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Optimising the treatment of patients with long bone metastases

Willeumier, J.J.

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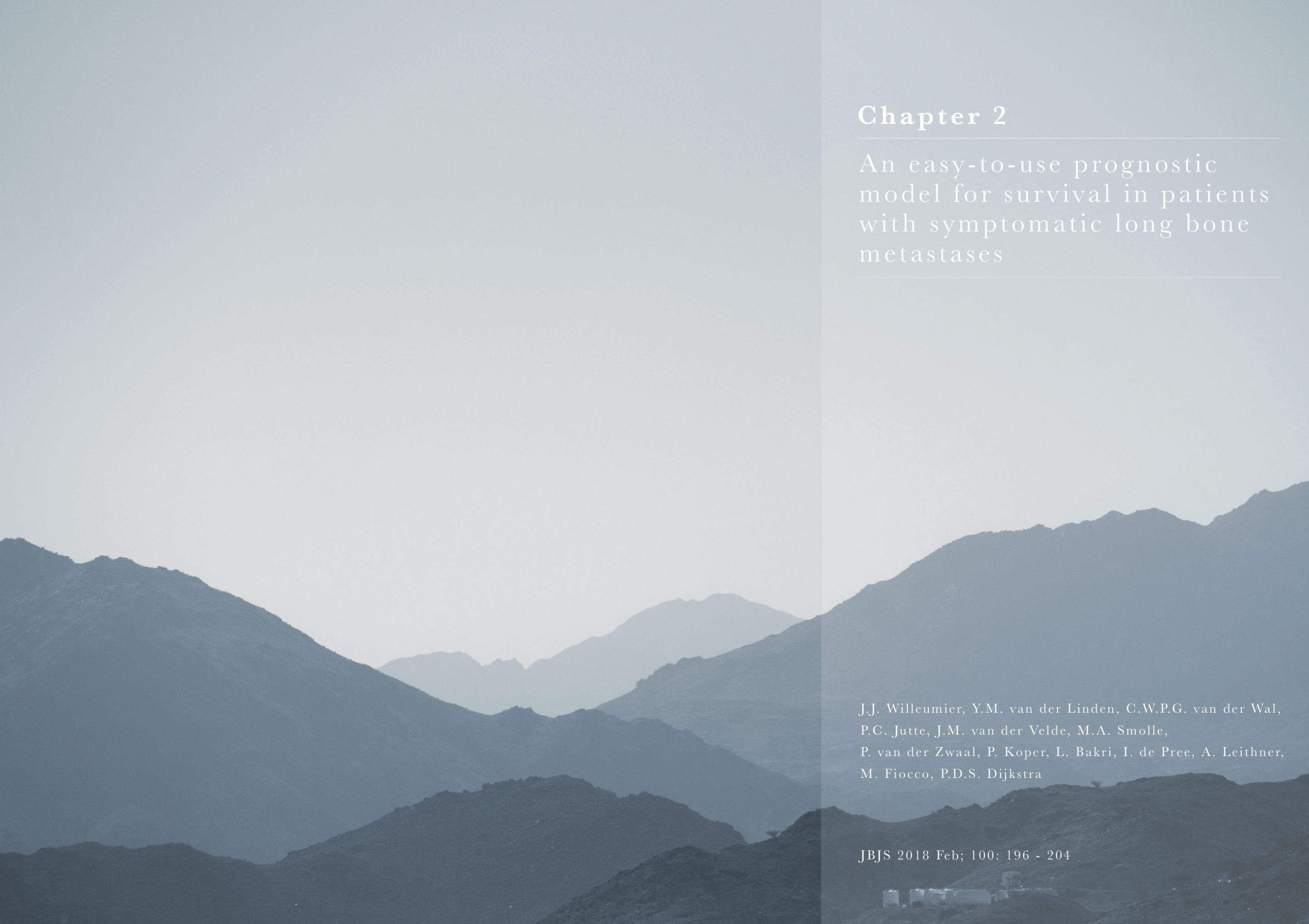


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Author: Willeumier, J.J.

