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An Easy-to-Use Prognostic Model for Survival Estimation for Patients with Symptomatic Long Bone Metastases

J.J. Willeumier, MD, Y.M. van der Linden, MD, PhD, C.W.P.G. van der Wal, MD, P.C. Jutte, MD, PhD, J.M. van der Velden, MD, M.A. Smolle, BSc, P. van der Zwaal, MD, PhD, P. Koper, MD, PhD, L. Bakri, MD, I. de Pree, MD, A. Leithner, MD, M. Fiocco, PhD and P.D.S. Dijkstra, MD, PhD

Investigation performed at Leiden University Medical Centre, Leiden; University Medical Centre Groningen, Groningen; University Medical Centre Utrecht, Utrecht; Haaglanden Medical Centre, The Hague; Reinier de Graaf Gasthuis, Delft; Erasmus Medical Center, Rotterdam, the Netherlands; and Medical University of Graz, Graz, Austria

Background: A survival estimation for patients with symptomatic long bone metastases (LBM) is crucial to prevent overtreatment and undertreatment. This study analyzed prognostic factors for overall survival and developed a simple, easy-to-use prognostic model.

Methods: A multicenter retrospective study of 1,520 patients treated for symptomatic LBM between 2000 and 2013 at the radiation therapy and/or orthopaedic departments was performed. Primary tumors were categorized into 3 clinical profiles (favorable, moderate, or unfavorable) according to an existing classification system. Associations between prognostic variables and overall survival were investigated using the Kaplan-Meier method and multivariate Cox regression models. The discriminatory ability of the developed model was assessed with the Harrell C-statistic. The observed and expected survival for each survival category were compared on the basis of an external cohort.

Results: Median overall survival was 7.4 months (95% confidence interval [CI], 6.7 to 8.1 months). On the basis of the independent prognostic factors, namely the clinical profile, Karnofsky Performance Score, and presence of visceral and/or brain metastases, 12 prognostic categories were created. The Harrell C-statistic was 0.70. A flowchart was developed to easily stratify patients. Using cutoff points for clinical decision-making, the 12 categories were narrowed down to 4 categories with clinical consequences. Median survival was 21.9 months (95% CI, 18.7 to 25.1 months), 10.5 months (95% CI, 7.9 to 13.1 months), 4.6 months (95% CI, 3.9 to 5.3 months), and 2.2 months (95% CI, 1.8 to 2.6 months) for the 4 categories.

Conclusions: This study presents a model to easily stratify patients with symptomatic LBM according to their expected survival. The simplicity and clarity of the model facilitate and encourage its use in the routine care of patients with LBM, to provide the most appropriate treatment for each individual patient.

Level of Evidence: Prognostic Level IV. See Instructions for Authors for a complete description of levels of evidence.

Long bone metastases (LBM) are a common occurrence in patients with advanced cancer, arising in up to 70% of patients with advanced disease[1]. As the prevalence of cancer rises[2] and survival rates for even metastatic cancer increase, the number of patients with symptomatic LBM is likely to grow. Pain is the most common symptom, followed by actual or impending pathologic fractures in 10% to 25% of the patients, causing immobility and a decreased quality of life[3]. Local treatment options primarily consist of radiation therapy and multiple types of surgical stabilization. All treatments have the same aim: to reduce pain, preserve the function of the extremities, and maintain or

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TABLE I Patient Demographics

Characteristic	
No. of patients	1,520
Age* *(yr)*	65.0 (12.8)
Sex *(no. [%])*	
Male	690 (46.4)
Female	830 (54.6)
Karnofsky Performance Score† *(no. [%])*	
80-100	648 (42.6)
≤70	512 (33.7)
Unknown†	360 (23.7)
Visceral metastases§ *(no. [%])*	
Present	588 (38.7)
Not present	890 (58.6)
Unknown†	42 (2.8)
Metastases to brain and/or central nervous system# *(no. [%])*	
Present	85 (5.6)
Not present	1,413 (93.0)
Unknown†	22 (1.4)
Tumor location *(no. [%])*	
Femur	1,029 (67.7)
Humerus	399 (26.3)
Tibia	60 (3.9)
Radius	14 (0.9)
Ulna	11 (0.7)
Fibula	7 (0.5)
Location in bone *(no. [%])*	
Proximal	1,066 (70.1)
Shaft	303 (19.9)
Distal	133 (8.8)
Unknown	18 (1.2)
Solitary bone metastasis *(no. [%])*	
Yes	162 (10.7)
No	1,181 (77.7)
Unknown	177 (11.6)

*The values are given as the mean, with the standard deviation in parentheses. †Determined on the basis of the clinical description in 47% of the patients. ‡In total, data were missing for 389 patients; for 35 patients, data for >1 of the variables were missing. §As reported in recent radiology reports. #Presence of metastases was determined on the basis of recent radiology reports; metastases were considered not present if there was no clinical suspicion of brain metastases (therefore, no radiology).

improve quality of life for patients with mostly limited life expectancy[4,5].

