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Original article

## Palliative radiotherapy: New prognostic factors for patients with bone metastasis



### Radiothérapie palliative : nouveaux facteurs pronostiques pour les patients atteints de métastases osseuses

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#### ABSTRACT

**Purpose.** – Many cancer patients develop bone metastases, however the prognosis of overall survival differs. To provide an optimal treatment for these patients, especially towards the end of life, a reliable prediction of survival is needed. The goal of this study was to find new clinical factors in relation to overall survival.

**Materials and methods.** – Prospectively 22 clinical factors were collected from 734 patients. The Kaplan–Meier and Cox regression models were used.

**Results.** – Most patients were diagnosed with lung cancer (29%), followed by prostate (19.8%) and breast cancer (14.7%). Median overall survival was 6.4 months. Fourteen clinical factors showed significance in the univariate analyses. In the multivariate analyses 6 factors were found to be significant for the overall survival: Karnofsky performance status, primary tumor, gender, total organs affected, morphine use and systemic treatment options after radiotherapy.

**Conclusion.** – Morphine use and systemic treatment options after radiotherapy, Karnofsky performance status, primary tumor, gender and total organs affected are strong prediction factors on overall survival after palliative radiotherapy in patients with bone metastasis. These factors are easily applicable in the clinic.

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#### RÉSUMÉ

**Objectif de l'étude.** – De nombreux patients atteints de cancer souffrent de métastases osseuses, mais la survie globale diffère. Afin d'offrir un traitement optimal, en particulier vers la fin de vie, une prédiction fiable de la survie est nécessaire. L'objectif de cette étude était de trouver de nouveaux facteurs cliniques en relation avec la survie globale.

**Matériel et méthodes.** – Vingt-deux facteurs cliniques ont été collectés prospectivement chez 734 patients. Les modèles de Kaplan–Meier et de régression de Cox ont été utilisés.

**Résultats.** – Le cancer du poumon a été diagnostiqué chez une majorité des patients (29 %), suivi par le cancer de la prostate (19,8 %) et le cancer du sein (14,7 %). La survie globale médiane était de 6,4 mois. Quatorze facteurs cliniques se sont révélés significatifs dans les analyses unifactorielles. Dans les analyses multifactorielles, six facteurs se sont avérés significatifs pour la survie globale : l'indice de Karnofsky, la tumeur primaire, le sexe, le nombre total d'organes touchés, l'utilisation de morphine et les options de traitement systémique après la radiothérapie.

##### Keywords :

Bone metastasis  
Radiotherapy  
Prognostic factors  
Overall survival  
Palliation

##### Mots clés :

Métastase osseuse  
Radiothérapie  
Facteurs de pronostic  
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**Conclusion.** – L'utilisation de morphine et les options de traitement systémique après la radiothérapie, l'indice de Karnofsky, la tumeur primaire, le sexe et le nombre total d'organes touchés sont des facteurs de prédiction importants de la survie globale dans la radiothérapie palliative de patients atteints de métastases osseuses. Ces facteurs sont facilement applicables en clinique.

