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Predicting survival in patients with spinal bone metastases

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Predicting survival in patients with spinal bone metastases

Proefschrift

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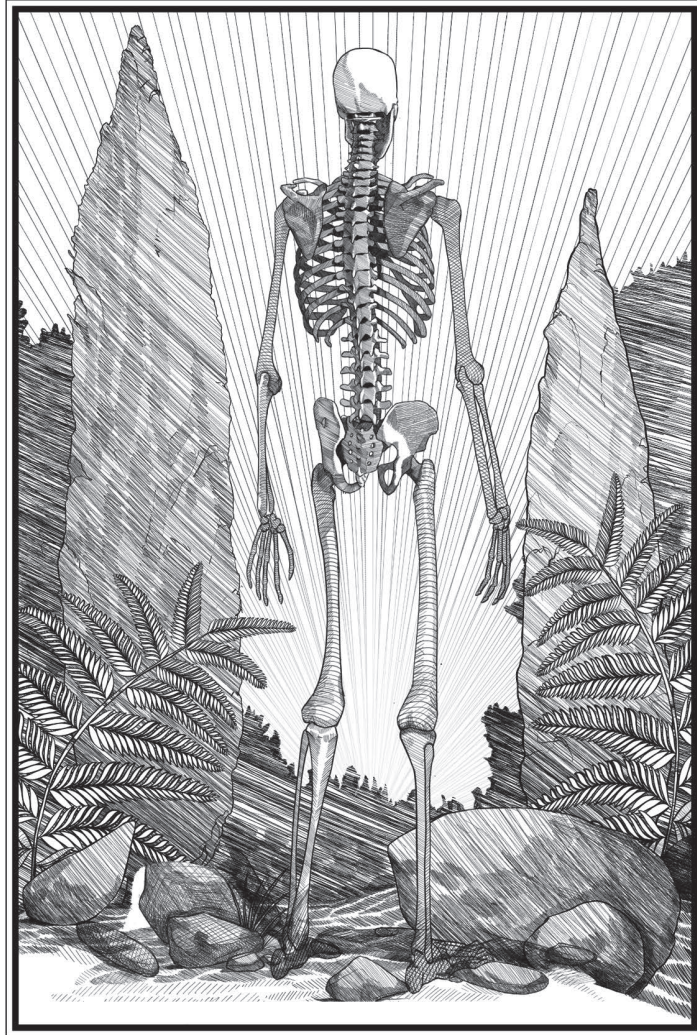
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Voor mijn ouders

CONTENTS

Chapter I	General introduction	9
Chapter II	A systematic review of prognostic factors predicting survival in patients with spinal bone metastases. L Bollen, WCH Jacobs, YM van der Linden, O van der Hel, W Taal, PDS Dijkstra. Eur Spine J. 2018;27(4):799-805.	17
Chapter III	Risk factors for survival in 106 surgically treated patients with symptomatic spinal epidural metastasis. L Bollen, GCW de Ruiter, W Pondaag , MP Arts, M Fiocco, TJT Hazen, WC Peul, PDS Dijkstra. Eur Spine J. 2013;22(6):1408-1416.	31
Chapter IV	Prognostic factors associated with survival in patients with symptomatic spinal bone metastases: a retrospective cohort study of 1043 patients. L Bollen, YM van der Linden, W Pondaag, M Fiocco, BPM Pattynama, CAM Marijnen, RGHH Nelissen, WC Peul, PDS Dijkstra. Neuro oncol. 2014;16(7):991-998.	49
Chapter V	Molecular phenotype is associated with survival in breast cancer patients with spinal bone metastases. L Bollen, C Wibmer, M Wang, YM van der Linden, A Leithner, CE Bünger, AB Jensen, M Fiocco, G Bratschitsch, W Pondaag, JVMG Bovée, PDS Dijkstra. Clin Exp Metastasis. 2015;32(1):1-5.	69

Chapter VI	Predictive value of six prognostic scoring systems for spinal bone metastases – An analysis based on 1379 patients. L Bollen, C Wibmer, YM van der Linden, W Pondaag, M Fiocco, WC Peul, CAM Marijnen, RGH Nelissen, A Leithner, PDS Dijkstra. Spine. 2016;41(3):155-62.	81
Chapter VII	Clinical evaluation of the Spinal Instability Neoplastic Score in patients treated with radiotherapy for symptomatic spinal bone metastases. L Bollen, K Groenen, W Pondaag, CSP van Rijswijk, M Fiocco, YM van der Linden, PDS Dijkstra. Spine. 2017;42(16):956-962.	97
Chapter VIII	General summary	113
Chapter IX	General discussion	117
Addendum	- Nederlandse samenvatting	129
	- List of publications	132
	- Curriculum vitae	135
	- Acknowledgements	136



CHAPTER I

General introduction

Updated and Adapted from:
L Bollen, YM van der Linden, RHMA Bartels, PDS Dijkstra.
The treatment of patients with spinal metastases in the Netherlands.
Ned Tijdschr Oncol 2012;9:81-8.

INTRODUCTION

Due to a rise in the incidence of malignant disease, as well as increased overall survival rates of patients with cancer, the incidence of metastatic disease is on the rise.¹⁻⁴ Following lung and liver, bone is the third most common site of metastatic spread⁵ and, depending on the extent and location, can be the cause of pain, pathologic fractures and neurologic deficit, resulting in a reduced quality of life.

Bone metastases are most commonly caused by breast, prostate and lung cancer. Other, less frequently observed primary malignancies are colorectal, kidney and upper-gastrointestinal cancers.⁶ Depending on the primary tumor causing the bone metastasis, the lesions can have a lytic, sclerotic or mixed appearance. The spinal column is the most frequently affected by bone metastases, followed by the long bones and pelvis.^{7,8}

Several types of spinal metastases are recognized. Intramedullary metastases are located within the spinal cord itself, whereas leptomeningeal metastases are located within the subarachnoid space. These types of spinal metastases are quite rare and are usually seen in end-stage disease. Spinal epidural metastases are located on the outside of the dura mater and the vast majority originates from the osseous parts of the spinal column.

In 90-95% of patients with spinal bone metastases (SBM), pain is the first presenting symptom.^{9,10} Patients can experience pain either due to fracturing or collapse of the vertebral body, pressure on the periosteum from within the vertebra, or nerve root compression. Neurologic deficit due to SBM mainly presents as sensory or motor deficit through nerve root compression, but in its most severe form, SBM can compromise the spinal cord or cauda equina, leading to paraplegia or cauda syndrome. This occurs approximately in 3% of patients with SBM¹¹ and can be an indication for emergency treatment with either radiotherapy or surgery.

Magnetic Resonance Imaging (MRI) is the modality of choice for demonstrating SBM (figure 1). It is capable of showing osseous metastatic disease, as well as providing essential information on spinal cord and nerve root compression.¹²⁻¹⁴ Both T1 and T2 weighted images are necessary, preferably in both axial and sagittal planes.^{15,16} SBM are generally hypo-intense on T1 weighted images and,

depending on their lytic or blastic characteristics, can be hyper- or hypo-intense on T2 weighted images, respectively. Gadolinium enhancement is not required for demonstrating SBM, however, leptomeningeal metastatic disease can be missed without the addition of contrast. Computed Tomography (CT) is required for surgical or radiotherapy planning, if an indication for treatment is present. Conventional X-ray has little added value in the diagnostic phase, but can be helpful in a post-operative setting. If the primary tumor is unknown at the time of diagnosis of the SBM, PET-CT imaging should be performed, complemented with a biopsy of one of the suspect lesions. Timing of all investigations should depend on the presence or absence of any neurologic symptoms requiring emergency treatment.



Figure 1. CT-scan versus T1-weighted MRI. Notice the hypo-intense lesion in the vertebral body of Th11 on MRI, which cannot be seen on the CT-scan

TREATMENT OF SPINAL BONE METASTASES

Therapy for symptomatic SBM consists of a local treatment through radiotherapy or surgery, or a combination of both, combined with adequate pain medication and – in the case of neurological deficit caused by spinal cord or nerve root compression – corticosteroids. Generally speaking, treatment will be palliative in nature and aimed at alleviating the aforementioned symptoms and achieving local control of the metastasis, thereby improving, or at least stabilizing the quality of life of the patient.

Radiotherapy is considered the cornerstone of treatment, achieving a 60-80% decline in pain and improving neurologic symptoms in 10-90% of cases.¹⁷⁻²⁰ The major benefit is that it is non-invasive and any side-effects are generally transient

in nature and well tolerated. The downside is that the effects take several days to weeks to become apparent, making it inferior to surgery in the acute setting of severe neurological deficits. Also, radiotherapy is not indicated in the case of spinal instability, as this would require surgical fixation for proper management. Surgical techniques range from minimal invasive options to en-bloc resection of the affected spinal segments. Vertebroplasty, kyphoplasty or percutaneous pedicle screw fixation can also be combined with radiofrequency ablation (RFA) in order to achieve better local control. Open techniques include decompressive surgery and corpectomies, which should always be followed by fixation of the spinal column in order to ensure stability. Even though these techniques are highly effective in achieving local control and alleviating or avoiding neurologic symptoms, the complication rate is high (20-33%)²¹ and recovery from major surgery can be especially challenging in this fragile patient population. Therefore careful patient selection with a focus on extent of disease, life expectancy and patient preference is needed in order to avoid overtreatment.

PROGNOSTIC MODELS

Prediction of survival has become an integral part of selecting the appropriate treatment for patients suffering from symptomatic spinal bone metastases (SBM). Depending on the symptoms, patients with a short expected survival are most likely to benefit from short radiotherapy regimens, best supportive care or minimally invasive surgery. Patients with a relatively long expected survival could in some cases benefit from high dose radiotherapy or – in the case of radioresistant tumors and biomechanical instability – more extensive surgical interventions. Several studies have shown that the estimation of survival by clinicians in terminally ill patients is inaccurate and have suggested the use of prognostication models in order to prevent exposure of patients to unnecessarily extensive treatments.²²⁻²⁴ Models to aid in the decision making process have been developed by Tokuhashi, Tomita and Van der Linden, amongst others.²⁵⁻²⁷ These models encompass prognostic factors such as primary tumor type, amount and location of spinal metastases, presence of visceral, brain and extraspinal bone metastases, functional status and neurological status. However, clinical applicability seems limited due to over- or under treatment and especially when predicting short survival the existing models fall short.^{28,29}

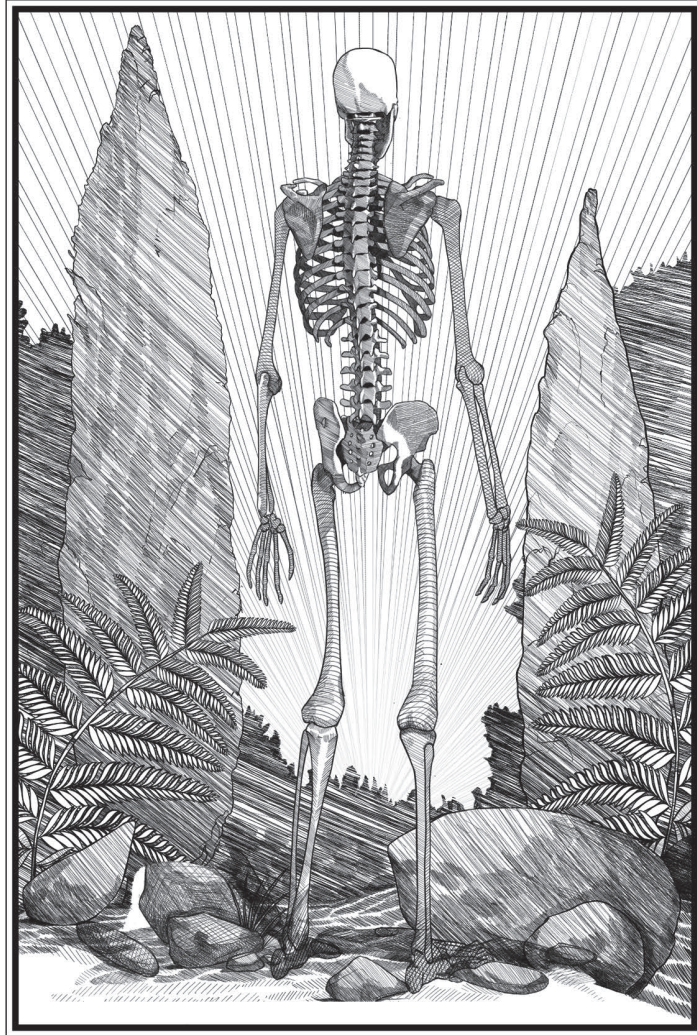
THESIS OUTLINE

Given the problems of patient selection described above, the primary aim of this thesis was to provide clinicians an accurate and easy to use risk stratification tool for survival, in order to guide clinical decision making. **Chapter II** presents a systematic review of risk factors for estimating survival in patients with SBM. Available literature over a period of sixteen years was studied and a level of evidence synthesis was performed to provide an insight into which risk factors are essential for accurate patient selection. **Chapter III** investigates the effect of risk factors on survival for surgically treated patients and gives an overview of postoperative complications. **Chapter IV** is the focal point of this thesis and describes a large retrospective series of patients treated with radiotherapy and/or surgery for symptomatic SBM. In this chapter the clinical model to assess survival is developed and validated on an external dataset. **Chapter V** provides an adjustment of the prognostic model presented in the previous chapter. It aims to further specify the most important risk factor *primary tumor* into more accurate subgroups. All available patients with SBM from breast cancer were stratified based on the molecular phenotype, resulting in a more accurate classification for this specific patient category. **Chapter VI** discusses the performance of the model presented in chapter IV and several other models available in the literature, based on an external dataset. Next to estimation of survival, assessing stability of the spine in metastatic disease is one of the major challenges in patient management. The Spinal Instability Neoplastic Score (SINS) provides a framework to guide clinicians and in **Chapter VII** the clinical applicability of the SINS is investigated. Finally, a general summary of this thesis is provided in **Chapter VIII** and conclusions, clinical implications and future perspectives are discussed in **Chapter IX**.

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CHAPTER II

A systematic review of prognostic factors predicting survival in patients with spinal bone metastases

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ABSTRACT

Purpose. For the selection of treatment in patients with spinal bone metastases (SBM), survival estimation plays a crucial role in order to avoid over- and undertreatment. To aid clinicians in this difficult task, several prediction models have been developed, consisting of many different risk factors. The aim of this systematic review was to identify prognostic factors that are associated with survival in patients with SBM in order to support development of predictive models.

Methods. A systematic review was performed with focus on prognostic factors associated with survival in patients with SBM. Two reviewers independently selected studies for inclusion and assessed the risk of bias. A level of evidence synthesis was performed for each prognostic factor. Inter-observer agreement for the risk of bias assessment was determined by the kappa-statistic.

Results. After screening, 142 full-text articles were obtained, of which 22 met the eligibility criteria. A total of 43 different prognostic factors were investigated in the included studies, of which 17 were relevant to pre-treatment survival estimation. The prognostic factors most frequently associated with survival were the primary tumor and the performance status. The prognostic factors most frequently not associated with survival were age, gender, number and location of the SBM and the presence of a pathologic fracture.

Conclusion. Prognostication for patients with SBM should be based on an accurate primary tumor classification, combined with a performance score. The benefit of adding other prognostic factors is doubtful.

INTRODUCTION

Spinal bone metastases (SBM) are a frequently observed complication of malignant disease. Due to an increase in the survival times of patients with malignancies, the incidence of SBM is expected to rise over the years.^{1,2} The majority of symptomatic SBM are caused by breast, prostate and lung cancer (56-74%)^{3,4,5} and most commonly arise from the thoracic part of the spine (51-67%).^{4,6} Patients present with pain due to destruction of bone tissue and/or and neurologic complaints due to nerve root and/or spinal cord compression.^{7,8} Both radiotherapeutical and surgical interventions are effective in treating these symptoms. However, due to the relatively short life expectancy of these patients, overtreatment is a common problem. Therefore, an accurate estimation of survival plays a pivotal role in selecting the appropriate treatment. Survival estimation by clinicians has been shown to be too optimistic⁹ and to provide an aid for this difficult task, several prediction models have been developed.^{4,8,10,11} These models employ different sets of prognostic factors such as performance score, primary tumor and the presence of visceral metastases to stratify patients with SBM according to survival risk, enabling clinicians to select a more appropriate treatment. Several studies have been undertaken to assess the prognostic value of these models and the factors being used.^{12,13} The aim of this systematic review was to identify prognostic factors that are associated with survival in patients with spinal bone metastases in order to help guide development of predictive models.

