it is unclear whether there is a difference in survival for patients with SBM from different subtypes of the same primary cancer, as is the case in breast cancer with estrogen, progesterone, and HER2 interactions.[23] These topics should be the subject of further SBM-specific studies.

A poor performance status nearly doubles the risk of death in all 3 clinical profiles and is the second most important variable to assess in patients with SBM. Even though the Karnofsky score is a subjective score and is highly susceptible to changes in neurological functioning, it remains an effective tool to assess a patient's general condition quickly. The use of a performance-related score as risk factor when estimating survival is also superior when compared to age, as age only gives an indirect measure of a patient's functional status. Contrary to the Tokuhashi and Van der Linden models, the KPS was divided into 2 categories instead of 3 to facilitate clinical decision-making.

To the authors' best knowledge, this is the first study to describe how the effect of visceral and brain metastases differs per primary tumor category. Overall, there was no influence of brain metastases, and the effect of visceral metastases was only marginal. However, after stratification for the clinical profile, a statistically significant effect on survival for visceral and brain metastases was found in the favorable category only. The presence of brain or visceral metastases was not associated with survival of patients in both the moderate and unfavorable profiles, obviating the need for additional radiologic examinations in these groups when estimating survival. Most likely, this is due to the fact that survival in these 2 categories is already very short based on the primary tumor, and the effect of visceral or brain metastases therefore becomes negligible.

Even though neurological status is one of the most important factors to consider when deciding on treatment, the presence of

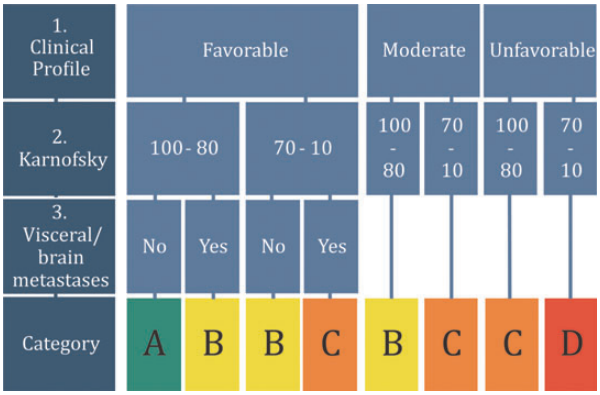

Fig. 4. Flowchart for stratification.

neurological deficit at the start of treatment does not directly influence survival in any of the 3 clinical profiles described in this study. Rades et al. have shown that the time of developing motor deficits is the most important factor predicting improvement of neurological functioning after treatment.[24] Neurological status should therefore be viewed as an indication for treatment rather than a predictive factor when estimating survival. Especially in the case of sudden paraplegia due to spinal cord compression, swift and decisive treatment is far more important than estimation of survival because the possible benefits of treatment in terms of quality of life far outweigh the possible risks in terms of a short remaining lifespan. When assessing neurological deficit in patients with SBM, the Frankel classification might not be the most suitable tool because it was originally designed for categorizing spinal cord injury only. Neurological symptoms caused by nerve root compression or compression of the cauda equina are not covered, necessitating the development of a SBM-specific classification for describing neurological deficit.

Even though the number and location of SBM influence treatment options such as possibilities of surgical fixation and range of radiation fields, they did not show a significant effect on survival. Sixty-nine percent of all patients studied had more than one confirmed spinal metastasis. It was also possible that a large proportion of patients classified as having a solitary metastasis actually had occult lesions.[25] Lastly, the presence of extraspinal bone metastases was not associated with survival.

New Model

A flowchart was created to guide the stratification of patients with symptomatic SBM (Fig. 4). Based on a maximum of 3 easy-to-obtain variables, patients were classified into 1 of 4 categories (A–D), each with a distinctly different estimated survival time. The effect of this approach is particularly striking in patients with a favorable clinical profile: by assessing 2 variables, the median survival is split from 18.6 months (95% CI, 15.1–22.1 months) overall down to 4.8 months (95% CI, 2.3–7.3 months) and up to 31.2 months (95% CI, 25.2–37.3 months) (Table 7).

Harrell's C statistic was almost identical when the new model was applied to an external database, indicating good reproducibility of our results. The current values of 0.71 and 0.69 indicate a good predictive value of the model and, with a more accurate classification of primary cancers into 1 of the 3 clinical profiles, the value of C should rise even further.

This large data collection provides a better understanding of how risk factors interact when stratified for primary tumor. It is shown that clinical profile and performance status have a strong impact on survival in all patients with symptomatic SBM. The presence of visceral and/or brain metastases is associated with a shortened survival only in patients with an unfavorable clinical profile.

The model presented in this study can be used as a simple stratification tool for patients presenting with symptomatic SBM. Also, it can be used in future studies to compare efficacy of radiotherapy regimens and various types of surgical intervention, as well as studies into the effects on quality of life of different treatment modalities.

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Conflict of interest statement. None declared.

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