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## 1. Introduction

Approximately 75% of patients with advanced cancer can develop bone metastasis [1]. These can cause different complaints: pain is the most common and most important, but also pathologic fractures, high calcium level and spinal cord compression with neurological complaints were mentioned in former studies [2–4]. Due to better systemic therapies for most primary tumors, patients with metastatic disease will in general, live longer. But the overall survival of patients with bone metastasis varies a lot and depends mostly on primary tumor and the extensiveness of the metastasis [5,6]. A quick and effective manner of decreasing the symptoms is to treat the patient with radiotherapy. More than half of all the patients who are treated with radiotherapy are radiated with a palliative intent. Several studies show, that approximately 60% of the patients have pain reduction after radiotherapy and approximately 25% of the patients have no pain at all after the radiotherapy. On average there is a pain reduction in 1–4 weeks after radiotherapy. In the last years several studies have shown, including the randomized trial of the Dutch Bone Metastasis Study Group, that there is no significant difference in pain reduction due to the chosen fractionation scheme: a single fraction of 8 Gy, 20 Gy in five fractions, 24 Gy in six fractions or 30 Gy in ten fractions [7–10]. However, for patients, in a later stage of the disease, it is possible that they have insufficient benefit from the radiotherapy [8,11–13]. Due to fact that the life expectancy of patients with bone metastasis is variable, it is important to make a good estimation of survival. Generally, the prediction of patient survival is based on a physician's estimation. Most physicians tend to overestimate the survival of those patients [14,15]. Many patients, who get palliative radiotherapy in the last 30 days of their live do not experience the benefit of the treatment [11,14–16]. To help the physician to determine the best possible treatment for the patient and not over-treat the patient due to a short survival time, prognostic factors are needed. Prognostic factors have been described for patients with oligometastases treated with stereotactic radiotherapy: Milano et al. reported that patients with bone-only oligometastases had a better prognosis than patients with non-bone-only oligometastases [17]. Patients with oligometastatic prostate cancer, treated with stereotactic body radiation therapy had a better prognosis if they were hormone sensitive [18]. From the randomized Dutch Bone Metastasis Study, the following prognostic factors for survival were found: a good Karnofsky score, the use of non-opioid medicine, the absence of visceral metastasis and having more than one bone metastasis [7]. The goal of this prospective study was to find unknown prognostic factors, to guide the choice of the physician.

## 2. Materials and methods

### 2.1. Patient inclusion

Since September 2015 palliative patients who have been referred to the department of radiation oncology of the Erasmus MC Cancer Institute in the Netherlands, were treated at the palliative rapid response clinic. The inclusion criteria for this study were:

patient with bone metastasis and a minimal age of 18 years. Patients who were reirradiated at the same treatment location or had spinal cord compression, were excluded.

This prospective study has been approved by the institutional review board of the Erasmus MC Cancer Institute, with approval number MEC-17-230. These patients gave their consent to participate in this study. Patients were seen by the radiation oncologists and treated, if possible, the same day. During the first consultation by the radiation oncologist patient demographics, medicine use and detailed information about disease status were collected from the patient and the electronic patient record. In total, 734 patients with painful bone metastasis, who were treated between September 2015 and September 2019, were analyzed. The patients were treated with the following fractionation schedules: one fraction of 8 Gy ( $n=422$ ), two fractions of 8 Gy ( $n=148$ ), five fractions of 4 Gy ( $n=125$ ), ten fractions of 3 Gy ( $n=35$ ) and other ( $n=4$ ). These patients were treated with the following irradiation technique: a posteroanterior field or two opposed fields ( $n=381$ ), three-dimensional conformal plans ( $n=237$ ) and volumetric arc therapy or intensity-modulated radiation therapy ( $n=116$ ).

The survival data were retrieved from the medical record, the population register or by contacting the general practitioner. After the first analysis 22 factors were collected with a possible impact on patients survival: gender, age, primary tumor, liver metastasis and lung metastasis, number of organs metastasized, number of metastasis, morphine use, Karnofsky performance status (KPS), residence during radiotherapy of patient, systemic treatment options after radiotherapy, date of first diagnosis, date of metastasis and need of extra care, synchronous metastases, location of metastases, systemic therapy before radiotherapy, curative treatment in history, paraplegia, soft tissue involvement, the risk of fracture and brain metastases. The subdivision for gender was male or female. Age was divided in 0–49, 50–59, 60–69, 70–79, 80–100 years. The primary tumor was breast, prostate, lung, colorectal cancer, multiple myeloma and “other”. For liver metastasis and lung metastasis, morphine use and systemic treatment options after radiotherapy the choice was yes or no. The total number of organs metastasized were divided in one organ, two or three organs and four organs or more, total number of metastasis in one to three, four to ten and more than ten and unknown. Both were determined on CT scan, MRI and/or PET scan. The KPS was divided in less than 80 and at least 80. The date of first diagnosis and first metastasis was divided in 0 to 6 months, 6 months to 3 years and more than 3 years. Extra care was categorized into palliative care unit, mental care, home care, other, none and unknown. Synchronous metastases were compared to metachronous metastases. Soft tissue involvement was scored as yes if there was over 5 cm tumor growth outside the bone. Fracture risk was defined as yes if the SINS score was at least 13 [19].