METHODS

Search strategy

The review protocol for this study was prospectively registered online at PROSPERO under registration number CRD42014006706 (www.crd.york.ac.uk/prospero). The search strategy was formulated in collaboration with a medical librarian to focus on the key terms survival, prognostic factors and spinal bone metastases, or variations thereof. The electronic databases Medline, Embase, Web of Science, Cochrane and Cinahl were searched from January 1999 up to September 2014. The complete search strategy is available as an online supplement.

Eligibility criteria

Both prospective and retrospective studies were eligible for inclusion if they met the following criteria: (1) Sample size of at least 100 patients with spinal bone metastases from solid tumors (i.e. no hematological malignancies); (2) The study did not focus on one single primary malignancy; (3) Prognostic factors for survival were assessed by means of a multivariate analysis; (4) Studies were published in the English, German or Dutch language. If studies were derived from identical databases, the most comprehensive study was selected; separately published subgroup analyses were disregarded. Eligibility of studies was assessed by two independent review authors (W.J. and L.B.). A consensus meeting was planned to resolve disagreements. If disagreements persisted, a third review author (P.D.S.D.) was consulted.

Risk of bias

The risk of bias was assessed according to the guidelines provided by Hayden et al.¹⁴ In short, six main sources of potential bias (study participation, study attrition, prognostic factor measurement, outcome measurement, confounding and analysis) were assessed using a 29-item checklist. The six sources of bias were scored as being 'high; 3 points', 'moderate; 2 points', or 'low; 1 point'. Therefore, the total number of points for each study ranged from 6-18, with a cut-off set at a maximum of 50% (≤ 9 points) for distinguishing a low risk of bias study from a high risk of bias study. Two review authors (W.J. and L.B.) independently scored the risk of bias for each study. A consensus meeting was planned to resolve disagreements. If disagreements persisted, a third review author (P.D.S.D.) decided on the risk of bias.

Data extraction

The data extracted from eligible studies consisted of the design, source of funding, setting, sample size, duration, inclusion and exclusion criteria, all prognostic factors investigated, duration of follow-up and results. If similar prognostic factors were investigated by different means, they were combined for the level of evidence analysis. For instance, the prognostic factor *Performance status* was assessed by means of the Karnofsky score¹⁵ or the Eastern Cooperative Oncology Group score.¹⁶ Other combined prognostic factors were *Neurologic deficit*; consisting of the Frankel score¹⁷ and ambulatory status, as well as the variable *Primary tumor*; consisting of several different sub classifications. Prognostic factors such as *Age*

and *Number or location of SBM* were also combined irrespective of any differences in cut-off points used. Two review authors (O.H and L.B.) extracted the data on standardized forms. When consensus could not be reached a third review author (P.D.S.D.) was consulted.

Statistical analysis

Statistical pooling of the results was not possible; therefore a level of evidence synthesis was performed for each prognostic factor. The levels of evidence were defined as follows:^{18,19}

- Strong evidence: consistent findings ($\geq 75\%$) in multiple high-quality cohorts.
- Moderate evidence: consistent findings ($\geq 75\%$) in multiple cohorts, of which only one cohort was of high quality.
- Limited evidence: findings of one high-quality cohort, or consistent ($\geq 75\%$) findings in one or more low-quality cohorts.
- Inconclusive: inconsistent findings ($< 75\%$) irrespective of study quality.

Inter-observer agreement for the risk of bias assessment was determined by the kappa-statistic²⁰. All analyses were performed using SPSS 20.0, Armonk NY, IBM Corp.

RESULTS

Study selection

The initial search yielded 4676 results (Medline n=1996; Embase n=1389; Web of Science n=1092; Cochrane n=145; Cinahl n=54). A total of 1687 duplicates were removed, leaving 2989 studies. After screening, 142 full-text articles were obtained, of which 120 did not meet the eligibility criteria: 33 studies were based on duplicate cohorts, 49 studies focused on a single primary tumor, 23 studies had less than 100 participants, 13 studies did not perform a multivariate analysis and two studies were excluded based on language. In total, 22 studies were included (figure 1).^{3,4,5,6,8,21-37} During the selection process, the reviewers disagreed on seven inclusions. Consensus was reached for all studies.

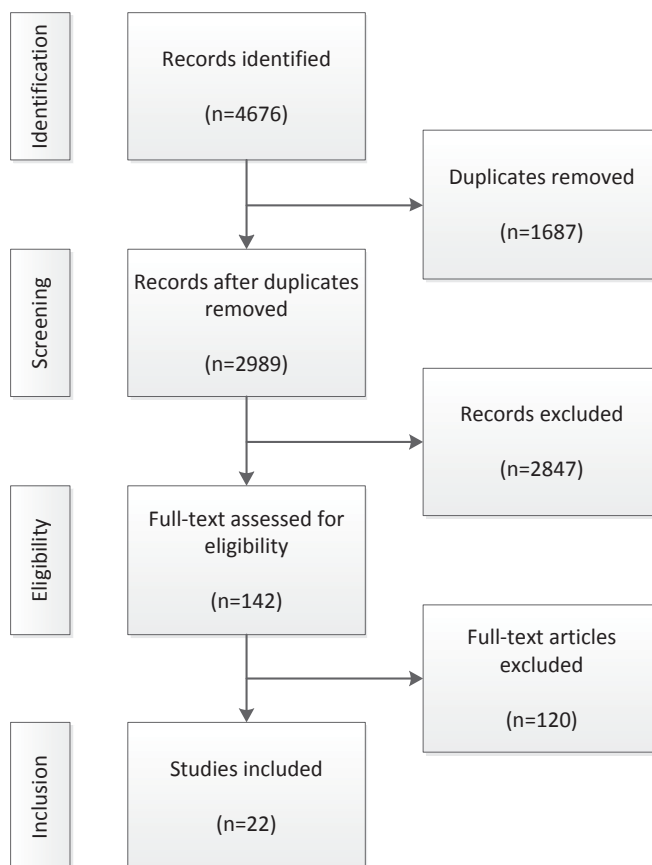


Figure 1. Patient inclusion flowchart.

Study characteristics

The characteristics of the 22 included studies are presented in table 1. Seven studies were based on prospectively collected data and the remaining fifteen inclusions were retrospective studies. The population of seven studies consisted of surgically treated patients only, whereas five studies were based on patients treated with radiotherapy only. Nine studies consisted of a mixed population and the treatment details of one study were not reported. Duration of follow-up was reported in nine studies and ranged from 8 to 72 months. Median duration of the period of recruitment was 8 years and ranged from 1 to 20 years.

Table 1. Characteristics of the 22 included studies. SUR: patients treated with surgery. RTC: patients treated with radiotherapy or conservative therapy. NR: not reported

Study ID	Author, year, country	Study type	No. patients	% SUR/RTC	Follow-up	Period recruitment	Duration recruitment	Risk of Bias
1	Helweg, 2000, Denmark	Prospective	153	0/100	NR	1996-1999	4 years	High
2	Riegel, 2002, Germany	Retrospective	139	NR	NR	1990-1997	8 years	High
3	Linden, 2004, Netherlands	Prospective	342	0/100	16 months	1996-1998	3 years	Low
4	Hosono, 2005, Japan	Retrospective	176	100/0	23 months	1985-2001	16 years	High
5	Ibrahim, 2008, International	Prospective	223	100/0	NR	2002-2003	2 years	High
6	Chi, 2009, USA	Prospective	101	50/50	8 months	1992-2002	11 years	High
7	Arrigo, 2011, USA	Retrospective	200	100/0	NR	1999-2009	11 years	Low
8	Bartels, 2011, International	Retrospective	567	9/91	NR	1996-2008	13 years	Low
9	Mizumoto, 2011, Japan	Retrospective	603	0/100	19 months	2002-2007	5 years	Low
10	Park, 2011, Korea	Retrospective	103	100/0	26 months	2001-2008	8 years	High
11	Pointillart, 2011, France	Prospective	142	83/17	NR	2005-2007	3 years	Low
12	Wibmer, 2011, Austria	Retrospective	254	25/75	36 months	1998-2006	9 years	Low
13	Chao, 2012, USA	Retrospective	174	0/100	9 months	2006-2009	4 years	High
14	Kataoka, 2012, Japan	Retrospective	143	50/50	21 months	1990-2008	19 years	Low
15	Tancioni, 2012, Italy	Retrospective	151	100/0	NR	2004-2007	4 years	High
16	Yang, 2012, Korea	Retrospective	217	100/0	NR	2001-2009	9 years	Low
17	Balain, 2013, UK	Prospective	199	52/48	NR	2010-NR	NR	High
18	Rades, 2013, Germany	Retrospective	2029	0/100	NR	1992-2011	20 years	High
19	Tabouret, 2013, France	Retrospective	148	100/0	24 months	2004-2010	7 years	Low
20	Bollen, 2014, Netherlands	Retrospective	1043	5/95	72 months	2001-2010	10 years	Low
21	Morgen, 2014, Denmark	Prospective	544	16/84	NR	2011	1 year	High
22	Yeung, 2014, Hong Kong	Retrospective	128	46/54	NR	2001-2011	11 years	High

Risk of bias

Of the 22 included studies, agreement on the overall risk of bias was obtained for 18 (82%). Consensus was reached for the remaining four studies. Inter-observer agreement for the overall risk of bias was substantial (kappa 0.62). Lower levels of agreement were mainly observed in the categories *study participation* (kappa 0.19) and *confounding* (kappa -0.13).

Prognostic factors levels of evidence

A total of 43 different prognostic factors were investigated in the 22 included studies. Seven prognostic factors pertained to post-treatment details and four prognostic factors were specific to the received treatment of the patients in the cohort. These prognostic factors were therefore not considered relevant to pre-treatment estimation of survival and were excluded. Fifteen prognostic factors were analyzed only once. As the level of evidence for these factors by definition could not exceed *limited* they are not mentioned in the results, but are presented in an online supplement. The remaining seventeen prognostic factors are detailed in table 2. Prognostic factors influencing survival in a certain study are mentioned in the column 'positive association' and studied prognostic factors not influencing survival are mentioned in the column 'no association'.

Strong evidence for a positive association with survival was found for the primary tumor, performance status and the American Society of Anesthesiologists (ASA) classification.³⁸ Strong evidence for no association with survival was found for gender, age, number of spinal bone metastases, location of spinal bone metastases, and the presence of a pathologic fracture. The evidence was inconclusive for visceral metastases, neurologic deficit, the interval between diagnosis of the primary tumor and start of treatment for SBM, the presence of extraspinal bone metastases, total number of bone metastases, pain, sphincter function, weight loss and cardiovascular disease.

Table 2. Level of evidence for investigated prognostic factors. Numbers refer to study identification from table 1. ASA: American Society of Anesthesiologists. SBM: spinal bone metastases. Studies with a low risk of bias are in bold.

Prognostic factor	Positive association	No association	Level of evidence
Primary tumor	2, 3, 4, 5, 6, 7, 8, 9 , 10, 11 , 12 , 14 , 15, 17, 18, 20 , 21, 22	13, 16 , 19	Strong – 86%
Performance status	2, 3 , 8 , 9 , 11 , 12 , 13, 17, 18, 19 , 20 , 21, 22	14	Strong – 93%
ASA classification	11 , 19		Strong – 100%
Age	6, 9 , 13	2, 7, 10, 11 , 12 , 14 , 15, 16 , 17, 18, 19 , 22	Strong – 80%
Gender	2, 8, 18	7, 9 , 10, 11 , 12 , 13, 14 , 16 , 17, 19 , 22	Strong – 79%
Number SBM	21	2, 11 , 12 , 14 , 16 , 17, 18, 19 , 20 , 22	Strong – 91%
Location SBM	8	2, 7, 10, 11, 16 , 19 , 20 , 22	Strong – 89%
Pathologic fracture		7, 11 , 12	Strong – 100%
Visceral metastases	3 , 9 , 12 , 14 , 15, 17, 18, 19 , 20 , 21, 22	2, 7, 11 , 13	Inconclusive – 73%
Neurologic deficit	1, 4, 5, 7, 18, 21	2, 12 , 14 , 16 , 17, 19 , 20 , 22	Inconclusive – 57%
Interval diagnosis	1, 13, 14 , 18	15, 16	Inconclusive – 67%
Extraspinal bone metastases	14 , 17, 18	12 , 19 , 20 , 21, 22	Inconclusive – 63%
Number bone metastases	9 , 15	3, 21	Inconclusive – 50%
Pain	4, 11	14	Inconclusive – 67%
Sphincter function	5	7, 11	Inconclusive – 67%
Weight loss	11	19	Inconclusive – 50%
Cardiovascular disease	11	19	Inconclusive – 50%

DISCUSSION

In this systematic review it is shown that the primary tumor, performance status and the ASA classification are associated with survival in patients with spinal bone metastases. Age, gender, number of SBM, location of SBM and the presence of a pathologic fracture are most likely not associated with survival.

Even though the eligibility criteria for this study were strict, several limitations were observed. Firstly, 68% of the included studies were conducted retrospectively and 55% of the studies consisted of populations that were treated either only with surgery or only with radiotherapy. This increased the risk of bias and therefore the quality of our results. Also, the way the studies evaluated the prognostic factors was heterogeneous and several different cut-off points were used.

The primary tumor was investigated as a potential prognostic factor in all but one study. Even though several different classifications were used, it was found to be associated with survival in 86% of the included studies, leaving no doubt that an accurate primary tumor classification is required for prognostication in patients with spinal bone metastases. The same applies to the performance status, with a positive association rate of 93%. Irrespective of which specific score is used, it provides essential information for accurate prognostication. The ASA classification was investigated in two studies with a low risk of bias and both found a positive association with survival. Because it is rather similar to the performance status, it remains to be seen whether there is a significant benefit to including both factors in a prognostic model.

Age was found not to be associated with survival in 80% of the included studies. Considering the fact that a performance score generally provides a much better measure of a patient's health – and therefore prognosis – than age does, it is not unexpected that this variable is not significantly associated with survival in a multivariate analysis. Gender also was not associated with survival, with a rate of 79%. Breast and prostate cancer make up a large percentage of the populations in the included studies. Since they are gender specific, it is not unlikely that any potential effect of gender is corrected on multivariate analysis. Gender might play a role in SBM prognostication for certain primary cancers with a more even distribution, such as lung cancer. Number and location of the SBM, as well as the presence of pathologic fractures, had no effect on survival in the majority of the included studies. Even though these factors are important to consider when deciding on treatment – for instance determining extent of radiation field or levels of surgical fixation – they most likely do not need to be considered with respect to survival.

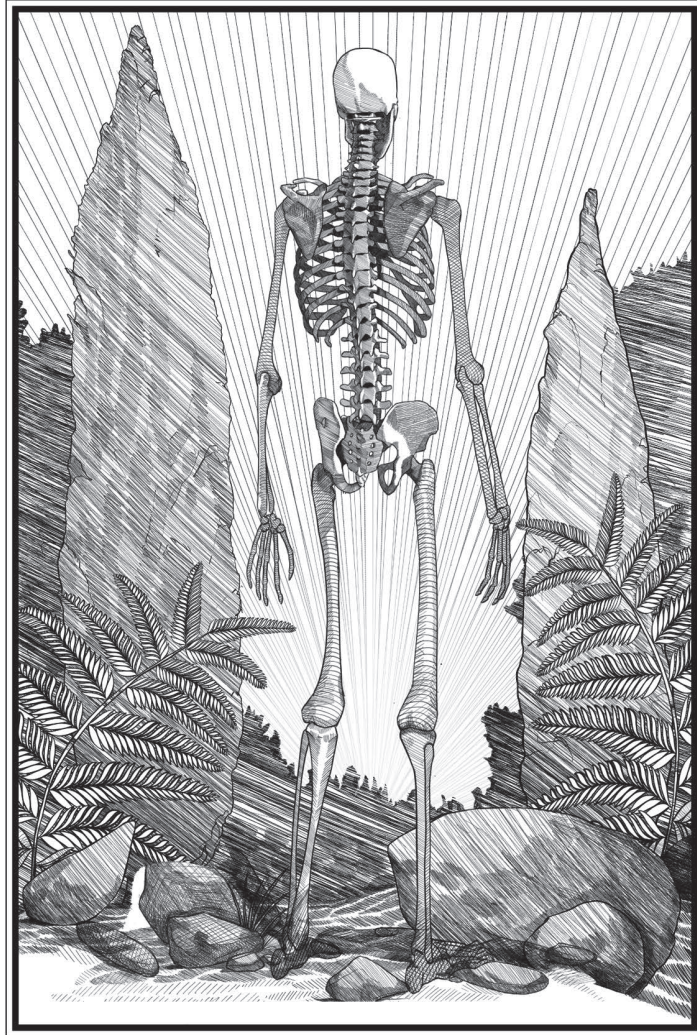
The rate of positive association for the presence of visceral metastases was 73%, meaning the level of evidence was only just inconclusive. A recent study that stratified the risk factor analysis based on the primary tumor classification found that the effect of visceral metastases on survival changed between different tumor categories⁴. The survival of patients with a fast growing, aggressive tumor was not affected by visceral metastases, whereas patients with a slow growing tumor did have a significantly shorter survival when visceral metastases were present. The included low risk of bias studies that found a positive association had, on average, 10% more breast cancer patients in their population than studies that did not find an association. This difference in composition of the population might explain the different findings in these studies. The prognostic factor *neurologic deficit* consisted of two variables; ambulatory status and the Frankel classification. Because of the interaction with the performance status of a patient, this variable can be difficult to obtain, especially retrospectively. Even though it is an important variable to consider when deciding on type of treatment, it is unclear whether this variable plays a role in estimating survival.