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Chapter 2

An easy-to-use prognostic model for survival in patients with symptomatic long bone metastases

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

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Abstract

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 1520 patients treated for symptomatic LBM between 2000 and 2013 at the radiation therapy and/or orthopedic departments was performed. Primary tumors were categorized into three clinical profiles (favorable, moderate, unfavorable) according to an existing classification system. Associations between prognostic variables and overall survival were investigated by using the Kaplan Meier method and multivariate Cox regression models. The discriminatory ability of the developed model was assessed with Harrell's C-statistic. Observed and expected survival was compared based on an external cohort.

Results

Median overall survival was 7.4 months (95% CI 6.7-8.1). Based on the independent prognostic factors clinical profile, Karnofsky Performance Score, and presence of visceral and/or brain metastases, twelve prognostic categories were created. Harrell's C statistic was 0.70. A flowchart was developed to easily stratify patients. Based on cut-off points for clinical decision-making, the twelve categories were narrowed down to four categories with clinical consequences. Median survival was 21.9 (95% CI 18.7-25.1), 10.5 (95% CI 7.9-13.1), 4.6 (95% CI 3.9-5.3) and 2.2 (95% CI 1.8-2.6) months, for the four categories.

Conclusion

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 routine care of patients with LBM, to provide the most appropriate treatment for each individual patient.

Introduction

Long bone metastases (LBM) are a common occurrence in patients with advanced cancer, arising in up to 70% of the patients with advanced disease.¹ As the prevalence of cancer rises² 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 aims: to reduce pain, preserve the function of the extremities, and maintain or 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, the 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 primary tumour;^{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 work-up (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 lack of sufficient follow-up data regarding final status (alive or dead). After exclusion of 72 patients (no LBM [19], no local treatment [43], duplicate patient [5], or lack of sufficient data [5]), 1520 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 carcinoma¹⁶ and Ewing sarcoma¹⁷ 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: $\leq 70\%$ (impaired functioning) and 80% to 100% (normal functioning).¹⁵ Eastern Cooperative Oncology Group/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 two 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 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 metastasis are more common in kidney cancer. To further analyze the effect of 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% confidence interval (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 between 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

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 2.1. The most common primary tumor types were breast (33%), lung (24%), prostate (15%), and kidney (8%) (table 2.2). Indications for treatment were pain (48%), and actual (30%) or impending fractures (23%). The details of the treatment strategies are given in table 2.3.

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) months, respectively (figure 2.1).

Prognostic factors

Univariate analyses showed that the clinical profile, the KPS, evidence of VBM, a solitary bone metastasis, and sex were significantly associated with OS ($p < 0.001$ for all). A multivariate Cox regression analysis was performed based on the basis of the 1131 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 the presence of VBM were associated with a shorter survival for all 3 profiles. A KPS of ≤ 70 doubled the risk of death in all profiles, with a 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 2.4. The discriminatory ability of these categories was 0.70. Figure 2.2 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 (figure 2.3), with a discriminatory ability of 0.69.

Table 2.1 Patient demographics

Characteristic	
No. of patients	1520
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	1413 (93.0)
Unknown‡	22 (1.4)
Tumor location (no. [%])	
Femur	1029 (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	1066 (70.1)
Shaft	303 (19.9)
Distal	133 (8.8)
Unknown	18 (1.2)
Solitary bone metastasis (no. [%])	
Yes	162 (10.7)
No	1181 (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 on recent radiology reports; metastases were considered not present if there was no clinical suspicion of brain metastases (therefore, no radiology).

Table 2.2 Primary tumors and their corresponding clinical profile

Primary tumor	No. (%) of patients	Median survival (95% CI) (mo)	Overall	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 (1.4)	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, proesterone or Her2/neu positive; †Hormone receptor status and Her2/neu status were unknown; ‡Consisting of 5 patients each with cervical carcinoma and with multiple primary tumors; 2 patients each with Merkel cel 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. Mo: months.

Table 2.3 Details of local treatment of bone metastasis

Treatment	No. (%) of patients
Overall	
Radiation therapy	1041 (68.5)
Surgery only	130 (8.6)
Surgery + adjuvant radiation therapy*	349 (23.0)
Radiation therapy	
1x8 Gy	656 (63.1)
2x8 Gy	83 (8.0)
5x4 Gy	124 (11.9)
6x4 Gy	133 (12.8)
Single fraction other	1 (0.1)
Multiple fractions other:	
Total dose <20 Gy	12 (1.2)
Total dose >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.