An accurate estimation of the survival at a specific time is essential to avoid overtreatment and undertreatment. Treatments that do not fit the expected survival time of patients with advanced cancer, with either recovery and rehabilitation times that are too long relative to a mostly limited survival, or insufficient stabilizations when a long survival is expected, have a negative effect on their mobility and independence and, hence, their quality of life. For patients expected to have a short survival, radiation therapy or minimally invasive surgical treatments (e.g., intramedullary nail fixation) would be preferable, while for patients expected to have a long survival, resection and reconstruction with a regular or modular tumor prosthesis could provide a lifelong solution. Correct estimates of survival, however, are difficult, and physicians tend to be inaccurate[6]. For patients with LBM, several tools have been developed to aid physicians[7-14]. However, they have several shortcomings. First, most models are based on small cohorts from either radiation therapy[11,14] or orthopaedic[7-9,12,13] departments, instead of both. Survival predictions that are based on a mixed cohort would be more consistent when discussing multidisciplinary treatment strategies. Second, many models include multiple myeloma as the primary tumor[7-10,12,13]; however, as a primary hematological cancer, it is a different entity and has a very different prognosis than osseous metastases from solid carcinomas. Third, the development of targeted treatments for several primary tumors has subdivided primary tumors into different entities, which makes some models outdated[7-9,11-14]. Finally, most models include numerous variables, including some that are not part of standard workup (e.g., laboratory results)[7,8,10,12,13]. The complexity of these models, caused by the number of variables, inhibits effective clinical use of survival estimation tools in daily practice.

With these limitations in mind, our group previously developed a simple prognostic model for overall survival in patients with spinal metastases from carcinoma[15]. The model contains only 3 clinical variables: the clinical profile, the Karnofsky Performance Score (KPS), and the presence of visceral and/or brain metastases (VBM). These led to a categorization in 4 prognostic groups with the following median overall survival results: 31.2 months (95% confidence interval [CI], 25.2 to 37.3 months), 15.4 months (95% CI, 11.9 to 18.2 months), 4.8 months (95% CI, 4.1 to 5.4 months), and 1.6 months (95% CI, 1.4 to 1.9 months).

The purposes of this study were to (1) identify prognostic factors for survival in patients with LBM, (2) develop an accurate and easy-to-use prognostic model similar to the previously developed model for spinal bone metastases, and (3) test the applicability of the model in an external cohort.

Materials and Methods

Patients

A multicenter, retrospective analysis of patients with cancer who were treated for symptomatic metastases in the long bones between 2000 and 2013 was performed. Consecutive patients from 4 orthopaedic departments and 4 radiation therapy departments in 6 Dutch hospitals were included. Exclusion criteria were a lesion due to multiple myeloma, solitary plasmacytoma or other hematological disease, or a

TABLE II Primary Tumors and Their Corresponding Clinical Profile

Primary Tumor	No. (%) of Patients	Median Overall Survival (95% CI) *(mo)*	Clinical Profile
Breast – positive*	369 (24.3)	18.7 (15.2-22.1)	Favorable
Breast – unknown†	112 (7.4)	18.7 (14.1-23.2)	Favorable
Kidney – solitary metastasis	25 (1.6)	18.1 (0.0-37.7)	Favorable
Thyroid	23 (1.5)	9.8 (0.0-23.5)	Favorable
Prostate	233 (15.3)	7.8 (6.5-9.1)	Moderate
Kidney – multiple metastases	85 (5.6)	8.1 (4.6-11.7)	Moderate
Other primary tumor‡	20 (1.3)	3.8 (0.0-12.4)	Moderate
Soft-tissue sarcoma	19 (1.3)	6.8 (5.5-8.1)	Moderate
Breast – triple negative§	16 (1.1)	3.4 (1.4-5.4)	Moderate
Kidney – unknown#	16 (1.1)	10.3 (4.1-16.4)	Moderate
Endometrial carcinoma	9 (0.6)	12.2 (4.3-20.2)	Moderate
Osteosarcoma	8 (0.5)	4.0 (0.2-7.9)	Moderate
Ewing sarcoma	7 (0.5)	17.4 (10.8-54.1)	Moderate
Ovary	6 (0.4)	2.6 (2.0-3.2)	Moderate
Lung	363 (23.9)	2.9 (2.4-3.3)	Unfavorable
Colorectal	48 (3.2)	3.9 (2.6-5.2)	Unfavorable
Unknown primary	44 (2.9)	3.3 (1.5-5.1)	Unfavorable
Esophagus	32 (2.1)	3.4 (1.4-5.4)	Unfavorable
Bladder	25 (1.6)	3.8 (1.9-5.7)	Unfavorable
Melanoma	23 (1.5)	3.9 (2.2-5.6)	Unfavorable
Head and neck cancer	19 (1.3)	3.2 (0.7-5.6)	Unfavorable
Liver and/or pancreas	10 (0.7)	2.3 (0.2-4.4)	Unfavorable
Stomach	8 (0.5)	2.1 (0.7-3.4)	Unfavorable

*Estrogen, progesterone, and HER2/neu positive. †Hormone receptor status and HER2/neu status were unknown. ‡Consisting of 5 patients each with a cervical carcinoma and with multiple primary tumors; 2 patients each with Merkel cell carcinoma, carcinoma of the adnexa, and uterine sarcoma; and 1 patient each with a retroperitoneal paraganglioma, a neuroblastoma, a fibrous tumor of the thorax, and a carcinoma of the vulva. §Estrogen, progesterone, and HER2/neu negative. #The number of metastases was unknown.

lack of sufficient follow-up data regarding final status (alive or dead). After exclusion of 72 patients (no LBM [19 patients], no local treatment [43], duplicate patient [5], or lack of sufficient data [5]), 1,520 patients were eligible for participation in the cohort.

Medical, radiology, and pathology records were reviewed to record the following data at baseline: sex, age, primary tumor, pretreatment performance score, presence of visceral and/or brain metastases, location of the metastasis, presence of (impending) pathologic fracture, and whether the metastasis was a solitary lesion. If patients were treated multiple times, the first treatment (radiation therapy or surgery, or both) in the study period was included.

The local medical ethical committees approved this study and granted a waiver for informed consent.