In conclusion, prognostication for patients with SBM should be based on an accurate primary tumor classification, combined with a performance score. The added benefit of including the ASA classification should be studied further, as should the influence of visceral metastases and the presence of neurologic deficit.

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CHAPTER III

Risk factors for survival of 106 surgically treated patients with symptomatic spinal epidural metastases

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ABSTRACT

Purpose. Evaluation of risk factors for survival in patients surgically treated for symptomatic spinal epidural metastases (SEM).

Methods. One-hundred-and-six patients who were surgically treated for symptomatic SEM in a ten-year period in two cooperatively working hospitals were retrospectively studied for nine risk factors: age, gender, site of the primary tumor, location of the symptomatic spinal metastasis, functional and neurologic status, the presence of visceral metastases and the presence of other spinal and extraspinal bone metastases. Analysis was performed using the Kaplan-Meier method, univariate log-rank tests and Cox-regression models.

Results. Overall median survival was 10.7 months (0.2 – 107.5 months). Overall 30-day complication rate was 33%. Multivariate Cox-regression analysis showed that fast growing primary tumors (HR 3.1, 95%CI 1.6-6.2, $p=0.001$), the presence of visceral metastases (HR 1.7, 95%CI 1.0-2.9, $p=0.033$) and a low performance status (HR 2.7, 95%CI 1.1-6.6, $p=0.025$) negatively influenced survival.

Conclusion. Primary tumor type, presence of visceral metastases and performance status are significant predictors for survival after surgery for symptomatic SEM and should be evaluated before deciding on the extent of treatment. More accurate prediction models are needed to select the best treatment option for the individual patient.

INTRODUCTION

Symptomatic spinal epidural metastases (SEM) continue to be a disabling consequence of cancer, causing a decrease in quality of life due to pain and neurological decline. With the development of better treatment options for the primary cancer, survival periods in metastatic disease will increase and will most likely lead to a rise in the incidence of metastatic spine disease. There is consensus on the fact that surgery can be beneficial to patients presenting with SEM,¹⁻³ however, the optimal type of surgery to be used on an individual patient remains unclear. The goals of surgical intervention are to relieve pain and neurologic deficit by decompression of the spinal cord or cauda equina and stabilization of the spine. Surgical strategies to achieve these goals vary greatly in extent of tumor removal (ranging from debulking to en bloc resection of the affected vertebra) and type of stabilization (ranging from none to circumferential reconstruction with vertebral body replacement). Secondary to open surgery, minimal invasive techniques such as percutaneous vertebroplasty (PVP) or kyphoplasty and percutaneous pedicle screw fixation are increasingly used.

In practice the surgeon will match the type of surgery to the expected survival time, thus balancing the increase in morbidity associated with more extensive surgery to the expected gain in quality of life and mobility.

Models to aid in the selection of surgical candidates have been developed by Tokuhashi^{4,5}, Tomita⁶, Van der Linden⁷ and Bauer⁸. Disadvantages of these models are that they vary in the amount and type of risk factors used (table 1) and the weight assigned to each of these factors, resulting in different scores for the same patient. Also, patient populations on which the models are based differ greatly; Van der Linden used data of radiotherapy patients only and Bauer based his model on a mixed group of patients with bone metastases to the extremities as well as the spine. As a consequence, the use of such a model entails a risk of over- or under treatment and clinical applicability is limited.

Table 1. Six risk factors used in the four predictive models.

	Tomita	Tokuhashi	Vd Linden	Bauer
Primary tumor	X	X	X	X
Karnofsky performance status		X	X	
Visceral metastases	X	X	X	X
Extraspinal bone metastases	X	X		X
Number spinal metastases	X	X		X
Frankel classification		X		

Since life expectancy is of such great influence on therapeutic decision-making, its accurate prediction is of the utmost importance.

The goal of this study is to retrospectively identify clinically relevant risk factors for estimating survival in 106 patients who were surgically treated in a ten-year period at our two centers.

MATERIALS AND METHODS

Patients

All patients who were surgically treated for symptomatic SEM between January 2001 and December 2010 by one surgical team in two tertiary referral centers in the Netherlands were included. Forty-seven patients were operated at the Leiden University Medical Center and 59 at the Medical Center Haaglanden. The surgical team performed the spinal interventions in both hospitals. Surgical treatment was defined as all invasive procedures, aimed at palliation or control of symptoms of SEM. These procedures consisted of percutaneous vertebroplasty, intralesional decompression, partial or complete corpectomy and a single en bloc resection, either through an anterior, posterior or combined approach. Choice of technique and approach were dependent on location of the metastasis, possibilities of fixation on adjacent levels, expected survival and surgeon preference.

Table 2 shows all baseline characteristics of the study population. One patient died during surgery due to myocardial infarction and was excluded from the analysis. For reasons of completeness, the patient is mentioned in the complication summary. A total of 106 patients were included in the study, 53 male and 53 female. The mean age at surgery was 59.0 years. The most commonly affected part

of the spine was the thoracic region (56%). During the course of treatment for the symptomatic SEM, 9 patients underwent systemic treatment (i.e. chemotherapy and/or hormone therapy), 31 patients received radiation therapy, and 55 patients received both. Thirty patients had radiation therapy preoperatively and 56 postoperatively. Forty-seven patients had no sign of neurologic deficit, indicating they were referred either for persisting pain, a pathologic fracture or for instability of the spinal column. The most prevalent primary tumors were breast (n=25), lung (n=20), kidney (n=19) and prostate (n=11) (table 3).

Table 2. Patient characteristics. SD: standard deviation.

Characteristic	Number (%)
Gender	
Male	53 (50)
Female	53 (50)
Age (mean, years, SD)	59.0 ± 10.9
Center	
LUMC	47 (44)
MCH	59 (56)
Location symptomatic spinal metastasis	
Cervical	23 (22)
Thoracic	60 (56)
Lumbar	23 (22)
Adjuvant therapy SEM, perioperatively	
None	11 (10)
Systemic Therapy	9 (9)
Radiation Therapy	31 (29)
Both	55 (52)
Neurologic deficit	
No (Frankel grade E)	47 (44)
Yes (Frankel grade A, B, C, D)	59 (56)

Table 3. Primary tumors and median survival for each primary. *Median could not be calculated, mean is given.

Primary tumor	Number (%)	Median survival (95% CI)
Breast	25 (23)	34.7 (11.8 – 46.8)
Lung	20 (18)	6.9 (0.0 – 21.6)
Kidney	19 (18)	14.9 (7.2 – 22.8)
Prostate	11 (10)	9.2 (1.2 – 16.8)
Colon	6 (6)	1.7 (0.0 – 13.2)
Sarcomas	5 (5)	8.8 (4.8 – 13.2)
Melanoma	4 (4)	3.4 (0.0 – 7.2)
Thyroid	3 (3)	35.6* (-)
Rectum	2 (2)	2.1 (-)
Esophagus	2 (2)	3.9 (-)
Pharynx	2 (2)	7.2 (-)
Other	7 (7)	2.7 (1.2 – 3.6)

Seven patients underwent percutaneous vertebroplasty, 46 had limited posterior decompressive surgery and 52 patients had extended decompressive surgery in the form of an intralesional corpectomy. One patient was treated with an en bloc resection. (table 4).

Table 4. Surgical details. *Patients treated with percutaneous vertebroplasty excluded

Surgical details	Number (%)
Type of surgery	
Percutaneous vertebroplasty	7 (7)
Decompression w/o fixation	24 (22)
Decompression with fixation	22 (21)
Partial corpectomy	12 (11)
Complete corpectomy	40 (38)
En bloc resection	1 (1)
Approach	
Posterior	86 (81)
Anterior	11 (10)
Combined	9 (9)
Means of stabilization*	
No additional stabilization	24 (24)
Pedicle screws / rods	30 (30)
Cage with additional fixation	45 (46)

Risk factors

All available patient records were retrospectively studied for gender, age, site of the primary tumor, location of the symptomatic spinal metastasis, preoperative functioning according to the Karnofsky performance status (KPS)^{9,10}, the presence of visceral metastases, the presence of other spinal and extraspinal bone metastases and neurologic functioning according to the Frankel classification¹¹. Based on the survival data from this study, the primary tumor scores of the Tomita and Van der Linden models were adapted to better reflect the study population: in the Van der Linden model, kidney cancer was added to the 'prostate group' and thyroid cancer was added to the 'breast group'. In the Tomita model, prostate cancer was moved to the 'moderate growth' category. KPS was scored in the period leading to surgery and not shortly before, to avoid the influence of acute neurologic decline. Date of surgery, date of complications and date of death were obtained from medical records or from general practitioners.

Statistical analysis

Survival time was calculated as the difference in months between date of surgery and date of death or last follow-up, with a minimum follow-up of eleven months.

Survival curves were estimated by using the Kaplan-Meier method. Influence of the risk factors was assessed by employing log rank tests for univariate analysis and for multivariate Cox analysis a backward stepwise procedure was used. A p -value of <0.05 was considered statistically significant. All analyses were performed using SPSS 18.0, SPSS Inc., Chicago IL.

RESULTS

Survival

The overall median survival was 10.7 months (0.2-107.5 months) (figure 1). Eighty patients (75%) died during follow-up, with a median survival of 6.5 months (0.2-106.8 months). Twenty-five patients (24%) died within 3 months after surgery and 13 patients (12%) died 3 to 6 months after surgery.

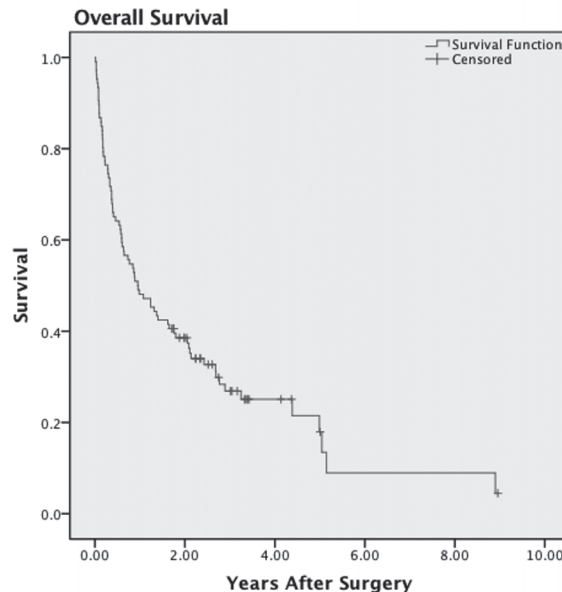


Figure 1. Overall survival.

The highest median survival time was found in patients with breast cancer (34.7 months), followed by kidney (14.9 months) and prostate cancer (9.3 months). Patients with colon cancer had the lowest median survival (1.7 months).

Complications

Within 30 days after surgery, 35 patients (33%) had one or more complication with a total of 53 recorded complications. Nine patients had multiple complications. The most common were wound infection (n=8), new minor neurologic deficits such as radicular pain or reduced sensibility (n=8), cerebrospinal fluid leak (n=6), and pneumonia (n=4) (see table 5). Three patients had to be re-operated due to instrumentation failure or acute neurologic decline. Ten patients died within 30 days, mostly due to systemic complications such as sepsis and respiratory failure. The complication rate in this group was 70%.

Table 5. 30-day complications. *Death occurred during surgery.

Complication	Number (%)
Cardiac	
Myocardial infarction*	1 (2)
Arrhythmia	2 (4)
Extensive blood loss	1 (2)
Gastrointestinal	
Ileus	1 (2)
Bleed	1 (2)
Infection	
Pneumonia	4 (8)
Sepsis	2 (4)
Neurologic	
New minor deficits	8 (15)
New major deficits	2 (4)
Delirium	3 (6)
Pulmonary	
Respiratory failure	2 (4)
Pleural empyema	1 (2)
Renal	
Acute renal failure	1 (2)
Metabolic	
Hyponatremia	1 (2)
Metabolic acidosis	1 (2)
Skeletal	
Pathologic fracture	1 (2)
Surgical site	
Wound infection	8 (15)
Wound dehiscence	1 (2)
Wound leakage	1 (2)
Hematoma	2 (4)
Cerebrospinal fluid leak	6 (11)
Instrumentation failure	3 (6)

Univariate analysis of risk factors

Results for the univariate analysis are shown in table 6 and figures 2-4. All primary tumor classifications were significant predictors for survival after surgery. However, none of the classifications were able to systematically differentiate between all of their subgroups (see Appendix A). The absence of visceral metastases ($p=0.014$) had a significant effect on survival. Gender, location of the symptomatic spinal metastasis, number of spinal metastases, presence of other bone metastases, age, KPS and Frankel classification had no effect on survival after surgery.

Table 6. Results of univariate analysis. *Including spinal metastases

Univariate analysis	<i>p</i> -value
Primary tumor classification	
Tomita (modified)	<i><0.001</i>
Tokuhashi (revised)	<i>0.001</i>
Van der Linden (modified)	<i>0.002</i>
Bauer (modified)	<i>0.008</i>
Karnofsky performance status	
100-80/70-50/40-10	0.169
Visceral metastases	
Present/removable/unremovable	<i>0.027</i>
Present/not present	<i>0.014</i>
Bone metastases	
Solitary/multiple*	0.946
0/1-2/ ≥ 3	0.970
Number of spinal metastases	
1/2/ ≥ 3	0.860
Frankel classification	
A+B/C+D/E	0.196
Age	
$<65/\geq 65$	0.089
Location	
C-Th6/Th7-L	0.163
Gender	
Male/female	0.159

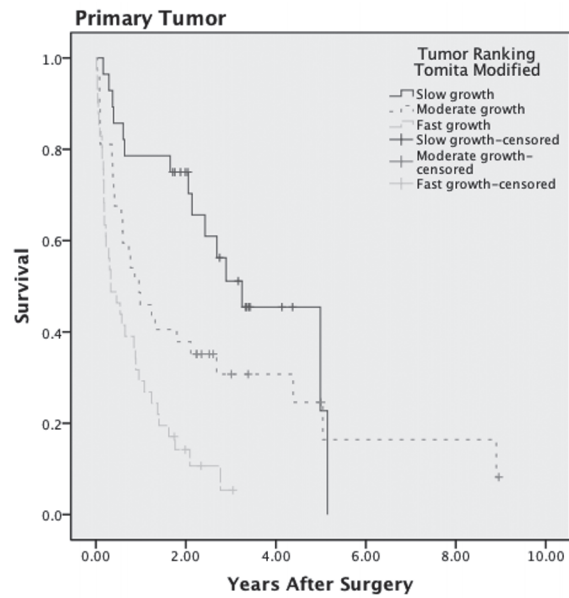


Figure 2. Primary tumor classification Tomita modified.

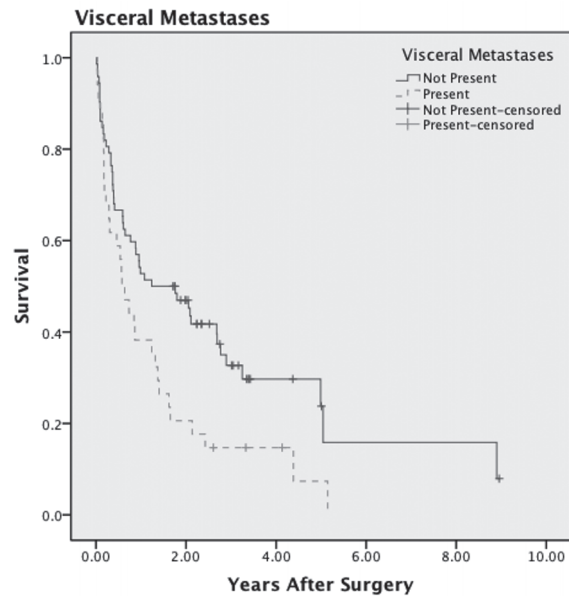


Figure 3. Visceral metastases.