### 2.2. Statistical analyses

The primary outcome of overall survival was defined as time between date of clinical assessment (date of clinic visit) and date of death. Patients still alive on date of database lock were censored.

**Table 1**  
Study on prediction factors on overall survival after palliative radiotherapy in patients with bone metastasis: study population characteristics (n = 734).

Factor	n (%)
Age: ≥ 65 years	429 (58)
Gender: male	442 (60)
Primary tumor	
Breast	108 (15)
Prostate	145 (20)
Lung	213 (29)
Colorectal	38 (5)
Other	183 (25)
Multiple myeloma	47 (6)
Karnofsky score < 80	439 (60)
Liver metastasis	
Yes	141 (19)
No	553 (75)
Unknown	40 (6)
Lung metastasis	
Yes	302 (41)
No	404 (55)
Unknown	28 (4)
Number of metastases	
≤ 10	276 (38)
> 10	447 (61)
Unknown	11 (1)
Morphine: yes	495 (67)
Date of first diagnosis	
0–6 months	213 (29)
6 months–3 years	263 (36)
□ 3 years	258 (35)
Date of first metastasis	
0–6 months	336 (46)
6 months–3 years	266 (36)
□ 3 years	132 (18)
Chemotherapy after radiotherapy: yes	283 (39)

Median survival estimates were calculated by using the Kaplan–Meier method and the log-rank test was used to test differences between levels of the factors. The Cox proportional hazards model was used to study the effects of the covariates on survival. Hazard ratios (HR) and 95% confidence intervals (CI) for various covariates were obtained by the univariate analyses and covariates with a *P*-value of up to 0.10 were taken into the multivariable analysis where the backward selection method was used with a significance level of  $P \leq 0.05$  to find the combination of factors significantly related to overall survival. Regarding variables with missing values we used list wise deletion. All analyses were performed using IBM SPSS statistics version 25.0 software package (SPSS Inc., Chicago, IL, USA).

### 3. Results

#### 3.1. Patient outcomes

The patient characteristics are listed Table 1. The median age was 68 years. Most patients were diagnosed with lung cancer, followed by prostate cancer, breast cancer and multiple myeloma. The second largest group was “other” and contains mainly patients with kidney, uterus, ovary, cervix cancer, sarcoma and melanoma. The largest part of the patient population had a KPS < 80. Almost half of the patients had metastasis within 6 months after diagnosis. The median overall survival was 6.4 months. At moment of analysis 557 patients had died. The median follow-up was 10.3 months (range: 0.1–51.3 months). Patients with a multiple myeloma had the best one-year survival of 61%, followed by breast cancer 57% and prostate cancer 43%. The one-year survival of “other” 25%, colorectal cancer 20% and lung cancer 18% are less. The median survival is listed in Table 2 per category. Furthermore, Fig. 1 shows the

Kaplan–Meier curves of overall survival based on primary tumor, morphine use, total organs metastatic and KPS.

#### 3.2. Univariate and multivariate analysis

All the results of the univariate analysis are shown in Table 2. The following factors were significant after the univariate analysis: gender, primary tumor, morphine use, liver metastasis and lung metastasis, total organs metastatic, total number of metastasis, date of first metastasis, KPS, systemic treatment options after radiotherapy, place of stay during radiotherapy. A less favorable survival rate is linked with a KPS < 80. Lung cancer had the worst overall survival in comparison with multiple myeloma. A multivariate analysis was performed, six factors remained significant: (1) primary tumor ( $\rho < 0.001$ , HR: 2.54; 95% CI: 1.53–4.22), (2) total organs metastatic ( $\rho < 0.001$ , HR: 0.44; 95% CI: 0.32–0.59), (3) KPS ( $\rho < 0.001$ , HR: 0.48; 95% CI: 0.39–0.59), (4) morphine use ( $\rho = 0.006$ , HR: 1.37; 95% CI: 1.09–1.71), (5) gender ( $\rho = 0.005$ , HR: 0.73; 95% CI: 0.58–0.91), (6) chemotherapy after radiotherapy ( $\rho = 0.078$ , HR: 0.83; 95% CI: 0.67–1.02).