Clinical Profile

Primary tumors were categorized into 3 clinical profiles (favorable, moderate, or unfavorable) on the basis of the classification system established by Bollen et al.[15]. Several tumor types that were not included in the previous classification were registered in the current study. Where reasonable, these were added to existing primary tumor types: carcinomas of the rectum were added to the group of colon carcinomas and the group "tongue cancer" was expanded to include all head and neck cancers. Soft-tissue sarcomas (STS) and "other primary tumors" were added as new tumor groups. Classification of STS was based on the literature[10]. Finally, the classification was adjusted from unfavorable to moderate for endometrial carcinoma[16] and Ewing sarcoma[17] on the basis of new insights in the literature. In addition, breast cancer and kidney cancer were divided over 2 clinical profiles on the basis of receptor (estrogen, progesterone, and HER2/neu) status for breast cancer[18] and the number of bone metastases for kidney cancer[19,20].

Pretreatment performance was scored by the KPS to reflect the performance before a fracture (if present); a higher score means the patient is better able to perform daily activities[21]. KPS scores were categorized into 2 groups: ≤70% (impaired functioning) and 80% to 100% (normal functioning)[15]. The Eastern Cooperative Oncology Group/

TABLE III Details of Local Treatment of Bone Metastasis

Treatment	No. (%) of Patients
Overall	
Radiation therapy	1,041 (68.5)
Surgery only	130 (8.6)
Surgery and adjuvant radiation therapy*	349 (23.0)
Radiation therapy	
1×8 Gy	656 (63.1)
2×8 Gy	83 (8.0)
5×4 Gy	124 (11.9)
6×4 Gy	133 (12.8)
Single fraction other	1 (0.1)
Multiple fractions other	
Total dose of <20 Gy	12 (1.2)
Total dose of ≥20 Gy	20 (1.9)
Unknown	2 (0.2)
Surgery	
Plate	30 (6.3)
Intramedullary nail	317 (66.2)
Endoprosthesis†	106 (22.1)
Dynamic hip screw	8 (1.7)
Resection only	7 (1.5)
Curettage and cement only	2 (0.4)
Unknown	9 (1.9)

*Radiation therapy was considered adjuvant if administered within 8 weeks of surgery. †Including total prosthesis, hemiprosthesis, and modular prosthesis.

World Health Organization (ECOG/WHO) scores, if used, were converted to the corresponding KPS group[22]. If the performance was recorded without use of a scoring system and only by descriptive notes (e.g., good health, vital, or poor status), the descriptions were categorized into the 2 groups by 1 of the authors (J.J.W.).

The presence of visceral metastases was determined on the basis of radiology reports available to the treating physician at the time of decision-making before treatment. If radiology reports were not available or the presence of visceral metastases was genuinely unclear, this was scored as unknown. The same approach was used to assess whether a bone metastasis was a solitary lesion. The presence of brain metastases (including metastases of the central nervous system) was based mainly on clinical reports because whole brain computed tomography (CT) or magnetic resonance imaging (MRI) scans were not routinely performed. Only when the presence was unclear for the treating physicians, was this scored as unknown.

Statistical Analysis

Statistical analyses were performed with the use of SPSS software (version 24.0; IBM).

Survival time was calculated as the difference between the date of first treatment for the bone metastasis and the date of death or latest follow-up. Survival curves were estimated with the Kaplan-Meier method. Median follow-up was estimated with the reversed Kaplan-Meier method[23]. The following variables were used to investigate a possible association with overall survival: clinical profile, KPS, presence of VBM, location of the metastasis, sex, and a solitary metastasis. A multivariate Cox regression model was estimated with the clinical profile, KPS, and the presence of VBM as risk factors. Sex and solitary metastases were not included in the multivariate analysis because they are strongly entwined with specific primary tumors; breast cancer is more common in women, and solitary metastases are more common in kidney cancer. To further analyze the effect of the KPS and the presence of VBM for each clinical profile, the multivariate analysis was stratified for clinical profile. Hazard ratios (HRs) and their corresponding 95% CI were estimated. Not all participating departments provided data for the entire study period. Two variables, "center" and "year of treatment," were included in all Cox regression analyses to account for the presence of heterogeneity among the treatment centers and the time period in which the patient was treated. P values of <0.05 were considered significant. Following the study design by Bollen et al.[15], combinations of the independent prognostic variables led to 12 prognostic categories that were visualized in a flowchart. To compress the 12 categories to a clinically applicable classification, median overall survival results of all categories were compared. As treatment strategies generally differ among an expected survival of <3 months, 3 to 6 months, >6 to 12 months, and >12 months, these cutoff points were applied to narrow the 12 survival categories down to these 4 clinically relevant categories. To assess the discriminatory ability of these categories, the Harrell C-statistic was used[24].

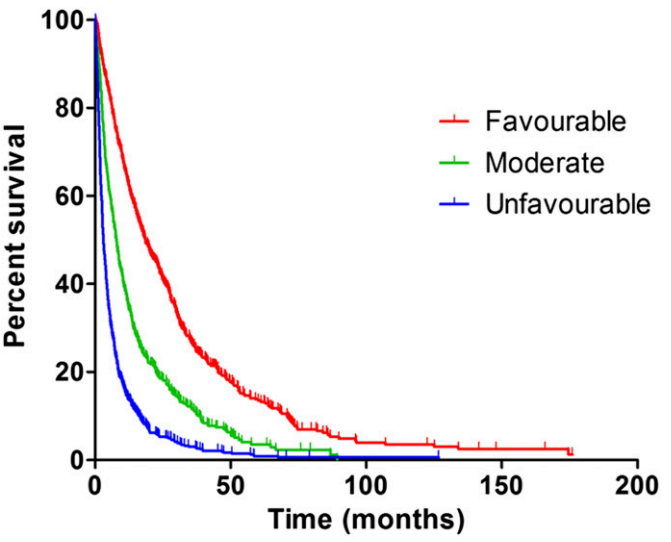

Fig. 1

Kaplan-Meier curve for overall survival stratified by the clinical profile and according to the time (in months) since treatment.