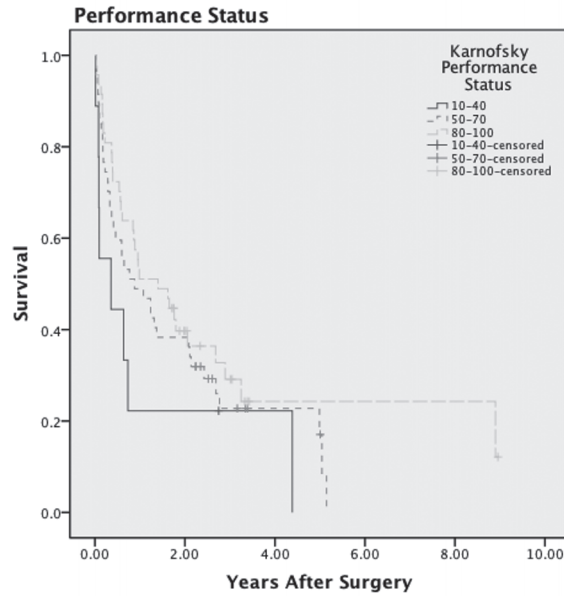


Figure 4. Karnofsky performance status.

Multivariate analysis of risk factors

A multivariate Cox regression analysis was performed by employing as risk factors primary tumor (Tomita modified, moderate growth HR 1.7, 95%CI 0.9-3.3, $p=0.099$, fast growth HR 3.1, 95%CI 1.6-6.2, $p=0.001$), presence of visceral metastases (HR 1.7, 95%CI 1.0-2.9, $p=0.033$) and performance status (KPS 50-70 HR 1.3, 95% CI 0.8-2.1, $p=0.292$, KPS 10-40 HR 2.7, 95%CI 1.1-6.6, $p=0.025$) (table 7).

Table 7. Results of multivariate Cox-regression analysis. HR: Hazard ratio; 95% CI: 95% confidence interval

Multivariate analysis	HR	<i>p</i> -value	95% CI
Tomita tumor classification			
Slow		0.004	
Moderate	1.7	0.099	0.9-3.3
Fast	3.1	0.001	1.6-6.2
Visceral metastasis			
Present/not present	1.7	0.033	1.0-2.9
Karnofsky performance status			
80-100		0.077	
50-70	1.3	0.292	0.8-2.1
40-10	2.7	0.025	1.1-6.6

DISCUSSION

In this study on 106 patients operated for symptomatic SEM, primary tumor type, presence of visceral metastases and functional status were found to be significant predictors of survival. Other risk factors as gender, presence of other bone metastases, number and location of spinal metastases, age and neurologic status did not have an effect on survival.

For the purpose of accurately evaluating the individual risk factors, modifications to two items were made. We agree with Wibmer et al. that the primary tumor classifications are not up to date¹². However, based on survival data in this study, the conclusion that patients suffering from kidney cancer have a prognosis comparable to those with breast cancer cannot be followed. Median survival in patients with prostate cancer was compatible with the 'moderate growth' category in the Tomita model and therefore it was decided to remove it from the 'slow growth' category. In 2004, Van der Linden et al. studied 342 patients with spinal metastases who were conservatively treated for pain by means of external beam radiation therapy⁷. Since patients with renal cell carcinoma were excluded and patients with thyroid cancer were underrepresented, these primary tumors are not mentioned separately in the model. Scoring these tumors in the 'other' category is incorrect and adjustments are needed: kidney cancer was added to the 'prostate group' and thyroid cancer was added to the 'breast group'.

The preoperative assessment of the Karnofsky performance score was standardized. In a patient population notoriously at risk for acute neurologic decline, we believe it is wrong to take such a measurement just prior to surgery because of the acute distorting effect of neurologic impairment on functional impairment. Therefore, it was decided by the authors that functional status had to be evaluated before the onset of acute neurologic decline.

When assessing primary tumor type, the Tomita classification was found to be the most practical and – after modification – also the most accurate of the four classifications. The difference in survival between slow and moderate growth tumors is not significant on both univariate ($p=0.073$) and multivariate analysis (HR 1.7, 95%CI 0.9-3.3, $p=0.099$), but the difference between slow and fast growth ($p<0.001$) and moderate and fast growth ($p=0.007$) is strongly significant.

Even though the results of the Van der Linden classification improved after modification, accuracy is still lacking, as is the case for the Tokuhashi and Bauer classifications. An explanation for this finding may be the relatively long survival of patients with lung cancer in this study (median survival 6.9 months). Bias might have been introduced by selection of only those lung cancer patients with preoperative estimated long survival. Whereas in the Tomita classification this primary is mixed with other fast growing tumors such as melanoma (median survival 3.4 months) and colon cancer (median survival 1.7 months), the other classifications use this primary as a separate entity. This underlines another advantage of the Tomita tumor classification: its adaptability. We believe it is impossible to present a globally valid tumor classification, considering the differences in incidences and ever-changing treatment options. By creating categories based on contemporary regional survival data, results will be more accurate than when adhering to semi-rigid classifications as presented in other classifications.

As a marker for progression of disease, the presence of visceral metastases does not directly influence survival. In their models, Tomita and Tokuhashi make use of a third category, namely operability. Tokuhashi initially based this category on a single patient out of the 64 studied⁴ and Tomita on 7 out of 67 patients⁶. As is shown in the results, operable visceral metastases have a similar median survival when compared to no visceral metastases. Unfortunately, the treatable visceral metastases group only consisted of 6 patients. These results are most likely due to patient selection. If a patient is considered fit enough to undergo metastasectomy, survival will most likely be prolonged based on their general condition and not the removal of the visceral metastasis. A recent retrospective study of 504 breast cancer patients irradiated for metastatic spinal cord compression by Rades et al.¹³ also found a strong negative effect on survival if visceral metastases were present, similar to Wibmer et al., Yamashita et al. and Crnalic et al.^{12,14,15}

Performance status is generally accepted as a strong prognostic factor for survival in metastatic disease¹⁶, but in case of spinal metastases it remains controversial. Even though both the Tokuhashi and the Van der Linden models make use of the KPS, evidence is still limited. In his article, Tokuhashi writes: “(...) the standard deviation was too great for the values to be sufficiently meaningful.”⁴⁹

Pointillart et al.¹⁷ found the KPS to be a significant predictor of survival on univariate analysis, but unfortunately did not perform an analysis for each category. In their study the HR was equal to 0.98 ($p=0.002$, 95%CI 0.96-0.99), indicating that performance status was not clinically relevant.

In a retrospective study, evaluation of performance status is challenging, especially when trying to avoid the influence of neurologic deficit. The data does suggest an effect of performance status on survival, but only on multivariate analysis and when divided in three groups. The HR for a KPS score 50-70 is equal to 1.3, ($p=0.292$, 95%CI 0.8-2.1), but the HR for a KPS score 10-40 is equal to 2.7 ($p=0.025$, 95%CI 1.1-6.6).

Chi et al.¹⁸ considered the effects of age in predicting survival as well as preservation of ambulation for patients treated for spinal metastases. We agree that particular age cutoff points can help in selecting patients, but did not find their suggested age of 65 to be accurate in this population ($p=0.089$).

Neurologic deficit has no significant effect on survival ($p=0.196$), stressing that this variable should be excluded when evaluating performance status. Even though survival is not affected by neurologic functioning, it is an important factor that should be considered when deciding on treatment.

In patients with malignancies, the presence of bone metastases can be used as a marker for progression of disease. However, if a patient is already affected by spinal bone metastases, the presence or absence of extraspinal bone metastases is inconsequential. Neither the classification according to Tokuhashi ($p=0.970$), nor the classification according to Tomita or Bauer ($p=0.946$) resulted in a significant effect. The amount ($p=0.860$) and location ($p=0.493$) of spinal metastases have no impact on survival. Similar to neurologic functioning it does however have consequences when deciding on treatment. Feasibility, approach and extent of surgery should be weighed against amount of metastatic involvement of the spinal column and location of the symptomatic metastases.

Based on these results it can be argued that there are several flaws in the current scoring systems. Firstly, the primary tumor classifications need to be updated based on larger populations. Our experience is that the Tomita classification is the ideal

framework for doing so. Secondly, several risk factors should be removed from the models. Other bone metastases, number of spinal metastases and neurologic deficit are all important factors to consider when deciding on surgery, but do not play a role in estimating survival. Lastly, provided neurologic deficit is excluded as a confounder, functional status should be included in any scoring system, as should the presence of visceral metastases. Currently, the only model to contain these risk factors, without the drawback of having to evaluate several others, is the Van der Linden model. If the primary tumor classification would be revised, preferably along the lines of the classification proposed by Tomita, this model would be superior in ease of use as well as accuracy.

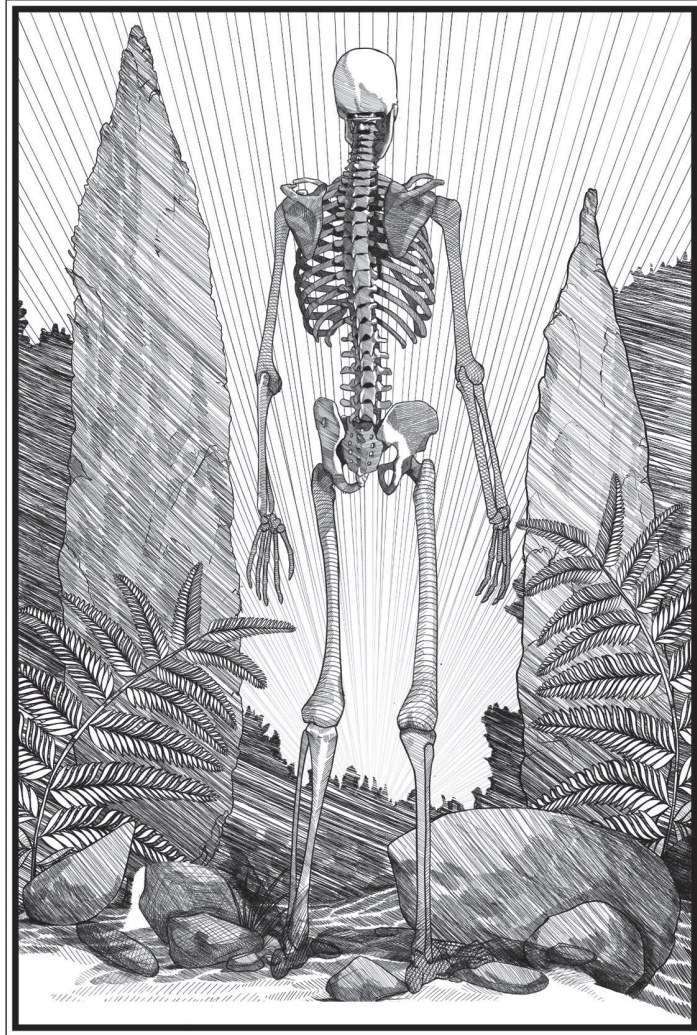
Even though estimating survival is an important part of the decision-making process concerning the treatment of symptomatic SEM, it should never be the only point of interest. Neurologic symptoms and their duration, pain, feasibility of other treatment options, stability of the spinal column and expected gain in quality of life should all be discussed, preferably in a multidisciplinary setting.¹⁹

Complication rate in this study is high (33%). This is mainly due to the fact that only surgically treated patients were included and that surgical techniques used were aggressive (50% partial or complete corpectomy). A limitation of this study is its retrospective design and the fact that only surgically treated patients are evaluated. Therefore, patients who were referred for surgical consultation but did not receive treatment are not represented in this study. The wide array of surgical interventions used is due to the lack of clinical guidelines during the period described in this study. Also, the heterogeneity of primary tumors can cause discrepancies in recorded survival times of the smaller groups when compared with other studies.

Primary tumor type, presence of visceral metastases and functional status are strong risk factors for determining survival in patients operated for symptomatic spinal epidural metastases and should always be carefully evaluated.

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CHAPTER IV

Prognostic factors associated with survival in patients with symptomatic spinal bone metastases: a retrospective cohort study of 1043 patients

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ABSTRACT

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

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

Results. A total of 1043 patients were studied. The most prevalent tumors were those of breast (n=299), lung (n=250) and prostate (n=215). Median follow-up duration was 6.6 years and six patients were lost to follow-up. Based on the results of the uni- and multivariate analyses, four categories were created.

Median survival in category A was 31.2 months (95%CI 25.2-37.3), 15.4 months (95%CI 11.9-18.2) for B, 4.8 months (95%CI 4.1-5.4) for C and 1.6 months (95%CI 1.4-1.9) for category D. Harrell's c-statistic was calculated after the model was applied to an external dataset, yielding a result of 0.69.

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

INTRODUCTION

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

Due to improvements in systemic treatment options for the primary tumor, overall survival times in patients suffering from metastatic disease are on the rise. Most likely, this will result in a prolonged palliative phase in which the incidence of patients presenting with symptomatic SBM will increase. It has been well established that treatment with radiotherapy and/or surgery can be beneficial to patients presenting with pain, neurological deficit or both²⁻⁶. However, the most optimal treatment algorithm for individual patients is not optimized yet. In practice, the treating physician will match extent and type of treatment not only to a patient's clinical presentation, but also to the expected survival time, thus balancing the increase in morbidity and mortality associated with more extensive treatment to the expected gain in quality of life.

Models to aid in therapy selection based on expected survival time have been developed by Tomita⁷, Tokuhashi^{8,9}, Bauer^{10,11} and our own group⁴. These models encompass prognostic factors such as primary tumor type, amount and location of spinal metastases, presence of visceral, brain and extraspinal bone metastases, functional status and neurological status. However, clinical applicability seems limited due to over- or under treatment and especially when predicting short survival the existing models fall short^{12,13}.

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

MATERIALS AND METHODS

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

Local treatment consisted of external beam radiotherapy for pain or minor neurologic deficit, surgery for rapidly progressive or severe neurologic deficit and instability, or a combination of both treatment modalities. Concomitant systemic anticancer treatments such as chemotherapy and bisphosphonates were considered to be secondary to the local treatment. For external validation of the final model, the database of the Dutch Bone Metastasis Study (DBMS) was used¹⁴.

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

The primary data sources were the patient's clinical files, radiology reports and admission forms. Baseline variables obtained before start of treatment were gender, age, primary tumor, location and number of SBM, the presence of visceral and/or brain metastases, the presence of extraspinal bone metastases, pretreatment functioning according to the Karnofsky performance status (KPS)^{15,16} and neurological functioning according to the Frankel classification¹⁷.

The primary tumors were categorized based on the Tomita classification⁷. The original classification used growth speed alone to assign a primary tumor into one of three groups. However, as growth speed is not the only factor determining survival, we renamed the classification 'clinical profile' encompassing other contributing factors such as the availability of effective systemic treatment options for the primary tumor. The clinical profile of a primary tumor was considered to be favorable, moderate or unfavorable.

Performance status was dichotomized into normal functioning (KPS 100-80%) and impaired functioning (KPS 70-10%). Neurological functioning was inferred from clinical exams and divided into three groups: no deficit present (Frankel E), minor motor or sensory deficit (Frankel D) and major motor or sensory deficit (Frankel A, B, C). The number of spinal and extraspinal bone metastases was obtained from radiology reports and further subdivided in three categories according to Tokuhashi⁹.

Statistical analysis

Survival time was calculated as the difference between start of treatment for the spinal metastasis and date of death or the last follow-up moment recorded. Survival curves were estimated using the Kaplan-Meier method. Follow-up was assessed by employing the reverse Kaplan-Meier method¹⁸. Cox proportional hazard models were fitted using Collett's method, consisting of a univariate analysis, followed by multivariate backward and multivariate forward selection¹⁹. Harrell's c-statistic was used for external validation of the predictive accuracy of the presented model²⁰. It estimates the probability of concordance between predicted and observed responses. Survival curves were compared using log-rank tests. A *p*-value of <0.05 was considered statistically significant. All analyses were performed using SPSS 20.0, SPSS Inc., Chicago IL.

RESULTS

A total of 1301 patients were treated for symptomatic spinal metastases during the study period. After excluding patients with direct ingrowth of a primary tumor into the vertebra (n=23), patients with bone metastases in the sacral or sacroiliac region (n=105), leptomeningeal metastases (n=24), intradural metastases (n=14), metastases deriving from primary tumors of hematological or of unknown origin (n=44) and metastases deriving from rare primary tumors (n=42), 1049 patients remained eligible for analysis. Primary tumors classified as adenocarcinoma of unknown primary (ACUP) were not excluded. Six patients moved abroad shortly after finishing treatment and were lost to follow-up (figure 1).