### 4. Discussion

A large number of patients with bone metastasis are referred for palliative radiotherapy to reduce their symptoms. Due to the fact that their survival varies a lot and physicians' estimation generally tends to be too optimistic, particularly patients with a short life expectancy receive an over-treatment in the last 2 months of their lives [12]. The purpose of this study was to find easy achievable prognostic factors, which have a strong influence on the survival of palliative patients with bone metastasis. Potential prognostic factors have already been found in previous research [5,6,20,21]: longer survival is associated with the type of the tumor, a good KPS and the absence of visceral metastasis. Furthermore, blood tests, previous chemotherapy and multiple bone metastases are reported as prognostic factors of survival. Blood test has not been taken into account for this analysis, because it is an invasive procedure and therefore not easy achievable. Beside these already known factors we were looking for other clinical factors as social factors, medication and details of the tumor. As to be expected from former studies, in our multivariate analysis, KPS and primary tumor resulted as prognostic factor for overall survival. Patients with a favorable primary tumor like multiple myeloma, breast or prostate cancer, have a significant better survival. For patients with a multiple myeloma the one-year's survival was 61%, for the breast cancer patients 57% and for the prostate cancer patients 43%. Furthermore, we found that the use or no use of morphine had a one-year's survival of respectively 25% and 47%. The study of Kim et al. recalculated the consumption of analgesics into the daily oral morphine-equivalent dose [22]. In this analysis we did not take the equivalent dose into account. For the total numbers of organs metastatic the 1-year survival rate was 49% for one organ, 30% for two to three organs and 15% for four organs. Patients had a 1-year survival rate of 49% with KPS ≥ 80 and 22% with KPS < 80. Regarding gender, the 1-year survival was 38% if patients were female and 30% if they were male. In case of systemic therapy after radiotherapy the 1-year survival rate was 38% and 22% if there was no option for systemic therapy after radiotherapy. Most studies only made a difference between visceral and brain metastasis or non-bone metastasis. The study by Krishnan et al. distinguished between the different locations of the visceral metastasis and found that liver metastasis had a negative influence on the overall survival [23]. The lung and liver metastasis were significant in our univariate analysis however not in the multivariate analysis. However, we found other, not necessarily tumor related factors, which had a strong influence on the

**Table 2**  
Study on prediction factors on overall survival in palliative radiotherapy of patients with bone metastasis: results of statistical analyses (n = 734).