TABLE IV Overall Survival in Months and Percentage of Patients Alive for Each Category

Category	Clinical Profile	KPS	VBM	No.	Overall Survival *(mo)*		Survival at Various Intervals *(%)*					Clinically Relevant Categories*
					Median	95% CI	1 Mo	3 Mo	6 Mo	12 Mo	24 Mo	
1	Favorable	80-100	No	145	30.4	26.8-33.9	97.9	93.1	87.6	81.4	58.4	Green (A)
2	Favorable	80-100	Yes	102	17.9	12.4-23.4	98.0	89.2	78.4	62.7	41.0	Green (A)
3	Favorable	0-70	No	77	12.8	9.5-16.0	94.0	83.1	75.3	53.2	27.3	Green (A)
4	Favorable	0-70	Yes	41	7.4	5.5-9.2	90.2	78.0	65.9	36.6	16.1	Yellow (B)
5	Moderate	80-100	No	108	11.4	8.9-14.0	98.1	88.0	72.2	48.1	24.9	Yellow (B)
6	Moderate	80-100	Yes	66	9.5	5.2-13.9	93.9	78.8	60.8	45.5	23.9	Yellow (B)
7	Moderate	0-70	No	104	5.0	3.7-6.4	88.5	66.3	43.3	21.2	12.4	Orange (C)
8	Moderate	0-70	Yes	37	3.4	2.4-4.4	81.1	54.1	29.7	8.1	0.0	Orange (C)
9	Unfavorable	80-100	No	100	5.4	2.7-8.1	96.0	69.0	49.0	25.0	9.0	Orange (C)
10	Unfavorable	80-100	Yes	109	4.5	3.7-5.3	88.1	62.4	36.7	19.3	8.3	Orange (C)
11	Unfavorable	0-70	No	120	2.2	1.7-2.7	85.0	40.0	23.3	11.4	1.8	Red (D)
12	Unfavorable	0-70	Yes	122	2.2	1.7-2.7	79.5	32.0	10.2	3.4	0.8	Red (D)

*The colors correspond to the 4 clinically relevant categories as seen in Figure 2.

External Cohort

The developed prognostic model was used on an external cohort. The cohort consisted of patients receiving surgical treatment between 2000 and 2013 at an Austrian hospital. Observed and expected survival (based on the external cohort) for each clinical profile at 1, 3, 6, 12, and 24 months were compared.

Results

Baseline characteristics of the patients and metastases are presented in Table I. The most common primary tumor types were breast (33%), lung (24%), prostate (15%), and kidney (8%) (Table II). Indications for treatment were pain (48%) and actual (30%) or impending fractures (23%). The details of the treatment strategies are given in Table III.

Survival

The median follow-up for all patients was 79.1 months (95% CI, 71.0 to 87.2 months). The median overall survival was 7.4 months (95% CI, 6.7 to 8.1 months). The 529 patients (35%) with a favorable clinical profile, 419 (28%) with a moderate profile, and 472 (38%) with an unfavorable profile had a median overall survival of 18.6 months (95% CI, 15.8 to 21.4 months), 7.7 months (95% CI, 6.6 to 8.7 months), and 3.1 months (95% CI, 2.7 to 3.5 months), respectively (Fig. 1).

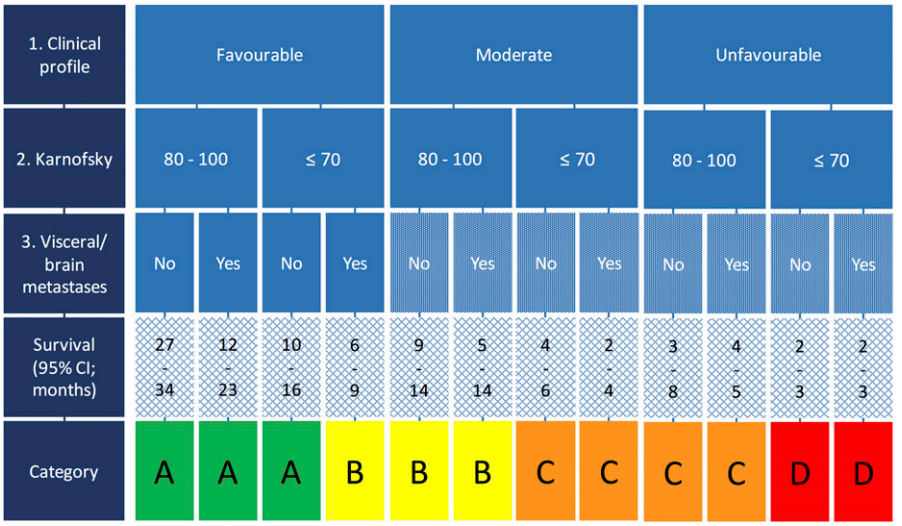

Fig. 2

Flowchart for stratification of patients with LBM.