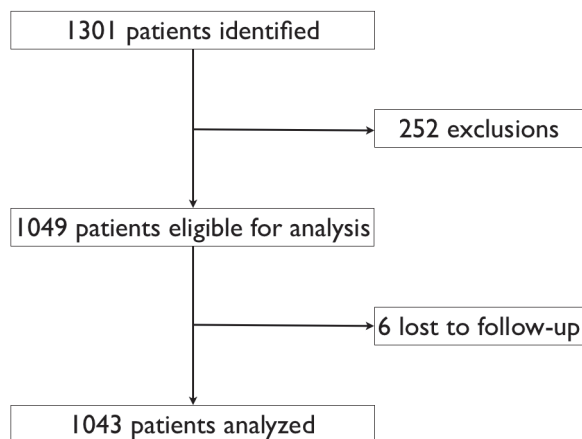


Figure 1. Patient flow diagram.

Table 1 summarizes the characteristics of the 1043 patients studied, of whom 542 (52%) were male and 501 (48%) were female. The mean age at start of treatment was 64.8 years (SD $\pm$ 12.5 years). At presentation, the majority of patients had no (n=518; 50%) or only minor (n=403; 39%) neurological complaints.

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

Table 1. Population characteristics. SD: standard deviation.

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

The most prevalent primary tumors were breast cancer (n=299), lung cancer (n=255), prostate cancer (n=215), kidney cancer (n=60) and colon cancer (n=55) (table 2).

Table 2. Primary tumor, related survival and clinical profile. UCC: urothelial cell carcinoma. ACUP: adenocarcinoma of unknown primary. CI: confidence interval.

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

Thirty percent of all patients were classified as having a favorable clinical profile with a median survival of 18.6 months (95%CI 15.1-22.1), followed by 29% with a moderate profile and a median survival of 5.9 months (95%CI 4.8-7.0) and 41% with an unfavorable profile and a median survival of 2.2 months (95%CI 1.9-2.6) (figure 2).

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

The DBMS database consisted of 342 SBM patients treated with radiotherapy. Median follow-up was 2.2 years and overall median survival was 8.9 months (95%CI 7.4-10.3). In total 258 patients (76%) died during follow-up. Further details of the patient population are published elsewhere⁴.

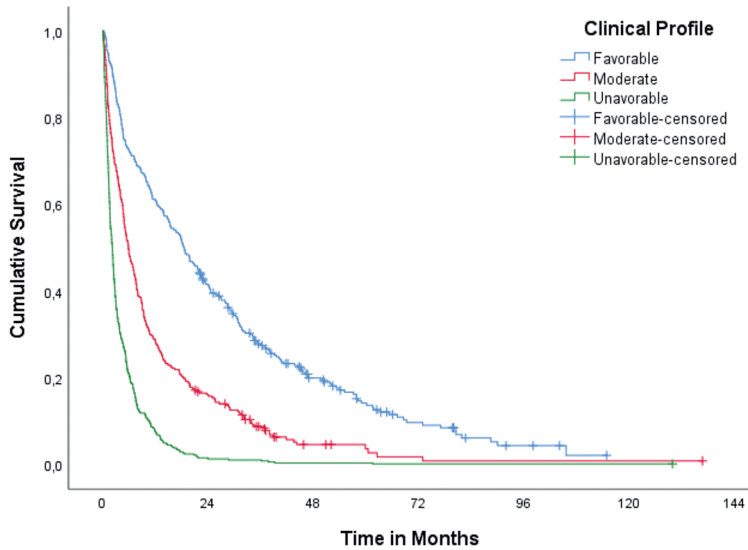


Figure 2. Survival curves of clinical profiles.

Table 3. Treatment details.

Treatment	N (%)
Overall	
Radiotherapy only	997 (95)
Surgery and radiotherapy	39 (4)
Surgery only	7 (1)
Radiotherapy regimens	
1x8 Gy	445 (43)
2x8 Gy	169 (16)
6x4 Gy or 5x4 Gy	322 (31)
Other – Total dose >24 Gy	100 (10)
Surgery	
Minimal invasive	10 (22)
Limited decompression and fixation	23 (50)
Extended decompression and fixation	13 (28)

Analysis of the entire cohort

Results of the univariate and multivariate analyses are detailed in table 4. The three clinical profiles (moderate HR1.6, 95%CI 1.3-2.1, $p<0.001$) (unfavorable HR3.5, 95%CI 2.9-4.4, $p<0.001$), the KPS (HR1.9, 95%CI 1.6-2.2, $p<0.001$) and the presence of visceral metastases (HR1.5, 95%CI 1.3-1.7, $p<0.001$) were shown to be of influence on survival. The Frankel classification, the number and location of the spinal metastases and the presence of brain and extraspinal bone metastases did not influence survival.

Table 4. Results of the uni- and multivariate analyses. HR: hazard ratio. CI: confidence interval. C: cervical. CT: cervicothoracic. T: thoracic. TL: thoracolumbar. L: lumbar. D: diffuse.

Univariate log-rank test			p-value
Clinical profile (Favorable/Moderate/Unfavorable)			<0.001
Karnofsky (100-80/70-10)			<0.001
Frankel classification (ABC/D/E)			<0.001
Visceral metastases (Yes/No)			<0.001
Brain metastases (Yes/No)			0.012
Number spinal metastases (1/2/≥3)			0.983
Extra-spinal metastases (0/1/≥2)			0.093
Location spinal metastases (C/CT/T/TL/L/D)			0.836
Multivariate Cox-regression model			p-value
Clinical profile			
Favorable	-	-	<0.001
Moderate	1.6	1.3-2.1	<0.001
Unfavorable	3.5	2.9-4.4	<0.001
Performance status			
Normal (100-80)	-	-	<0.001
Impaired (70-10)	1.9	1.6-2.2	<0.001
Visceral metastases			
Not present	-	-	<0.001
Present	1.5	1.3-1.7	<0.001

Table 5. Results of the uni- and multivariate analyses stratified for clinical profile. HR: hazard ratio. CI: confidence interval.

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

Analysis stratified for clinical profile

Results of the univariate and multivariate analyses for the three clinical profiles are illustrated in table 5. A poor KPS (HR 1.7, 95%CI 1.3-2.2, $p<0.001$), the presence of visceral metastases (HR 2.0, 95%CI 1.5-2.7, $p<0.001$) and the presence of brain

metastases (HR 1.8 95%CI 1.1-3.0, $p=0.016$) were shown to have an association with survival in the favorable profile. In the moderate and unfavorable profiles, only the KPS affected survival (HR 2.3. 95%CI 1.7-3.0, $p<0.001$) and (HR 1.9, 95%CI 1.5-2.3, $p<0.001$), respectively.

Training data set and validation data set

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

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

Table 6. Groups based on multivariate analysis

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

KPS: Karnofsky Performance Status. VM/BRM: visceral and/or brain metastases. MOS: median overall survival.

Table 7. Survival times training and validation data sets. CI: Confidence interval. HR: Hazard ratio. MOS: Median overall survival

Category	MOS (95%CI)	N (%)	HR	95% CI	p-value
<i>Training data set</i>					
A	31.2 (25.2-37.3)	116 (12)	-	-	<0.001
B	15.4 (11.9-18.2)	226 (23)	1.8	1.4-2.3	<0.001
C	4.8 (4.1-5.4)	374 (37)	4.4	3.5-5.6	<0.001
D	1.6 (1.4-1.9)	278 (28)	9.3	7.2-12.1	<0.001
<i>Validation data set</i>					
A	16.3 (11.1-21.6)	64 (19)	-	-	<0.001
B	12.8 (9.5-16.0)	111 (33)	1.5	1.0-2.2	0.029
C	7.0 (5.1-9.0)	91 (27)	2.8	1.9-4.1	<0.001
D	3.6 (2.6-4.6)	73 (21)	6.0	3.9-9.2	<0.001

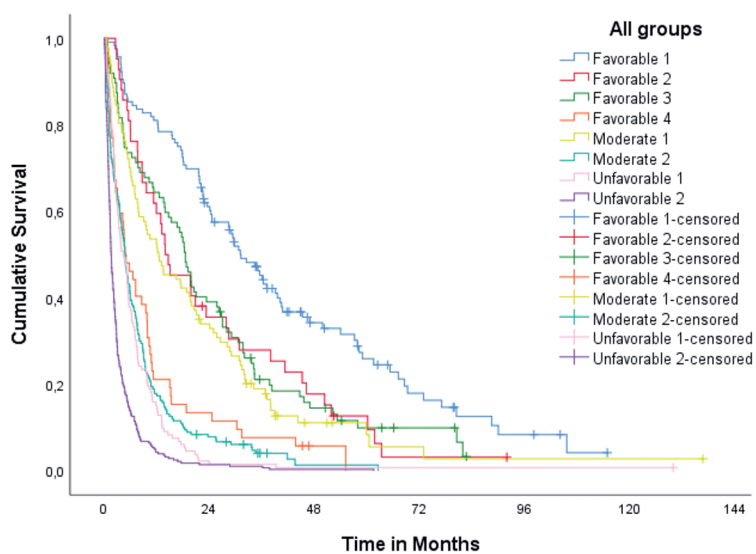


Figure 3A. Eight categories prior to merging.

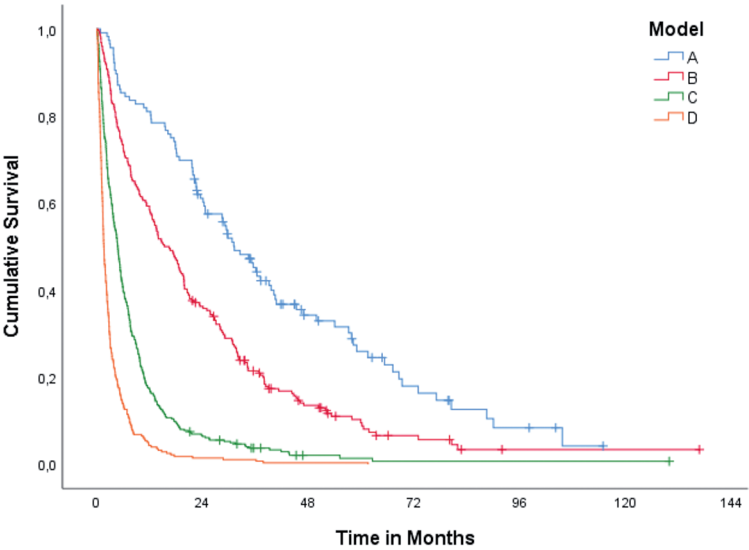


Figure 3B. Stratification model after merging.

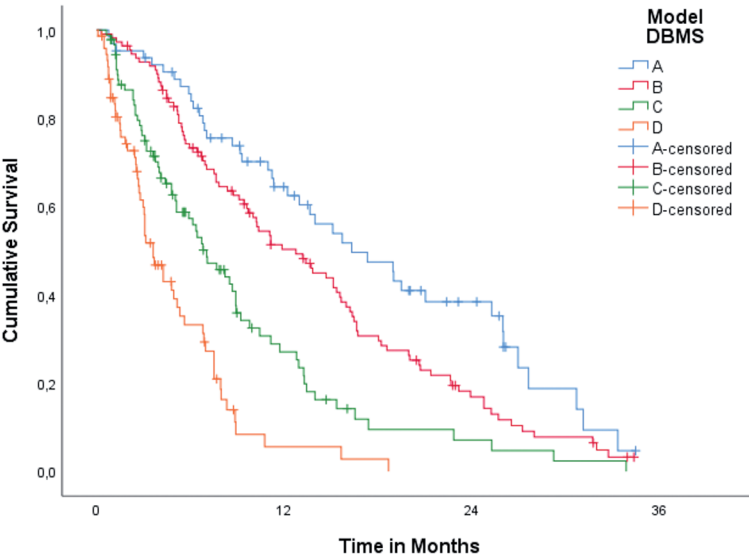


Figure 3C. Stratification model applied to DBMS database.

DISCUSSION

In this retrospective study of 1043 patients treated for symptomatic SBM it is shown that the clinical profile of the primary tumor, performance status and – in the subgroup of a favorable clinical profile only – the presence of visceral and brain metastases are associated with survival. Other prognostic factors such as the presence of extraspinal bone metastases, number and location of spinal metastases and neurological functioning did not show a significant effect on survival.

The most important limitation of this study is its retrospective design. Due to the fact that all patients were treated in a single institution, clinical information was readily available, including radiology reports. However, this does not rule out the possibility of inaccuracy of the source data. Furthermore, no SBM-specific treatment protocols existed, exemplified by the fact that the landmark study by Patchell et al.² resulted in more surgical interventions being performed in the period after publication. However, as this study analyzes survival only and therapy for SBM is not directly aimed at prolonging survival, it is unlikely that our results are influenced by this change in therapeutic approach. It is possible that the presence of brain metastases is underrepresented in this study population, as whole-brain scans were not routinely performed, contrary to thoracic and abdominal scans. As a result, most of the patients with brain metastases had symptomatic lesions. It is unclear whether asymptomatic brain metastases have the same predictive value in this specific patient population. Lastly, in our institution treatment for SBM only takes place in symptomatic patients and only patients treated locally for their SBM by means of surgery or radiotherapy were included. As a consequence, patients with symptomatic SBM that received only supportive care are not represented in this study.

In contrast to the previous study by our group – which was based on a prospective database with only radiotherapy patients – patients with a cervical located SBM were not excluded, nor were patients with renal cell carcinoma, leading to better generalizability of the data. Because the prospective DBMS database was closed after an inclusion period of 2.5 years, median follow-up times are distinctly different. Survival times in category A are therefore limited. Since the DBMS inclusion criteria were stricter and contained more patients with a favorable clinical profile and fewer with an unfavorable profile, median survival times were

better than in the current database. However, as a nearly identical c-score shows, the presented model is still capable of stratification based on the identified risk factors.

As has been established in literature, primary tumor type – in this study represented by clinical profile – is shown to be the factor of greatest influence on survival in patients with symptomatic SBM²¹. This means that an accurate and up-to-date tumor classification is essential for prognostication. The positive effect of new treatments such as anti-VEGF therapy will mean that in the near future survival with symptomatic SBM may increase considerably for certain tumors²². Also, it is unclear whether there is a difference in survival for patients with SBM from different subtypes of the same primary cancer, as is the case in breast cancer with estrogen, progesterone and HER2 interactions²³. These topics should be the subject of further SBM-specific studies.

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

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

Even though neurological status is one of the most important factors to consider when deciding on treatment, the presence of neurological deficit at the start of treatment does not directly influence survival in any of the three clinical profiles described in this study. Rades et al. have shown that the time of developing motor deficits is the most important factor predicting improvement of neurological functioning after treatment²⁴. Neurologic status should therefore be viewed as an indication for treatment, rather than a predictive factor when estimating survival. Especially in the case of sudden paraplegia due to spinal cord compression, swift and decisive treatment is far more important than estimation of survival, as the possible benefits of treatment in terms of quality of life far outweigh the possible risks in terms of a short remaining lifespan. When assessing neurological deficit in patients with SBM, the Frankel classification might not be the most suitable tool, as it was originally designed for categorizing spinal cord injury only. Neurological symptoms caused by nerve root compression or compression of the cauda equina are not covered, necessitating the development of a SBM-specific classification for describing neurological deficit.

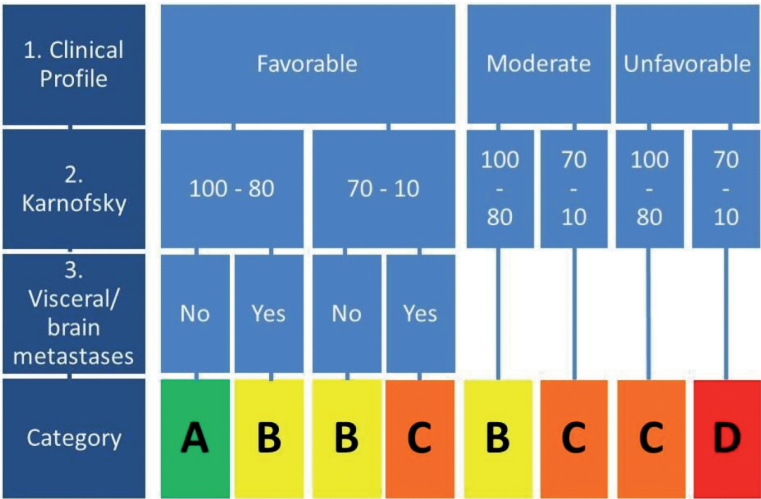


Figure 4. Flowchart for stratification.