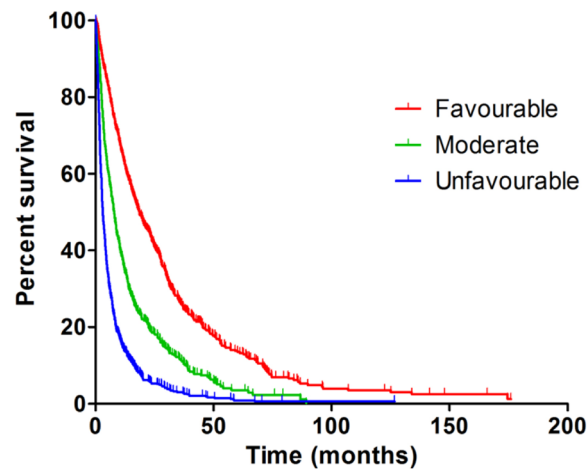


Figure 2.1 Kaplan-Meier curve for overall survival stratified by the clinical profile and according to the time (in months) since treatment.

Table 2.4 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 four clinically relevant categories as seen in figure 2.2. Mo: months.

Table 2.5 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 (68.4)
≤70	171 (31.6)
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 on recent radiology reports; metastases were considered not present if there was no clinical suspicion of brain metastases (therefore, no radiology).

External cohort

The external cohort included 250 patients (45% were male, with a mean age 66.3 [and standard deviation] of 66.3 ± 11.4 years) (table 2.5). The median duration of follow-up and overall survival of the patients in the external dataset 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 2.6. A large difference in overall survival between observed and expected 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.

1. Clinical profile	Favourable				Moderate				Unfavourable			
2. Karnofsky	80 - 100		≤ 70		80 - 100		≤ 70		80 - 100		≤ 70	
3. Visceral/ brain metastases	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
Survival (95% CI; months)	27 34	12 23	10 16	6 9	9 14	5 14	4 6	2 4	3 8	4 5	2 3	2 3
Category	A	A	A	B	B	B	C	C	C	C	D	D

Figure 2.2 Flowchart for stratification of patients with LBM.

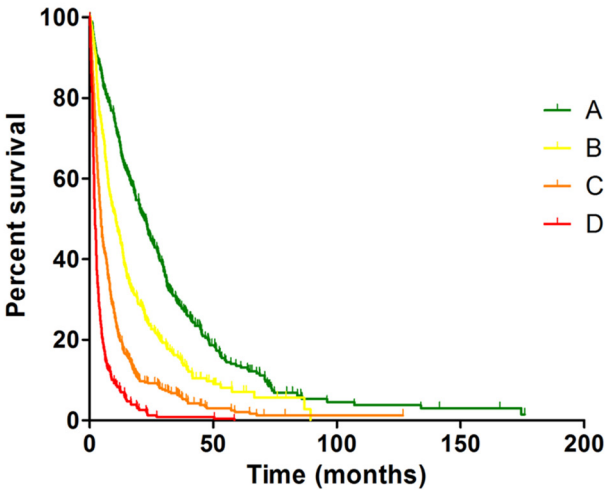


Figure 2.3 Kaplan Meier curve for overall survival stratified by prognostic groups A-D. Time in months since treatment.

Table 2.6 Overall survival in months and percentage of patients alive for each category of the original and external cohort (surgical patients only)*

Category	Clinical profile	KPS	VBM	O/E† (no. of patients)	Median overall survival (95% CI) (mo)		Survival at various intervals (%)					
					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 cohort, respectively. Mo: months.

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 based on clinical profile, KPS, and the 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 the evidence of VBM is less consistent. Although incorporated in several models,^{8,10-13} others state that the effect of VBM is not¹¹ or only partially¹⁵ 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 between 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 individuals' treatment. The 4 grouped categories (A through D) are based on the cutoff points relevant for more general decision-making (i.e. 3, 6, 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 2.2.

An important limitation of the present study is the retrospective design. With this design, uniformity in diagnostics and treatments are 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 to the model recently reported by Westhoff et al. 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 to 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 towards appropriate treatments of patients with metastases of the long bones to improve their quality of life.

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