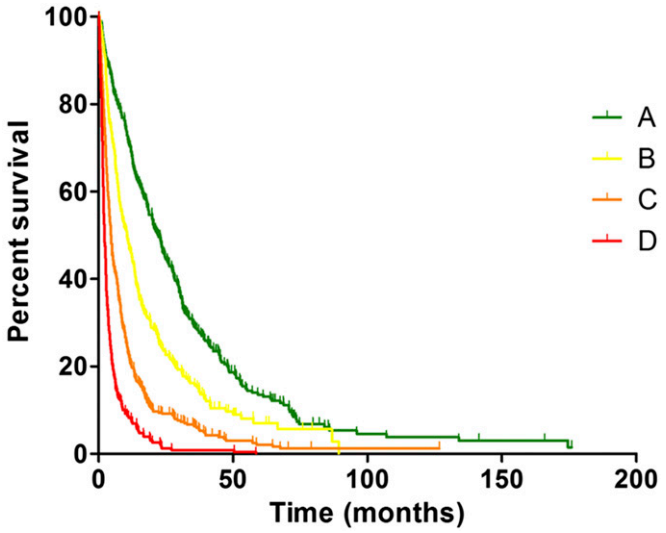

Fig. 3

Kaplan-Meier curve for overall survival stratified by prognostic groups A through D and according to the time (in months) since treatment.

Prognostic Factors

Univariate analyses showed that the clinical profile, KPS, evidence of VBM, a solitary bone metastasis, and sex were significantly associated with overall survival ($p < 0.001$ for all). A multivariate Cox regression analysis was performed on the basis of the 1,131 patients for whom full information was available. The clinical profile (moderate [HR of 1.8; 95% CI, 1.5 to 2.1] or unfavorable [HR of 3.3; 95% CI, 2.8 to 3.8]), a KPS of ≤70 (HR of 2.0; 95% CI, 1.8 to 2.3), and evidence of VBM (HR of 1.4; 95% CI, 1.2 to 1.5) were significantly associated with a higher risk of death. Stratification according to clinical profile in the multivariate analysis showed that a low KPS and evidence of VBM were associated with a shorter survival for all 3 profiles. A KPS of ≤70 doubled the risk of death for all profiles, with an HR of 1.9 (95% CI, 1.5 to 2.4), 2.2 (95% CI, 1.7 to 2.8), and 2.0 (95% CI, 1.7 to 2.5) for a favorable, moderate, and unfavorable clinical profile, respectively. The effect of VBM was the largest in the favorable profile, with an HR of 1.7 (95% CI, 1.3 to 2.1), 1.3 (95% CI, 1.0 to 1.7), and 1.3 (95% CI, 1.0 to 1.5) for a favorable, moderate, and unfavorable clinical profile, respectively.

Prognostic Model

The cohort was divided into 12 categories on the basis of the combination of the 3 prognostic variables. The median survival and survival at 1, 3, 6, 12, and 24 months per category are presented in Table IV. The discriminatory ability of these categories was 0.70. Figure 2 shows the flowchart to guide the stratification of patients with symptomatic LBM, with the corresponding 95% CIs for median overall survival for each category. The 4 clinically relevant categories (A [29% of the patients], B [19%], C [31%], and D [21%]) represent median survival of 21.9 months (95% CI, 18.7 to 25.1 months), 10.5 months (95% CI, 7.9 to 13.1 months), 4.6 months (95% CI, 3.9 to 5.3 months), and 2.2 months (95% CI, 1.8 to 2.6 months), respectively (Fig. 3), with a discriminatory ability of 0.69.

External Cohort

The external cohort included 250 patients (45% were male, with a mean age [and standard deviation] of 66.3 ± 11.4 years) (Table V). The median duration of follow-up and overall survival of the patients in the external data set were 84.7 months (95% CI, 58.4 to 111.1 months) and 7.8 months (95% CI, 6.2 to 9.3 months), respectively. Overall survival rates at 1, 3, 6, 12, and 24 months (after stratification) are given in Table VI. A large difference in overall survival between observed and expected survival was seen for category 5. This was predominantly due to 2 patients in the external cohort with kidney cancer and a long survival of 89 and 110 months.

TABLE V Patient Demographics of External Cohort

Characteristic	
No. of patients	250
Age* *(yr)*	66.3 (11.4)
Sex *(no. [%])*	
Male	112 (44.8)
Female	138 (55.2)
Karnofsky Performance Score† *(no. [%])*	
80-100	79 (31.6)
≤70	171 (68.4)
Visceral metastases† *(no. [%])*	
Present	129 (51.6)
Not present	121 (48.4)
Metastases to brain and/or central nervous system‡ *(no. [%])*	
Present	15 (6.0)
Not present	235 (94.0)
Tumor location *(no. [%])*	
Femur	189 (75.6)
Humerus	39 (15.6)
Tibia	21 (8.4)
Ulna	1 (0.4)
Location in bone *(no. [%])*	
Proximal	162 (64.8)
Shaft	61 (24.4)
Distal	27 (10.8)

*The values are given as the mean, with the standard deviation in parentheses. †As reported in recent radiology reports. ‡Presence of metastases was determined on the basis of recent radiology reports; metastases were considered not present if there was no clinical suspicion of brain metastases (therefore, no radiology).