Even though the number and location of SBM influence treatment options such as possibilities of surgical fixation and range of radiation fields, they did not show a significant effect on survival. Sixty-nine percent of all studied patients had more

than one confirmed spinal metastasis and it is not unlikely that a large proportion of patients classified as having a solitary metastasis in fact have occult lesions not yet detected²⁵. Lastly, the presence of extraspinal bone metastases was not associated with survival.

New model

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

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

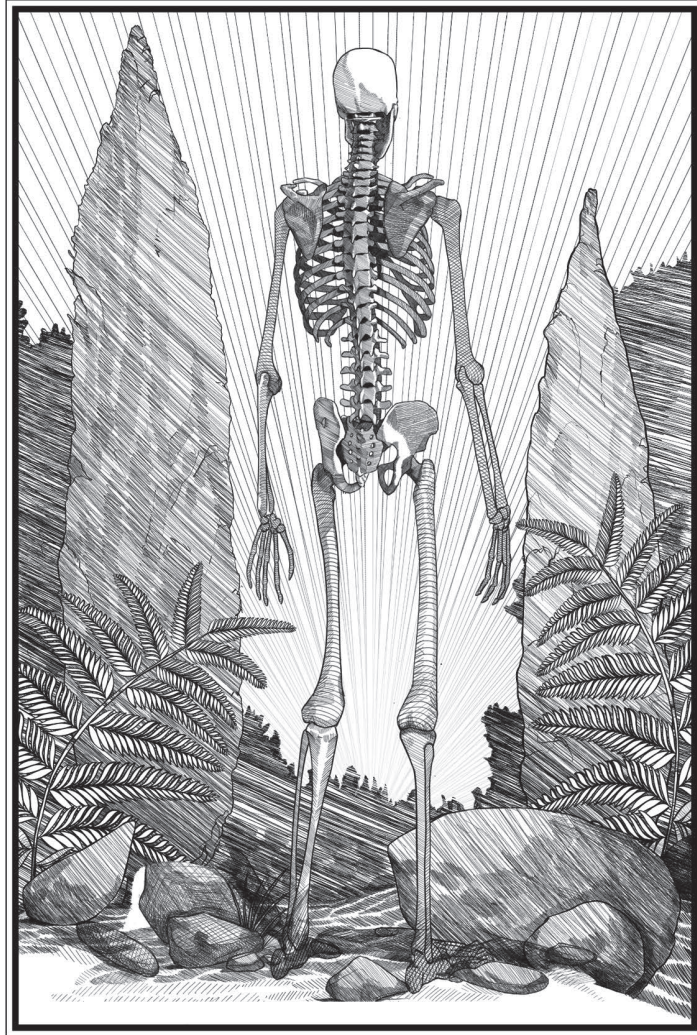
This large data collection provides a better understanding of how risk factors interact when stratified for primary tumor. It is shown that clinical profile and performance status have a strong impact on survival in all patients with symptomatic SBM. The presence of visceral and/or brain metastases is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

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

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CHAPTER V

Molecular phenotype is associated with survival in breast cancer patients with spinal bone metastases

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ABSTRACT

Background. To aid in therapy selection for patients with spinal bone metastases (SBM), predictive models have been developed. These models consider SBM from breast cancer a positive predictive factor, but do not take phenotypes based on estrogen (ER), progesterone (PR) and human epidermal growth factor 2 (HER2) receptors into account. The aim of this study was to ascertain whether receptors are associated with survival, when the disease has progressed up to SBM.

Methods. All patients who were treated for SBM from breast cancer between 2005 and 2012 were included in this international multi-center retrospective study (n=110). Reports were reviewed for ER, PR and HER2 status and subsequently subdivided into one of four categories; luminal A, luminal B, HER2 and triple negative. Survival time was calculated as the difference between start of treatment for SBM and date of death. Analysis was performed using the Kaplan-Meier method and log-rank tests.

Results. Median follow-up was 3.7 years. Survival times in the luminal B and HER2 categories were not significantly different to the luminal A category and were joined into a single receptor positive category. Eighty-five patients (77%) had a receptor positive phenotype and 25 (23%) had a triple negative phenotype. Median survival time was 22.5 months (95%CI 18.0-26.9) for the receptor positive category and 6.7 months (95%CI 2.4-10.9) for the triple negative category ($p<0.001$).

Conclusions. Patients with SBM from breast cancer with a triple negative phenotype have a shorter survival time than patients with a receptor positive phenotype. Models estimating survival should be adjusted accordingly.

INTRODUCTION

The treatment of patients with symptomatic spinal bone metastases (SBM) has made considerable progress over the past two decades. Even though radiotherapy remains the cornerstone of treatment, surgical interventions are being increasingly used, ranging from minimally invasive surgery to total en-bloc spondylectomy. Patients with SBM generally have a short remaining life span, making risk of overtreatment a common concern. Therefore, extent and type of treatment should not only depend on a patient's symptoms, but also on expected survival. Several survival prediction models have been developed to aid in clinical decision making and whilst they differ in approach, it is accepted that the primary tumor causing the SBM is the strongest predictor of survival^{1,2}. Patients with symptomatic SBM from breast cancer tend to live longer than patients with SBM from, for instance, prostate or lung cancer^{3,4}. This is reflected in all predictive models, where breast cancer is considered a favorable prognostic factor, as opposed to other primary cancers⁵⁻⁹.

Based on estrogen receptor status (ER), progesterone receptor status (PR) and human epidermal growth factor receptor 2 status (HER2), several molecular phenotypes of breast cancer can be distinguished^{10,11}. It has been established that these phenotypes are predictive of survival from the time of diagnosis of the primary tumor^{12,13}, however, it is unclear whether this effect remains when the disease has progressed up to the point of symptomatic SBM. If so, the manner in which the aforementioned predictive models stratify patients based on primary tumors needs to be adjusted, distinguishing between different breast cancer phenotypes.

The aim of the present study was to ascertain whether breast cancer molecular phenotypes are associated with survival of patients presenting with symptomatic SBM and to provide guidelines for improvement of the existing predictive models, if necessary.

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METHODS

In this international multicenter retrospective cohort study, all consecutive breast cancer patients presenting with symptomatic SBM between January 2005 and December 2012 at tertiary referral centers in Leiden, Graz, and Aarhus were included. The primary data sources were the patient's clinical files, pathology reports and admission forms. ER, PR and HER2 information was obtained from reports at the time of diagnosis of the primary tumor. Due to the fact that the process of decalcification can influence the results of the receptor status determination, only information derived from material of the primary tumor was entered into the study. Receptor information derived from the metastasis was disregarded. In all three participating centers, tumors were considered positive for ER or PR when $\geq 10\%$ of the tumor cells displayed nuclear staining. Initial screening for HER2 was performed using immunohistochemistry. When results were equivocal (weakly positive; score 2+) additional molecular testing was performed using in situ hybridization. In Leiden, chromogenic in situ hybridization (CISH) was used, whereas in Graz and Aarhus fluorescent in situ hybridization (FISH) was used. All laboratories participated in quality assurance programs during the study period.

Based on the ER, PR and HER2 expression, tumors were further subdivided into four categories; luminal A, luminal B, HER2 and triple negative. The luminal A subtype is ER positive and/or PR positive without HER2 overexpression. The luminal B subtype is ER positive and/or PR positive with HER2 overexpression. The HER2 subtype is ER and PR negative, with HER2 overexpression. Finally, the triple negative subtype is negative for all three receptors. To avoid confounding of our results based on the availability of systemic treatment options, 2005 was chosen as the starting year of this study. At this time, the testing for HER2 status was common practice and guidelines in all participating centers had implemented the routine use of agents such as trastuzumab in both adjuvant and palliative settings.

Statistical analysis

Survival time was calculated as the difference between start of treatment for the spinal metastasis and date of death or last follow-up moment recorded. Survival curves were estimated by using Kaplan-Meier method. Follow-up was assessed by employing the reverse Kaplan-Meier method¹⁴. Cox proportional hazard

models were used to assess the effect of the molecular phenotypes on survival. Survival curves were compared using log-rank tests. Harrell's C-statistic was used as a measure of the predictive accuracy of the model before and after adjustment. The C-statistic estimates the probability of concordance between predicted and observed responses¹⁵. A *p*-value of <0.05 was considered statistically significant. All analyses were performed using SPSS 20.0, Armonk NY, IBM Corp.

RESULTS

Table 1 summarizes the characteristics of the 111 patients studied, of whom 110 (99%) were female and one (1%) was male. The mean age at the start of treatment for the spinal metastasis was 59.9 years (SD ± 13.9 years). The symptomatic SBM were most commonly located in the thoracic (n=34, 31%) part of the spine. Primary treatment of the spinal metastasis consisted either of radiotherapy (n=69, 62%), surgery (n=21, 19%) or systemic therapy only (n=21, 19%). Patients were classified as luminal A (n=67, 60%), luminal B (n=9, 8%), HER2 (n=11, 10%) and triple negative (n=24, 22%).

Median follow-up was 3.2 years (minimum 0.6, maximum 5.5 years) and there was no loss to follow-up. The overall median survival was 18.0 months (95%CI 12.7-23.2) and there was no significant difference in median survival times between the participating centers (*p*=0.529) (table 2). In total 82 patients (74%) died during follow-up.

Survival analysis showed that median survival times in the luminal A, luminal B and HER2 categories were not significantly different, whereas the median survival time in the triple negative category was shorter (figure 1A and table 2). Due to the fact that there were few patients in the luminal B and HER2 categories, these were added to the luminal A group, creating a new category 'receptor positive' as opposed to the triple negative category.

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Table 1. Patient characteristics. SD: standard deviation.

Characteristic	N (%)
Gender	
Female	110 (99)
Male	1 (1)
Age (mean, years $\pm$ SD)	59.9 $\pm$ 13.9
Location treated spinal metastases	
Cervical only	None
Cervicothoracic	12 (11)
Thoracic only	34 (31)
Thoracolumbar	25 (22)
Lumbar only	17 (15)
Diffuse	23 (21)
Visceral and/or brain metastases	
Present	56 (50)
Not present	55 (50)
Karnofsky performance status	
Normal (100-80%)	58 (52)
Impaired (70-10%)	52 (47)
Missing	1 (1)
Initial SBM treatment	
Radiotherapy	69 (62)
Surgery	21 (19)
Systemic / Palliative	21 (19)
Molecular phenotype	
Luminal A	67 (60)
Luminal B	9 (8)
HER2	11 (10)
Triple negative	24 (22)

Table 2. Survival data per hospital and phenotype. MOS: median overall survival. P-values refer to overall log-rank comparison.

Variable	N (%)	MOS (95%CI)	p-value
Hospital			0.529
Leiden	61 (55)	18.0 (9.5-26.4)	
Graz	39 (35)	16.6 (8.8-24.4)	
Aarhus	11 (10)	14.7 (3.1-26.4)	
Molecular phenotype			<0.001
Luminal A	67 (60)	22.5 (17.9-27.0)	
Luminal B	9 (8)	26.9 (9.1-44.7)	
HER2	11 (10)	20.9 (1.1-40.8)	
Triple negative	24 (22)	5.5 (2.0-9.0)	
Receptor Status			<0.001
Receptor positive	87 (78)	23.4 (19.0-27.8)	
Triple negative	24 (22)	5.5 (2.0-9.0)	

The subsequent survival analysis showed a median survival time of 23.4 months (95%CI 19.0-27.8) for the receptor positive category and 5.5 months (95%CI 2.0-9.0) for the triple negative category ($p < 0.001$) (figure 1B and table 2). The corresponding hazard ratio was 3.6 (95%CI 2.1-5.9, $p < 0.001$). The median time to development of symptomatic SBM from diagnosis of the primary tumor was 11.0

months (95%CI 2.0-20.0) in the triple negative category and 21.1 months (95%CI 14.0-28.2) in the receptor positive category (p=0.005).

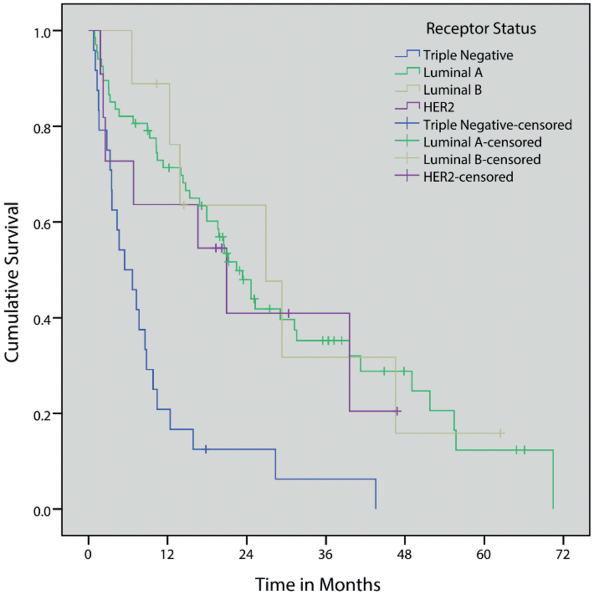


Figure 1A. Survival curves of all four phenotypes

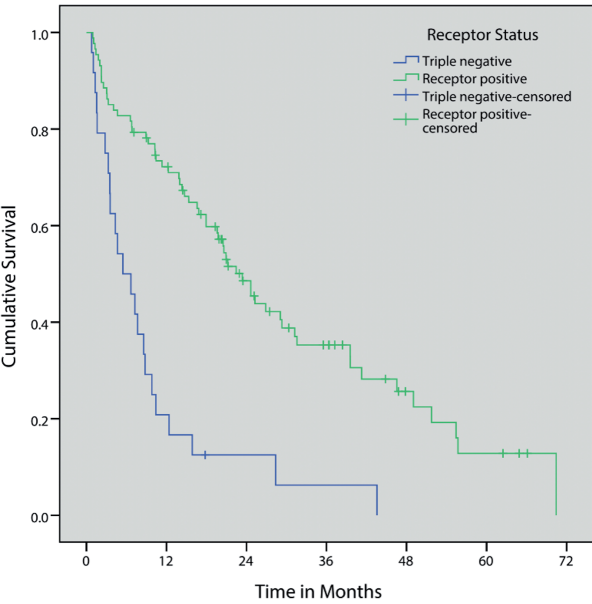


Figure 1B. Survival curves after merging

To illustrate the effects of discerning between receptor positive and triple negative breast cancer, the cohort was stratified into three categories according to a previously published predictive model⁹, both before and after adjusting the primary tumor classification. Before adjustment, all breast cancer patients were considered to have a ‘favorable clinical profile’. The current results, however, suggest that triple negative breast cancer should be considered as having a ‘moderate clinical profile’, since a median survival of 5.5 months is in line with survival times described in this category. Receptor positive breast cancer remains in the ‘favorable’ category. The number of patients in category A decreased from 32 (29%) to 27 (25%) and the median survival time has risen from 31.2 months (95%CI 14.6-47.9) to 39.6 months (95%CI 19.2-60.0). Patients with a triple negative phenotype have been assigned to categories B and C, decreasing median survival times in those categories slightly (table 3). The C-statistic before the adjustment was 0.61 and after the adjustment 0.64, suggesting an improvement in the accuracy of the model.

Table 3. Median survival times before and after model adjustment for molecular phenotype. MOS: median overall survival. HR: hazard ratio. CI: confidence interval.

Predictive Category	N (%)	MOS (95%CI)	HR	95%CI	p-value
Before adjustment					
A	32 (29)	31.2 (14.6-47.9)	-	-	0.007
B	48 (44)	15.9 (8.7-23.1)	1.8	1.0-3.1	0.046
C	30 (27)	9.8 (7.6-12.0)	2.7	1.5-4.9	0.002
D	None	N/A	N/A	N/A	N/A
After adjustment					
A	27 (25)	39.6 (19.2-60.0)	-	-	0.001
B	51 (46)	14.7 (9.9-19.5)	2.5	1.3-4.7	0.004
C	32 (29)	9.3 (7.1-11.5)	3.8	1.9-7.3	<0.001
D	None	N/A	N/A	N/A	N/A

DISCUSSION

In this international multi-center retrospective study of 111 patients treated for symptomatic SBM caused by breast cancer, it is shown that, even though the disease has progressed up to end stage disease, patients with a triple negative phenotype have a much shorter median survival time (5.5 months, 95%CI 2.0-9.0) than patients with a receptor positive phenotype (23.4 months, 95%CI 19.0-27.8). This suggests that models estimating survival in patients with symptomatic SBM should at least differentiate between these two types of breast cancer.