	n (%)	Kaplan–Meier analysis: median overall survival (months [95% CI])	Cox regression, univariate	
			HR [95% CI]	P
1	Age		1.002 [0.99–1.01]	< 0.001
	0–49 years	49 (6.7%)	11.5 [6.8–16.3]	
	50–59 years	114 (15.5%)	6.2 [3.7–8.7]	
	60–69 years	271 (36.9%)	6.3 [4.5–8.1]	
	70–79 years	213 (29%)	5.8 [4.5–7.0]	
	80–100 years	87 (11.9%)	6.4 [5.1–7.7]	
2	Gender		0.777 [0.66–0.92]	0.004
	Female	292 (40%)	7.4 [5.1–9.5]	
	Male	442 (60%)	5.8 [4.9–6.6]	
3	Primary tumor			< 0.001
	Breast	108 (14.7%)	17.9 [11.8–24.0]	1.32 [0.84–2.09]
	Prostate	145 (19.8%)	9.8 [7.2–12.3]	2.06 [1.34–3.18]
	Lung	213 (29%)	3.5 [2.7–4.3]	4.07 [2.69–6.16]
	Colorectal	38 (5.2%)	6.1 [4.2–8.1]	3.04 [1.81–5.11]
	Other	183 (24.9%)	5.6 [4.6–6.7]	2.95 [1.94–4.49]
	Multiple myeloma	47 (6.4%)	25.4 [4.9–46.0]	
4	Karnofsky performance score		0.71 [0.66–0.78]	< 0.001
	100–80	295 (40.2%)	11.5 [8.8–14.1]	
	< 80	439 (59.8%)	4.3 [3.8–4.8]	1.95 [1.64–23.2]
5	Liver metastasis		0.777 [0.65–0.94]	0.08
	Yes	141 (19.3%)	4.0 [3.0–5.0]	
	No	553 (75.5%)	7.1 [5.8–8.3]	
	Unknown	40 (5.2%)	5.1 [2.9–7.2]	
6	Lung metastasis		0.675 [0.58–0.79]	< 0.001
	Yes	302 (41.2%)	4.4 [3.8–5.0]	
	No	404 (55%)	9.4 [7.7–11.1]	
	Unknown	28 (3.8%)	4.3 [2.8–5.7]	
7	Number of organs		1.16 [1.11–1.23]	< 0.001
	1 organ	212 (28.9%)	11.7 [8.8–14.6]	
	2 or 3 organs	393 (53.5%)	5.8 [4.9–7.9]	
	4 organs	121 (16.5%)	3.2 [4.0–6.3]	
	Unknown	8 (1.1%)	10.9 [0–23.8]	
8	Number of metastases		1.17 [1.09–1.25]	< 0.001
	1–3	67 (9.1%)	18.2 [8.1–28.3]	
	4–10	209 (28.5%)	7.5 [5.8–9.2]	
	> 10	447 (60.9%)	5.7 [4.8–6.6]	
	Unknown	11 (1.5%)	2.4 [1.5–3.2]	
9	Morphine		0.91 [0.87–0.95]	< 0.001
	Yes	495 (67.4%)	4.9 [4.1–5.7]	
	No	171 (23.3%)	10.2 [7.0–13.4]	
	Unknown	68 (9.3%)	15.9 [8.5–23.3]	
10	Extra care		1.049 [1.01–1.09]	< 0.001
	Palliative care	3 (0.4%)	12.3 [0–30.5]	
	Mental care	3 (0.4%)	7.4 [0–18.5]	
	Home care	41 (5.6%)	3.2 [2.0–4.5]	
	Other	14 (1.9%)	6.0 [0–19.8]	
	None	345 (47.3%)	8.8 [7.2–10.4]	
	Unknown	324 (44.4%)	4.8 [3.8–5.8]	
11	Date of first diagnosis		0.796 [0.72–0.88]	< 0.001
	0–6 months	213 (29%)	4.6 [3.3–5.9]	
	6 months–3 years	263 (35.8%)	5.2 [4.3–6.1]	
	> 3 years	258 (35.1%)	10.5 [8.7–12.4]	
12	Date of first metastasis		0.814 [0.73–0.91]	< 0.001
	0–6 months	336 (45.8%)	5.2 [4.4–6.2]	
	6 months–3 years	266 (36.2%)	6.7 [5.5–7.8]	
	> 3 years	132 (18%)	11.5 [7.9–15.2]	
13	Place of stay		1.03 [1.00–1.07]	0.011
	Home	581 (79.6%)	6.7 [5.8–7.7]	
	Hospice and other	111 (15.2%)	2.9 [1.6–4.2]	
	Unknown	38 (5.2%)	8.3 [4.0–12.5]	
14	Systemic treatment after radiotherapy		1.096 [1.00–1.20]	0.034
	Yes	283 (38.7%)	7.4 [5.9–8.9]	
	No	180 (24.6%)	5.1 [4.3–5.9]	
	Unknown	268 (36.7%)	5.8 [4.4–7.1]	
15	Location		0.87 [0.88–1.16]	0.698
	Other	374 (51%)	6.6 [5.4–7.7]	
	Vertebrae	321 (43.7%)	6.2 [5.1–7.3]	
	Sacrum	39 (5.3%)	9.2 [2.3–16.1]	
16	Systemic therapy before radiotherapy		1.03 [0.90–1.19]	0.526
	Yes	226 (30.8%)	7.4 [5.7–9.1]	
	No	431 (58.7%)	5.8 [4.9–6.7]	
	Unknown	45 (6.1%)	6.2 [1.2–11.1]	
	Immunotherapy	32 (4.4%)	6.0 [2.9–9.1]	