TABLE VI Overall Survival in Months and Percentage of Patients Alive for Each Category of the Original and External Cohorts (Surgical Patients Only)*

Category	Clinical Profile	KPS	VBM	O/E† *(no. of patients)*	Median Overall Survival (95% CI) *(mo)*		Overall Survival at Various Intervals (O/E) *(%)*				
					Original	External	1 Mo	3 Mo	6 Mo	12 Mo	24 Mo
1	Favorable	80-100	No	48/16	29 (13-47)	25 (1-48)	100/94	92/88	88/88	79/69	58/50
2	Favorable	80-100	Yes	31/8	28 (10-46)	30 (0-64)	97/100	90/88	77/75	61/75	51/50
3	Favorable	0-70	No	28/25	13 (10-16)	7 (1-13)	100/96	89/72	79/60	50/44	29/28
4	Favorable	0-70	Yes	14/24	7 (7-8)	5 (3-6)	93/83	79/63	64/40	29/31	21/18
5	Moderate	80-100	No	25/15	14 (7-21)	33 (13-53)	96/93	80/93	64/93	52/86	28/50
6	Moderate	80-100	Yes	27/12	14 (10-18)	12 (0-63)	93/100	82/92	70/58	56/50	33/50
7	Moderate	0-70	No	19/13	5 (0-10)	9 (1-16)	95/100	74/77	47/62	21/31	16/8
8	Moderate	0-70	Yes	11/28	6 (2-10)	6 (1-10)	91/93	64/68	46/46	18/29	0/21
9	Unfavorable	80-100	No	40/8	7 (0-15)	7 (3-11)	98/100	68/89	50/63	33/31	10/16
10	Unfavorable	80-100	Yes	43/8	5 (2-7)	5 (1-9)	98/88	61/63	40/38	16/25	9/13
11	Unfavorable	0-70	No	33/22	4 (1-6)	4 (1-6)	91/86	52/55	21/27	11/14	0/0
12	Unfavorable	0-70	Yes	34/30	3 (2-3)	3 (1-6)	94/77	41/53	10/18	3/7	0/4

*O = original cohort, and E = external cohort. †Data concerning 1 of the 3 variables were missing for 126 and 41 patients for the original and external cohorts, respectively.

Discussion

To offer patients with cancer and symptomatic LBM the most appropriate and tailored treatment, thus balancing morbidity and adverse effects with effectiveness, an accurate estimation of the expected survival is crucial. The survival estimation should be as precise as possible while obtainable in daily clinical practice. This study shows that a simple and clinically relevant estimation can be made on the basis of the clinical profile, KPS, and presence of VBM.

The prognostic significance of these 3 variables has been reported previously[8-11,13,14]. The primary tumor, which is the basis for the clinical profile in this study, is the foundation of all prognostic models. Performance status is also included in almost all recent models[8-11,13,14]. The role of evidence of VBM is less consistent. Although incorporated in several models[8,10-13], others have stated that the effect of VBM is not[11] or is only partially[15] present. The transition from 12 to 4 categories in the current study shows that, while the presence of VBM is associated with survival in all profiles, the impact on clinical decision-making is minimal. This is in accordance with the spinal metastasis prognostic model by Bollen et al.[15], in which the presence of VBM affects only the favorable clinical profile.

Considering some of the shortcomings of previous prognostic models, the present study aimed to develop a quick and easy-to-use yet accurate prognostic model. The current model is thus based on a multidisciplinary cohort, excludes patients with multiple myeloma, and is up-to-date and easy to use. The clinical profile ensures sustainability of the model because of its dynamic description; it encompasses not only tumor growth speed but also contributing factors, such as the effectiveness of evolving systemic treatments, which allow adjustment of the classification of a primary tumor. The increase of targeted therapies will create subtypes in various primary tumor types in the future, and thus flexibility in the categorization is essential. Future adjustments could be changes in the classification of lung tumors with EGFR (epidermal growth factor receptor) mutations[25], melanomas with BRAF mutations[26], and prostate cancers with low initial prostate-specific antigen (PSA) levels and favorable Gleason scores[27].

The presented flowchart is simple to use; only 3 common variables are required, without the need for scoring. The chart stratifies among 12 different categories that can be narrowed down to 4 clinically relevant categories. The 12 categories provide a detailed insight into the expected survival, which can be helpful knowledge to fine-tune an individual's treatment. The 4 grouped categories (A through D) are based on the cutoff points relevant for more general decision-making (i.e., 3, 6, and 12 months) in a clinical setting and can be used to translate the median survival times to clinical decisions. This more simplistic version of the model could be envisioned without the shaded areas (VBM for moderate and unfavorable clinical profiles, and the 95% CI for the median overall survival) in Figure 2.

An important limitation of the present study is the retrospective design. With this design, uniformity in diagnostics and treatments is not possible. The time frame of diagnostic tests has an influence on the interpretation of the presence of visceral, brain, and other bone metastases. Differences in local treatments between centers and over time are possible. Although a large influence of these factors on survival is not expected, they were incorporated in the multivariate analyses to correct for any possible effect. Systemic treatments were not

taken into account in the analysis because they were beyond the scope of this study. Missing data are also a drawback of retrospective studies. In this study, the KPS was the most common missing variable. This was partly solved by interpreting clinical descriptions, but the latter is also a limitation as it is less objective than a scoring system. Finally, the cohort includes only patients who received local treatment for a symptomatic bone metastasis. This introduces confounding by indication because patients who received solely systemic and/or supportive care were not represented in this study. This might have led to selection bias and possibly to estimations in this study that are too optimistic. Although this could have some influence on the generalizability of the study, the minimal life expectancy for referral for palliative radiation therapy is approximately 2 months, so the effect of selection is expected to be minimal[28].

The discriminatory ability of the model presented in this study (0.70) is comparable with the model recently reported by Westhoff et al.[11]. They described a model that was based only on patients treated with radiation therapy for bone metastases throughout the skeleton and contained 2 variables (primary tumor and KPS) that yielded a C-statistic of 0.71.