Even though in general patients with symptomatic SBM from breast cancer have a relatively long survival, the limited availability of systemic treatment options in patients with a triple negative phenotype results in a shorter survival. Predictive models based on previous studies overestimated survival in these patients, leading to overtreatment. The effect of correcting for molecular phenotypes was confirmed when a previously published survival prediction model was adjusted for the current findings, resulting in an improvement of the accuracy (table 3 and figure 2). A precise model can be a useful tool for clinicians. Extensive surgical treatment and long-course radiotherapy regimens could be avoided in patients with a short expected survival and in patients with a longer expected survival extent of treatment could be increased, if needed.

The most important limitation of this study is its retrospective design. However, since the endpoint was death and the only clinical information gathered was derived from pathology reports, the design is not expected to have a large impact on the quality of our results. Also, receptor status was assessed in different laboratories and by different pathologists. HER2 immunohistochemistry can be difficult to interpret, however, in all three institutes equivocal cases were subjected to molecular testing using *in situ* hybridization. The distribution of patients over the four categories was slightly different when compared to larger studies^{16,17}. The luminal B category was underrepresented and the luminal A category was overrepresented in this study. However, since the luminal B and HER2 categories contained few patients and were joined with the luminal A category the overall effect on the survival data was negligible. This means that a statement on the exact survival times in the luminal B and HER2 categories cannot be made based on small sample size. From a clinical perspective however, we believe it is more relevant to identify patients with a short survival in order to avoid overtreatment, than to give an exact estimation of survival for patients that have an expected survival of more than a year.

A previously published study on SBM from breast cancer investigated the role of ER and PR status on survival¹⁸ and found that patients negative for ER had a decreased survival when compared to patients with a positive ER status. As this study was conducted before the onset of HER2 testing, the effects of this receptor were not considered. A study conducted by Rades et al.¹⁹ examined the effects of several other risk factors, such as performance status and the presence of visceral

metastases. Based on these results a predictive model specifically for patients with SBM from breast cancer was created, but unfortunately the authors did not analyze the effects of receptor status on survival.

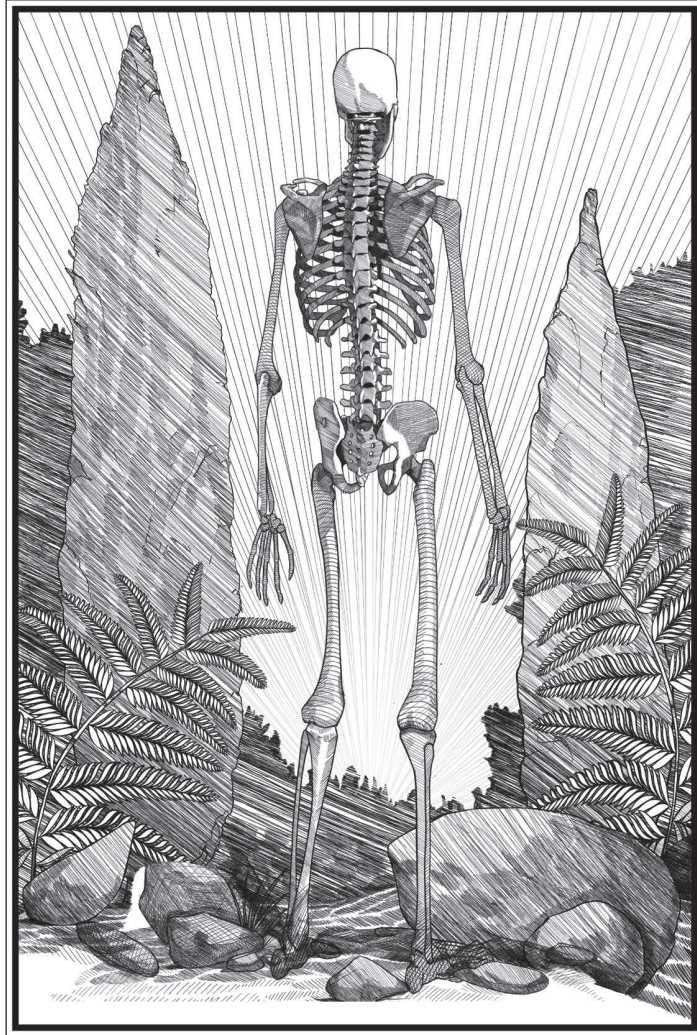
In conclusion, in this study it is shown that patients with a triple negative phenotype have a much shorter survival than patients with a receptor positive phenotype. The data presented in this study can guide the adjustment and development of models estimating survival in patients with SBM, increasing predictive accuracy and reducing the risk of overtreatment.

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CHAPTER VI

Predictive value of six prognostic scoring systems for spinal bone metastases – An analysis based on 1379 patients

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ABSTRACT

Background. Models to aid in the decision making process for the treatment of spinal bone metastases (SBM) have been developed by Tomita, Tokuhashi, Van der Linden, Bauer, Rades and Bollen. The aim of this study was to assess the predictive accuracy of these six models designed to estimate survival of patients suffering from SBM.

Methods. All patients who were treated for SBM between 2000 and 2010 were included in this international multi-center retrospective study (n=1379). Medical records were reviewed for all items needed to employ the models. Survival time was calculated as the difference between start of treatment for SBM and date of death. Survival curves were estimated using the Kaplan-Meier method and accuracy was assessed with the c-statistic. Survival rates of the worst prognostic groups were evaluated at four months.

Results. Median follow-up was 6.7 years (95%CI 5.6-7.7) with a minimum of 2.3 years and a maximum of 12.3 years. The overall median survival was 5.1 months (95%CI 4.6-5.6). The most common primary tumors were breast (n=388, 28%), lung (n=318, 23%) and prostate cancer (n=259, 19%). The Tokuhashi, Bauer, Tomita and Van der Linden models performed similar with a c-statistic of 0.64-0.66 and a 4-month accuracy of 62-65%. The Rades model (c-statistic 0.44) and Bollen model (c-statistic 0.70) had a 4-month accuracy of 69% and 75%, respectively.

Conclusion. The Bollen model performs better than the other models. However, improvements are still warranted to increase the accuracy.

INTRODUCTION

Prediction of survival has become an integral part of selecting the appropriate treatment for patients suffering from symptomatic spinal bone metastases (SBM). Depending on the symptoms, patients with a short expected survival are most likely to benefit from short radiotherapy regimens, best supportive care or minimally invasive surgery. Patients with a relatively long expected survival will most likely benefit from high dose radiotherapy or – in the case of radioresistant tumors and biomechanical instability – more extensive surgical interventions. Several studies have shown that the estimation of survival by clinicians in terminally ill patients is inaccurate and have suggested the use of prognostication models in order to prevent exposure of patients to unnecessarily extensive treatments¹⁻³.

Models to aid in the decision making process have been developed by Tokuhashi, Bauer – later modified by Leithner – Tomita, Van der Linden, Rades and Bollen⁴⁻¹⁰. These models make use of a combination of different risk factors to estimate the survival of individual patients. Several smaller studies have been undertaken to assess the predictive value of some of the models^{6,11-13}, however, a large international validation study assessing all the models simultaneously has not yet been performed.

The aim of this study was to assess the validity and predictive accuracy of six models designed to estimate survival in a large cohort of patients with spinal bone metastases.

MATERIALS AND METHODS

In this international multicenter retrospective cohort study, all patients presenting with symptomatic SBM at two tertiary referral centers in Leiden, the Netherlands and Graz, Austria between January 2000 and December 2010 were included.

Patients were identified through database searches linking treatment and diagnostic codes and through database searches based on surgical coding. Information on date of death was obtained from medical records or by contacting the general practitioner or the civil registry office.

The primary data sources were the patient's clinical files, radiology reports and admission forms. Baseline variables obtained before start of treatment were gender, age, primary tumor, location and number of SBM, the presence of visceral and/or brain metastases, the presence of extraspinal bone metastases, pretreatment functioning according to the Karnofsky performance status¹⁴ (KPS) and neurological functioning according to the Frankel classification¹⁵. The Eastern Cooperative Oncology Group (ECOG) performance status¹⁶ was obtained based on the KPS values. Time to development of SBM was defined as the interval from primary cancer diagnosis to the diagnosis of SBM⁴. If required for a specific scoring system, primary tumors were classified as slow, moderate or rapid growing^{5,6,11}. All variables were further subdivided according to the instructions of each predictive model, resulting in different classifications for the same variable.

During the creation of the current database, visceral metastases were scored as either being present or not present. The models of Tomita and Tokuhashi models further distinguish visceral metastases as either being removable or not removable. In our analysis, if visceral metastases were present, they were scored as 'not removable'. Also, the model of Rades scores the time to development of motor deficits. Retrospectively, this variable could not accurately be obtained from the medical records used to create this database. Therefore, the maximum number of points in the model was reduced from 25 to 21 and the minimum from 6 to 5. The cutoff scores for the predictive groups were changed accordingly. The Bollen model was created based on a large percentage of patients also included in this study. Therefore, an additional analysis based on external data only was conducted for this model.

Statistical analysis

Survival time was calculated as the time between start of treatment for the spinal metastasis and date of death or latest follow-up. Survival curves were estimated by using the Kaplan-Meier method and were compared using log-rank tests. Follow-up was assessed by employing the reverse Kaplan-Meier method¹⁷. Hazard ratios were estimated by using Cox proportional hazard models. All multivariate models were corrected for differences in survival between the participating centers. Harrell's c-statistic was used to assess the predictive power of each model. It estimates the probability of concordance between predicted and observed responses, with a value of 1.0 being perfect agreement¹⁸. For each model, survival rates of the

predictive group with the lowest expected survival were assessed at four and six months. Survival rates of the predictive groups with the highest expected survival were assessed at one and two years. A p -value of <0.05 was considered statistically significant. All analyses were performed using SPSS 20.0, Armonk NY, IBM Corp.

RESULTS

Table 1 summarizes the characteristics of the 1379 patients studied. Fifty-two percent were male and at baseline the mean age was 64.6 ± 12.4 years. The SBM were most commonly located in the thoracic part of the spine ($n=376$, 27%) and most patients had three or more SBM ($n=730$, 53%). Extraspinal bone metastases were found in 913 patients (66%) and visceral or brain metastases were found in 611 patients (44%). The majority of patients had no ($n=746$, 54%), or only minor ($n=464$, 34%) neurological deficit. Treatment consisted of radiotherapy in 1141 patients (83%) and 109 patients (8%) underwent a combination of surgery and radiotherapy. Thirty-three patients (2%) underwent only surgery and 96 patients (7%) had conservative treatment. The most prevalent primary tumors were breast

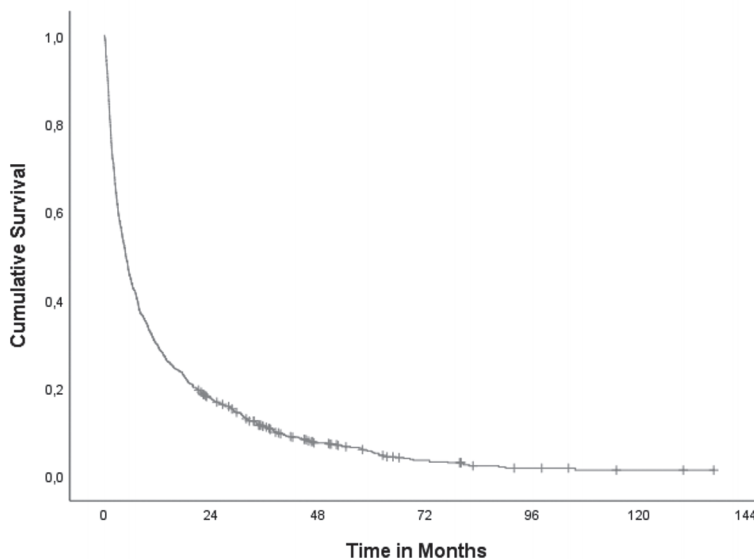


Figure 1. Overall survival

cancer (n=388, 28%), lung cancer (n=318, 23%), prostate cancer (n=259, 19%), kidney cancer (n=90, 7%) and colon cancer (n=73, 5%). The remaining 18% consisted of 16 different primary tumors (table 2).

Table 1. Patient characteristics. SD: standard deviation.

Characteristic		N (%)
Sex		
Male		718 (52)
Female		661 (48)
Age (years, mean $\pm$ SD)		64.6 $\pm$ 12.4
Location treated spinal metastasis		
Cervical		53 (4)
Cervicothoracic		63 (5)
Thoracic		376 (27)
Thoracolumbar		351 (25)
Lumbar		332 (24)
Diffuse		204 (15)
Number spinal metastases		
One		415 (30)
Two		234 (17)
Three or more		730 (53)
Number extraspinal bone metastases		
None		466 (44)
One or two		336 (24)
Three or more		577 (42)
Karnofsky performance status $\Rightarrow$	ECOG performance status	
100	0	22 (2)
80-90	1	518 (37)
60-70	2	466 (34)
40-50	3	294 (21)
10-30	4	30 (2)
Missing	Missing	49 (4)
Visceral/Brain metastases		
Present		611 (44)
Not present		768 (56)
Frankel score		
A		8 (<1)
B		8 (<1)
C		143 (10)
D		464 (34)
E		746 (55)
Missing		10 (<1)
Treatment		
Radiotherapy		1141(83)
Surgery		33 (2)
Radiotherapy and surgery		109 (8)
Palliative/conservative		96 (7)
Hospital		
Leiden		1043 (76)
Graz		336 (24)

Table 2. Primary tumors and median survival times. ACUP: adenocarcinoma of unknown primary. CI: confidence interval.

Primary	N (%)	Median survival (95%CI)
Breast	388 (28)	18.6 (15.8-21.4)
Lung	318 (23)	2.0 (1.6-2.4)
Prostate	259 (19)	7.4 (5.9-9.0)
Kidney	90 (7)	7.8 (4.2-11.3)
Colon	73 (5)	3.1 (2.3-3.9)
Urothelial cell carcinoma	36 (3)	1.7 (0.9-2.5)
ACUP	31 (2)	2.8 (1.9-3.6)
Melanoma	28 (2)	1.5 (0.2-2.8)
Pancreaticobiliary	28 (2)	2.5 (1.7-3.3)
Esophagus	27 (2)	2.1 (1.1-3.0)
Thyroid	15 (1)	7.3 (0.0-22.3)
Stomach	14 (1)	1.4 (0.0-3.4)
Hepatocellular carcinoma	13 (<1)	4.8 (3.9-5.7)
Ewing sarcoma	12 (<1)	2.7 (0.3-5.1)
Osteosarcoma	9 (<1)	6.3 (0.0-12.6)
Ovary	9 (<1)	5.4 (4.1-6.6)
Cervix	8 (<1)	2.3 (0.0-7.7)
Uterus sarcoma	8 (<1)	7.2 (0.8-13.5)
Endometrium	6 (<1)	1.9 (0.0-17.7)
Tongue	4 (<1)	0.8 (0.0-2.8)
Liposarcoma	3 (<1)	13.4 (0.0-34.7)

Median follow-up from start of treatment was 6.7 years (95%CI 5.6-7.7) with a minimum of 2.3 years and a maximum of 12.3 years. Six patients moved abroad after treatment and were lost to follow-up. The overall median survival was 5.1 months (95%CI 4.6-5.6) (figure 1). A total of 1318 patients (96%) died during follow-up. Within two months after starting treatment, 379 patients (27%) died, whereas 257 patients (19%) survived for more than two years.

Multivariate analysis of each separate model showed that the primary tumor, performance status, the presence of visceral metastases and the time to development of SBM were associated with survival. Neurological functioning or ambulatory status, the number of spinal bone metastases and the number of extraspinal bone metastases were not significantly associated with survival in any of the models (table 3).

The median survival times and corresponding hazard ratios for each subgroup of all six models are shown in table 4. Even though all models are able to distinguish between short and long expected survival, the number of patients in each category differs greatly. Model based survival curves are shown in figures 2A-2F.

Table 3. Multivariate analysis of the variables for survival prediction as presented in the six models.

Tokuhashi	HR	95%CI	p-value
Primary tumor	1.3	1.2-1.3	<0.001
Performance status	1.8	1.6-1.9	<0.001
Visceral metastases	1.2	1.1-1.3	<0.001
Other bone metastases	-	-	n.s.
Spinal bone metastases	-	-	n.s.
Neurologic functioning	-	-	n.s.
Bauer	HR	95%CI	p-value
Primary tumor	2.0	1.8-2.2	<0.001
Visceral metastases	1.4	1.4-1.8	<0.001
Bone metastases	-	-	n.s.
Tomita	HR	95%CI	p-value
Primary tumor	1.5	1.4-1.6	<0.001
Visceral metastases	1.1	1.0-1.1	<0.001
Bone metastases	-	-	n.s.
Van der Linden	HR	95%CI	p-value
Primary tumor	1.4	1.3-1.5	<0.001
Performance status	1.7	1.6-1.9	<0.001
Visceral metastases	1.4	1.3-1.6	<0.001
Rades	HR	95%CI	p-value
Primary tumor	1.6	1.5-1.7	<0.001
Performance status	1.2	1.1-1.2	<0.001
Visceral metastases	1.1	1.1-1.2	<0.001
Interval to SBM	1.2	1.1-1.3	<0.001
Other bone metastases	-	-	n.s.
Ambulatory status	-	-	n.s.
Bollen	HR	95%CI	p-value
Primary tumor	1.9	1.7-2.0	<0.001
Performance status	2.0	1.8-2.2	<0.001
Visceral metastases	1.4	1.1-1.6	<0.001

HR: hazard ratio. CI: confidence interval. NS: not significant.