Table 2 (Continued)

		n (%)	Kaplan–Meier analysis: median overall survival (months [95% CI])	Cox regression, univariate	
				HR [95% CI]	P
17	Synchronous metastases			0.90 [0.78–1.05]	0.296
	Yes	423 (57.9%)	5.8 [4.8–6.8]		
	No	305 (41.8%)	7.5 [5.8–9.3]		
18	Unknown	2 (0.3%)	1.2	1.07 [0.97–1.18]	0.212
	Curative treatment in history				
	Yes	309 (42.3%)	7.5 [5.9–9.1]		
19	No	418 (57.2%)	5.7 [4.7–6.8]	1.03 [0.92–1.16]	0.714
	Unknown	4 (0.5%)	2.1 [0–9.6]		
	Paraplegia				
20	Yes	6 (0.8%)	3.3 [0.9–5.7]	1.02 [0.96–1.10]	0.467
	No	720 (98.2%)	6.4 [5.7–7.2]		
	Unknown	7 (1%)	6.6 [4.1–9.1]		
21	Soft tissue involvement			1.03 [0.97–1.09]	0.101
	Yes	226 (30.9%)	6.1 [4.3–7.8]		
	No	448 (61.3%)	6.5 [5.8–7.3]		
22	Unknown	20 (2.7%)	5.9 [0.6–11.3]	0.682 [0.49–0.95]	0.076
	Risk of fracture				
	Yes	297 (40.7%)	6.6 [5.7–7.6]		
22	No	412 (56.4%)	6.4 [5.2–7.6]	0.682 [0.49–0.95]	0.076
	Unknown	21 (2.9%)	6.2 [4.7–7.6]		
	Brain metastases				
22	Yes	41 (5.6%)	4.9 [3.6–6.2]	0.682 [0.49–0.95]	0.076
	No	691 (94.1%)	6.6 [5.7–7.5]		
	Unknown	2 (0.3%)	10.7		

HR: hazard ratio; CI: confidence interval. Bold characters :  $p \leq 0.05$  was considered as significant.