It is possible that higher discriminatory abilities might be obtainable in models with numerous variables; however, studies with such models have not noted C-statistics and therefore cannot be compared[12,13,29]. Additionally, it is important to note that the discriminatory ability in the current study is an accepted trade-off against the simplicity, and thus convenience, of the current model in comparison with models with numerous variables. Also, while models with numerous complex variables might be able to discriminate in great detail, it is relevant to wonder whether such models lead to more relevant or better clinical decision-making.

The application of the model to the external cohort shows similar results between observed and expected survival, suggesting that the model stratifies sufficiently in other data sets. Patients with a moderate clinical profile and good KPS (mostly patients with prostate or kidney cancer) showed better survival in the external population. This could be attributed to the heterogeneity of the populations and differences in systemic treatment and local treatment regimens between the 2 countries.

In conclusion, the current study presents a model for easy and accurate stratification of patients with symptomatic LBM according to their expected survival. The versatility of the model enables easy adaptation to future developments concerning systemic treatments of primary tumors. The simplicity of the model should facilitate its use and result in an overall movement toward appropriate treatments of patients with metastases in the long bones to improve their quality of life. ■

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J.J. Willeumier, MD[1]
Y.M. van der Linden, MD, PhD[1]
C.W.P.G. van der Wal, MD[1]
P.C. Jutte, MD, PhD[2]
J.M. van der Velden, MD[3]
M.A. Smolle, BSc[4]
P. van der Zwaal, MD, PhD[5]
P. Koper, MD, PhD[5]
L. Bakri, MD[6]
I. de Pree, MD[7]
A. Leithner, MD[4]
M. Fiocco, PhD[1,8]
P.D.S. Dijkstra, MD, PhD[1]

[1]Departments of Orthopaedic Surgery (J.J.W, C.W.P.G.v.d.W., and P.D.S.D.), Radiotherapy (Y.M.v.d.L.), and Medical Statistics and Bioinformatics (M.F.), Leiden University Medical Centre, Leiden, the Netherlands

[2]Department of Orthopaedic Surgery, University Medical Centre Groningen, Groningen, the Netherlands

[3]Department of Radiotherapy, University Medical Centre Utrecht, Utrecht, the Netherlands

[4]Department of Orthopaedic Surgery, Medical University of Graz, Graz, Austria

[5]Departments of Orthopaedic Surgery (P.v.d.Z) and Radiotherapy (P.K.), Haaglanden Medical Centre, The Hague, the Netherlands

[6]Department of Radiotherapy, Reinier de Graaf Gasthuis, Delft, the Netherlands

[7]Department of Radiotherapy, Erasmus Medical Center, Rotterdam, the Netherlands

[8]Mathematical Institute, Leiden University, Leiden, the Netherlands

E-mail address for J.J. Willeumier: j.j.willeumier@lumc.nl

ORCID iD for J.J. Willeumier: 0000-0002-4591-1532

References

1. Galasko C. The anatomy and pathways of skeletal metastases. In: Weiss L, Gilbert HA, editors. Bone metastasis. Boston: G.K. Hall; 1981. p 49-63.

2. Cancer Research UK. http://www.cancerresearchuk.org/health-professional/cancer-statistics/incidence/all-cancers-combined - heading-1. Accessed 2016 Sep 1.

3. Coleman RE. Clinical features of metastatic bone disease and risk of skeletal morbidity. Clin Cancer Res. 2006 Oct 15;12(20 Pt 2):6243s-9s.

4. Frassica DA. General principles of external beam radiation therapy for skeletal metastases. Clin Orthop Relat Res. 2003 Oct;415(Suppl):S158-64.

5. Bickels J, Dadia S, Lidar Z. Surgical management of metastatic bone disease. J Bone Joint Surg Am. 2009 Jun;91(6):1503-16.

6. Chow E, Harth T, Hruby G, Finkelstein J, Wu J, Danjoux C. How accurate are physicians' clinical predictions of survival and the available prognostic tools in estimating survival times in terminally ill cancer patients? A systematic review. Clin Oncol (R Coll Radiol). 2001;13(3):209-18.

7. Nathan SS, Healey JH, Mellano D, Hoang B, Lewis I, Morris CD, Athanasian EA, Boland PJ. Survival in patients operated on for pathologic fracture: implications for end-of-life orthopedic care. J Clin Oncol. 2005 Sep 01;23(25):6072-82.

8. Forsberg JA, Eberhardt J, Boland PJ, Wedin R, Healey JH. Estimating survival in patients with operable skeletal metastases: an application of a Bayesian belief network. PLoS One. 2011;6(5): e19956

9. Ratasvuori M, Wedin R, Keller J, Nottrott M, Zaikova O, Bergh P, Kalen A, Nilsson J, Jonsson H, Laitinen M. Insight opinion to surgically treated metastatic bone disease: Scandinavian Sarcoma Group Skeletal Metastasis Registry report of 1195 operated skeletal metastasis. Surg Oncol. 2013 Jun;22(2):132-8. Epub 2013 Apr 4.

10. Katagiri H, Okada R, Takagi T, Takahashi M, Murata H, Harada H, Nishimura T, Asakura H, Ogawa H. New prognostic factors and scoring system for patients with skeletal metastasis. Cancer Med. 2014;3(5):1359-67 Oct;3(5):1359-67. Epub 2014 Jul 10.

11. Westhoff PG, de Graeff A, Monninkhof EM, Bollen L, Dijkstra SP, van der Steen-Banasik EM, van Vulpen M, Leer JW, Marijnen CA, van der Linden YM; Dutch Bone Metastasis Study Group. An easy tool to predict survival in patients receiving radiation therapy for painful bone metastases. Int J Radiat Oncol Biol Phys. 2014 Nov 15;90(4):739-47. Epub 2014 Sep 24.

12. Janssen SJ, van der Heijden AS, van Dijke M, Ready JE, Raskin KA, Ferrone ML, Hornicek FJ, Schwab JH. 2015 Marshall Urist Young Investigator Award: prognostication in patients with long bone metastases: does a boosting algorithm improve survival estimates? Clin Orthop Relat Res. 2015 Oct;473(10):3112-21. Epub 2015 Jul 9.

13. Sørensen MS, Gerds TA, Hindsø K, Petersen MM. Prediction of survival after surgery due to skeletal metastases in the extremities. Bone Joint J. 2016 Feb;98-B (2):271-7.

14. Zhang WY, Li HF, Su M, Lin RF, Chen XX, Zhang P, Zou CL. A simple scoring system predicting the survival time of patients with bone metastases after RT. PLoS One. 2016;11(7): e0159506.

15. Bollen L, van der Linden YM, Pondaag W, Fiocco M, Pattynama BP, Marijnen CA, Nelissen RG, Peul WC, Dijkstra PD. Prognostic factors associated with survival in patients with symptomatic spinal bone metastases: a retrospective cohort study of 1,043 patients. Neuro Oncol. 2014;16(7):991-8 Jul;16(7):991-8.

16. Doğer E, Çakiroğlu Y, Özdamar Ö Ceylan Y, Köle E, Yücesoy I, Çaliskan E. Bone metastasis in endometrial cancer: evaluation of treatment approaches by factors affecting prognosis. Eur J Gynaecol Oncol. 2016;37(3):407-16.

17. Ladenstein R, Pötschger U, Le Deley MC, Whelan J, Paulussen M, Oberlin O, van den Berg H, Dirksen U, Hjorth L, Michon J, Lewis I, Craft A, Jürgens H. Primary disseminated multifocal Ewing sarcoma: results of the Euro-EWING 99 trial. J Clin Oncol. 2010 Jul 10;28(20):3284-91. Epub 2010 Jun 14.

18. Bollen L, Wibmer C, Wang M, van der Linden YM, Leithner A, Bünger CE, Jensen AB, Fiocco M, Bratschitsch G, Pondaag W, Bovée JV, Dijkstra PD. Molecular phenotype is associated with survival in breast cancer patients with spinal bone metastases. Clin Exp Metastasis. 2015 Jan;32(1):1-5. Epub 2014 Oct 31.

19. Ratasvuori M, Wedin R, Hansen BH, Keller J, Trovik C, Zaikova O, Bergh P, Kalen A, Laitinen M. Prognostic role of en-bloc resection and late onset of bone metastasis in patients with bone-seeking carcinomas of the kidney, breast, lung, and prostate: SSG study on 672 operated skeletal metastases. J Surg Oncol. 2014;110(4):360-5 Sep;110(4):360-5. Epub 2014 May 29.

20. Laitinen M, Parry M, Ratasvuori M, Wedin R, Albergo JI, Jeys L, Abudu A, Carter S, Gaston L, Tillman R, Grimer R. Survival and complications of skeletal reconstructions after surgical treatment of bony metastatic renal cell carcinoma. Eur J Surg Oncol. 2015;41(7):886-92 Jul;41(7):886-92. Epub 2015 Apr 29.

21. Karnofsky DA. Clinical evaluation of anticancer drugs: cancer chemotherapy. Gann Monogr. 1967;2:223-31.

22. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982 Dec;5(6):649-55.

23. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. Control Clin Trials. 1996 Aug;17(4):343-6.

24. Harrell FE Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med. 1996 Feb 28;15(4):361-87.

25. Ogunleye F, Ibrahim M, Stender M, Kalemkerian G, Jaiyesimi I. Epidermal growth factor receptor tyrosine kinase inhibitors in advanced non-small cell lung cancer a paradigm shift in stage IV non-small cell lung cancer treatment. Am J Hematol Oncol. 2015;11(1);16-25.

26. Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J, Dummer R, Garbe C, Testori A, Maio M, Hogg D, Lorigan P, Lebbe C, Jouary T, Schadendorf D, Ribas A, O'Day SJ, Sosman JA, Kirkwood JM, Eggermont AM, Dreno B, Nolop K, Li J, Nelson B, Hou J, Lee RJ, Flaherty KT, McArthur GA; BRIM-3 Study Group. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med. 2011 Jun 30;364(26):2507-16. Epub 2011 Jun 5.

27. Cheville JC, Tindall D, Boelter C, Jenkins R, Lohse CM, Pankratz VS, Sebo TJ, Davis B, Blute ML. Metastatic prostate carcinoma to bone: clinical and pathologic features associated with cancer-specific survival. Cancer. 2002 Sep 01;95 (5):1028-36.

28. Meeuse JJ, van der Linden YM, van Tienhoven G, Gans RO, Leer JW, Reyners AK; Dutch Bone Metastasis Study Group. Efficacy of radiotherapy for painful bone metastases during the last 12 weeks of life: results from the Dutch Bone Metastasis Study. Cancer. 2010 Jun 01;116(11):2716-25.

29. Piccioli A, Spinelli MS, Forsberg JA, Wedin R, Healey JH, Ippolito V, Daolio PA, Ruggieri P, Maccauro G, Gasbarrini A, Biagini R, Piana R, Fazioli F, Luzzati A, Di Martino A, Nicolosi F, Camnasio F, Rosa MA, Campanacci DA, Denaro V, Capanna R. How do we estimate survival? External validation of a tool for survival estimation in patients with metastatic bone disease-decision analysis and comparison of three international patient populations. BMC Cancer. 2015 May 22;15:424.