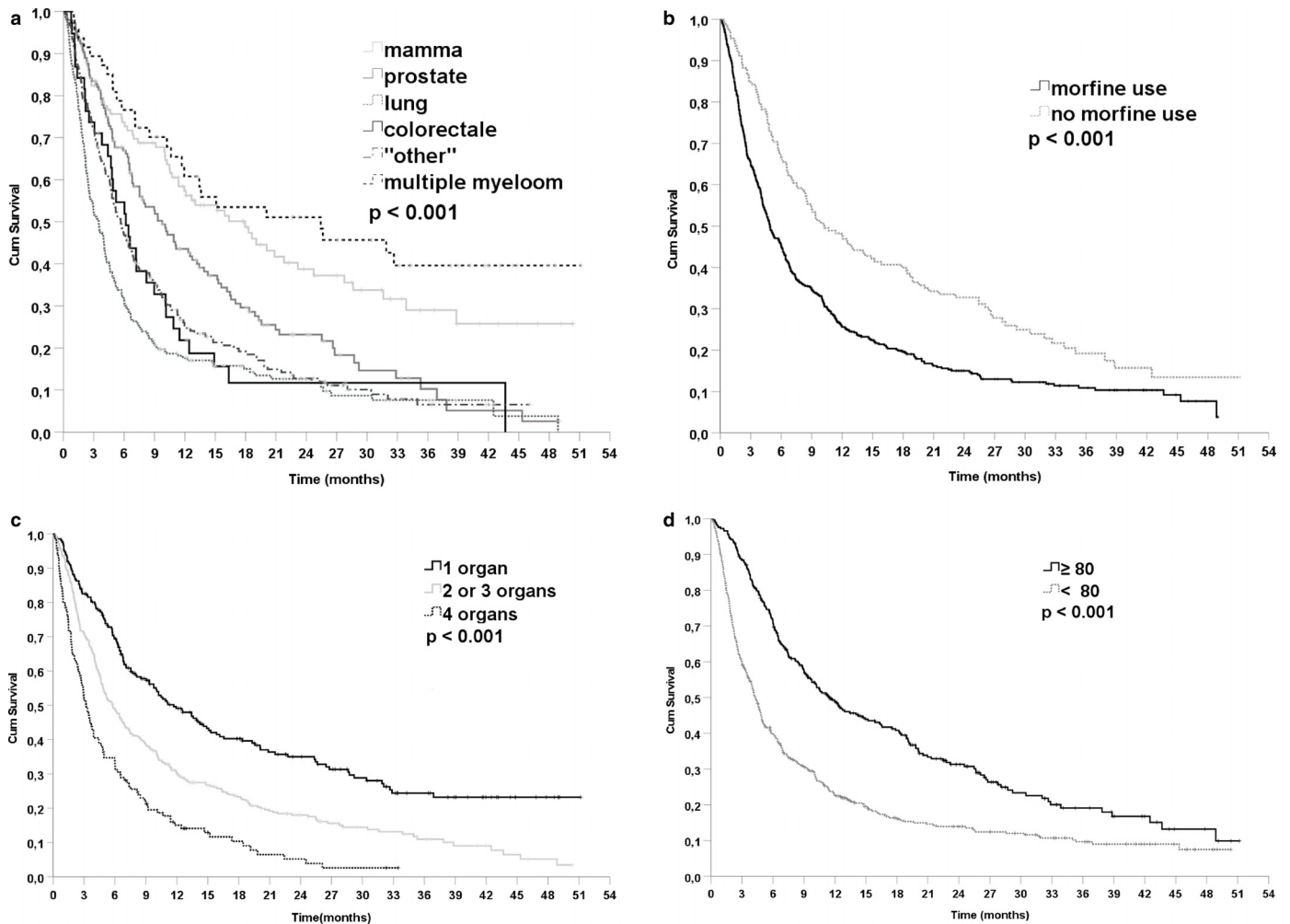


Fig. 1. Overall survival of patients with bone metastasis based on primary tumor (a), morphine use (b), total organs metastatic (c) and Karnofsky score (d) ( $n = 734$ ).

overall survival. These factors were “place of stay” during the radiotherapy treatment, whether morphine is used or not and systemic therapy treatment after radiotherapy. These factors had not been taken in to account in former analysis as far as we know. Systemic therapy after radiotherapy is a whole new factor and based on decisions made in tumor boards regarding the further treatment of the patient. This study has also its limitations. Different factors from other studies, which are important for the overall survival have not been taken into account in this study such as weight loss, cachexia, cognitive impairment or delirium [24]. Cognitive impairment or delirium have not been taken into account due to the fact that these patients are usually not treated with palliative radiotherapy, because of a certain level of understanding is needed to undergo the treatment. But, the great advantage of this study is that the prospectively collected data, represents a large group of patients, which reflects the real life. Furthermore, a long follow-up time was realized for a vulnerable group of patients.

## 5. Conclusion

We found six factors in the multivariate analyses wherefrom two factors: morphine use and systemic treatment options after radiotherapy, were found in this multivariate analyses and were not found in earlier studies. These factors are easy achievable and therefore useable in daily practice. The four other factors: KPS, gender, number of organs affected, and primary tumor had already been found in former studies. The median survival for patients with bone metastases was 6.4 months with a large variation. Therefore, it is important to know which factors can be monitored to prognosticate the overall survival.

## Disclosure of interest

The authors declare that they have no conflict of interest.

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