Table 4. Results survival analysis and multivariate analysis for survival prediction categories. MOS: median overall survival. CI: confidence interval. HR: hazard ratio.

Tokuhashi	N (%)	MOS, months (95%CI)	HR (95%CI)	p-value
Excisional	259 (20)	17.9 (12.8-22.9)	-	<0.001
Palliative	493 (37)	8.4 (7.0-9.8)	1.6 (1.4-1.9)	<0.001
No surgery	573 (43)	2.7 (2.4-3.0)	3.5 (3.0-4.2)	<0.001
Bauer	N (%)	MOS, months (95%CI)	HR (95%CI)	p-value
Local control	344 (25)	18.7 (15.8-21.7)	-	<0.001
Palliative	546 (40)	5.9 (4.9-6.9)	2.1 (1.8-2.4)	<0.001
Supportive care	489 (35)	2.5 (2.2-2.8)	3.8 (3.3-4.5)	<0.001
Tomita	N (%)	MOS, months (95%CI)	HR (95%CI)	p-value
Long-term	299 (22)	21.8 (18.6-25.0)	-	<0.001
Middle-term	277 (20)	5.9 (4.7-7.1)	2.2 (1.9-2.7)	<0.001
Short-term	410 (30)	4.9 (3.8-5.9)	2.7 (2.3-3.1)	<0.001
Terminal	393 (28)	2.5 (2.2-2.8)	4.3 (3.7-5.1)	<0.001
Van der Linden	N (%)	MOS, months (95%CI)	HR (95%CI)	p-value
A	146 (11)	29.8 (23.1-36.5)	-	<0.001
B	559 (42)	9.7 (8.2-11.1)	2.3 (1.9-2.8)	<0.001
C	625 (47)	2.5 (2.3-2.7)	5.8 (4.7-7.2)	<0.001
Rades	N (%)	MOS, months (95%CI)	HR (95%CI)	p-value
Extensive	1111 (84)	6.8 (6.1-7.6)	-	<0.001
Palliative	216 (16)	1.8 (1.4-2.3)	2.7 (2.3-3.1)	<0.001
Bollen	N (%)	MOS, months (95%CI)	HR (95%CI)	p-value
A	149 (11)	29.8 (22.7-36.9)	-	<0.001
B	318 (24)	16.5 (14.0-19.0)	1.8 (1.4-2.2)	<0.001
C	489 (37)	4.9 (4.4-5.4)	4.1 (3.2-5.1)	<0.001
D	374 (28)	1.7 (1.4-2.0)	9.2 (7.3-11.4)	<0.001

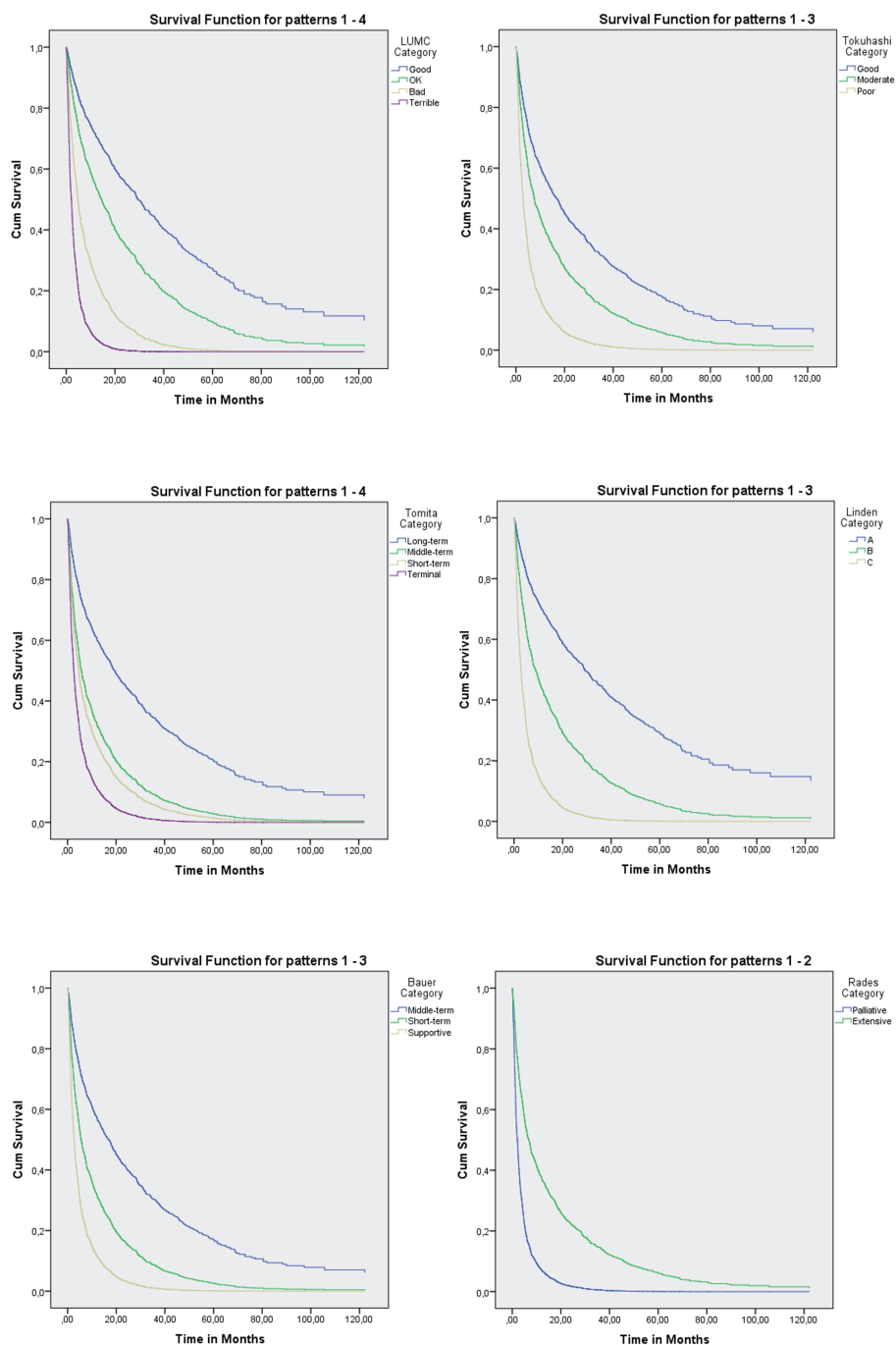


Figure 2a-2f. Model based survival curves.

Table 5 shows the c-statistic for each model, and the percentage of patients that were stratified correctly at four, six, twelve and twenty-four months. At four and six months, survival data from patients classified in the worst prognostic group of each model were used (e.g. Tomita category ‘Terminal’ or Bauer category ‘Supportive care’) and at twelve and twenty-four months survival data from patients classified in the best prognostic group of each model were used (e.g. Tomita category ‘Long-term’ or Bauer category ‘Local control’).

Table 5. Model performance. Four and six months based on worst prognostic group, twelve and twenty-four months based on best prognostic group.

Model	% dead within			% alive after	
	c-statistic	4 months	6 months	12 months	24 months
Tokuhashi	0.64	62%	74%	61%	39%
Bauer	0.64	64%	76%	58%	35%
Tomita	0.64	65%	78%	68%	47%
Van der Linden	0.66	64%	77%	80%	60%
Rades	0.44	69%	81%	37%	22%
Bollen (all data)	0.70	75%	86%	80%	60%
Bollen (external data)	0.69	67%	83%	82%	65%

The Tokuhashi, Bauer and Tomita models have an identical c-statistic and a relatively low predictive ability, both for their worst and best prognostic groups. The Van der Linden model has a similar c-statistic, but is much better at identifying patients with a longer survival. The Rades model has the lowest c-statistic, but shows relatively good predictive power for patients with short survival. However, patients with a long survival are poorly identified. The Bollen model has the highest c-statistic and is good at identifying patients with short survival and patients with long survival. When the results from the external data analysis are observed, the c-statistic remains almost identical. However, the number of patients stratified correctly at four months drops considerably.

DISCUSSION

In this multicenter retrospective study of 1379 patients treated for symptomatic SBM it is demonstrated how predictive models perform on a large independent dataset.

The most important limitation of this study is its retrospective design and the possibility of inaccurate interpretation of the source data. Also, the data were obtained from centers in two different European countries. Even though the quality of oncological care is considered to be excellent, differences in survival times between the centers were observed for some primary tumors, possibly resulting in lower predictive accuracy of the models. The multivariate analyses were adjusted for this center effect.

The Rades model was adjusted due to the fact that information concerning time to development of motor deficits could not reliably be obtained. Considering that neurologic deficit or ambulatory status were not associated with survival, it is unlikely that omitting this variable had a large effect on our results. Also, resectability of visceral metastases could not be assessed and all visceral metastases were considered unresectable. The effect of this on the accuracy of the Tokuhashi and Tomita models is unclear.

In order to predict survival, the evaluated models utilize a total of seven different variables. Each model has different guidelines on how to further categorize each variable, leading to different results for identical variables. As has been demonstrated, primary tumor, visceral metastases and performance status are associated with survival, whereas the number of SBM and the presence of extraspinal bone metastases are not.

On multivariate analysis, neurological functioning was also not associated with survival. Furthermore, including neurological functioning as a negative predictive factor in a model could prove to be disadvantageous. Restoration of ambulatory function in patients with acute deficit is the greatest gain possible in the treatment of SBM. If the estimated life expectancy would be too short based on a model incorporating neurological functioning, this patient would be denied the more aggressive, optimal treatment needed to improve his neurological functioning. Consequently, the use of a model would undermine, instead of improve the decision-making process. We therefore carefully suggest that neurological functioning and the duration of neurological deficit will be viewed as an indication for treatment, instead of a prognostic factor for estimating survival.

In 1990 Tokuhashi et al. created the first predictive model for SBM¹⁹ and the 2005 revised version⁹ is still one of the most commonly reported models to date. It was based on a retrospective analysis of 246 patients and uses six items to assign patients into one of three categories. In this study, three of these items were not associated with survival. The primary tumor classification was based on average survival periods for each cancer, but due to the low number of patients this was not very accurate. Low scores for both the worst and best predictive groups make it difficult to justify the use of this model in a clinical setting.

The original Bauer model was based on a retrospective analysis of 88 patients with spinal metastases and 153 patients with bone metastases in the extremities. Due to the fact that the presence of a pathologic fracture negatively influenced survival only in the extremities group, Leithner et al. modified the score for use in SBM. Even though it is one of the easiest models to use, the simple primary tumor classification and the lack of a performance score resulted in a low accuracy.

The Tomita model was based on a retrospective analysis of 67 patients and essentially consists of four items, as the 'bone metastases' category includes both spinal and extraspinal metastases. The primary tumor classification in slow, moderate and fast growing tumors has been shown to be quite accurate. Unfortunately, this model also lacks the incorporation of a performance score, resulting in a c-statistic identical to the Tokuhashi and Bauer models.

The Van der Linden model was based on 342 patients treated for painful SBM by means of radiotherapy within a multicenter randomized phase III trial. The model contained all three risk factors that were shown to be associated with survival in this article and has a c-statistic of 0.66. It performs better than the previous models, especially when identifying patients with a longer expected survival.

The Rades model was based on a retrospective analysis of 2029 patients, all of whom were treated with radiotherapy. With seven items, it is the most elaborate score. The aim of this model was to identify patients with poor survival who may be candidates for best supportive care and it achieved this goal. In a clinical setting however, patients with a longer survival also need to be identified correctly and the model fails to do so. It is the only score that takes time to development of SBM

into account. This variable was associated with survival on multivariate analysis and could potentially be used to increase the accuracy of the predictive models.

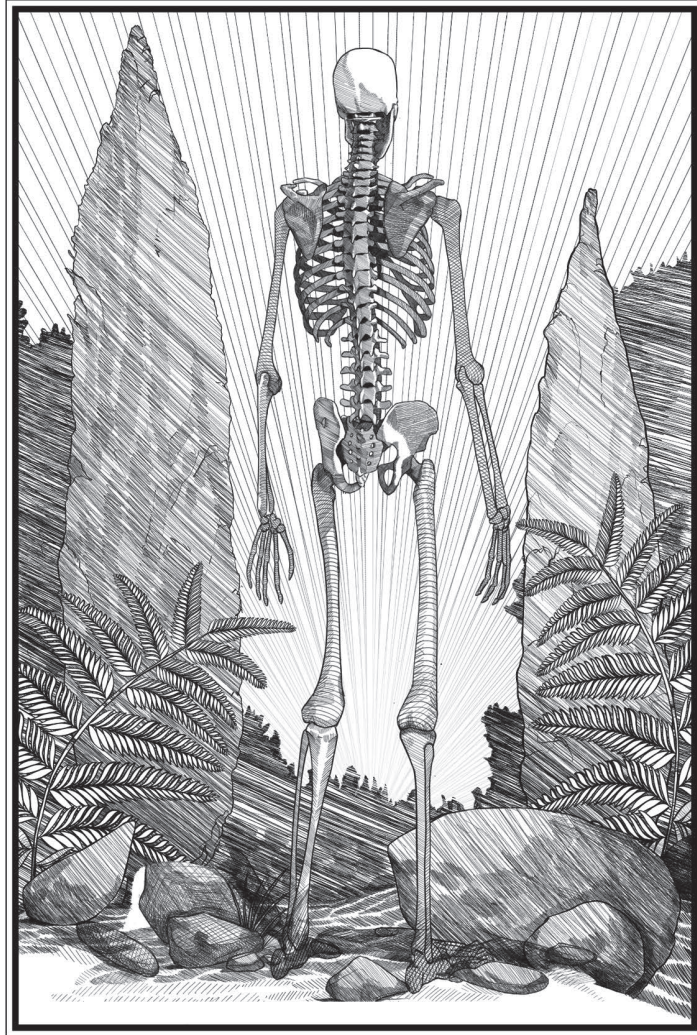
Lastly, the recently published Bollen model was based on a retrospective analysis of 1043 patients treated with surgery and radiotherapy. Essentially a hybrid of the Tomita and Van der Linden models, it has quite good results on both the short and long end of the survival spectrum. Even though the primary tumor classification is reasonably accurate, it still requires further specification of the malignancies in order to increase the discriminative ability.

CONCLUSION

This study provides an insight on how the available SBM models perform on a large dataset. The results suggest that the Bollen model performs best when identifying patients with a short and patients with a long expected survival. With the predicted survival outcome, appropriate choices for treatment can be made by patients and their treating physicians.

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CHAPTER VII

Clinical evaluation of the Spinal Instability Neoplastic Score in patients treated with radiotherapy for symptomatic spinal bone metastases

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ABSTRACT

Objective. To determine the predictive value of the Spinal Instability Neoplastic Score (SINS) in a cohort of patients treated with radiotherapy for spinal bone metastases.

Summary of background data: Assessment of spinal stability in metastatic disease is challenging and is mostly done by relying on clinical experience, in the absence of validated guidelines or an established predetermined set of risk factors. The SINS provides clinicians with a tool to assess tumor-related spinal instability.

Methods. A total of 110 patients were included in this retrospective study. Time to event was calculated as the difference between start of radiotherapy and date of occurrence of an adverse event or last follow-up, with death being considered a competing event. A competing risk analysis was performed to estimate the effect of the SINS on the cumulative incidence of the occurrence of an adverse event.

Results. Sixteen patients (15%) experienced an adverse event during follow-up. The cumulative incidence for the occurrence of an adverse event at 6 and 12 months was 11.8% (95%CI 5.1%-24.0%) and 14.5% (95%CI 6.9%-22.2%), respectively. Competing risk analysis showed that the final SINS classification was not significantly associated with the cumulative incidence of an adverse event within the studied population.

Conclusion. The clinical applicability of the SINS as a tool to assess spinal instability seems limited.

INTRODUCTION

Spinal bone metastases (SBM) develop in up to 70% of cancer patients¹. Back pain and neurological deficit are the most frequently reported symptoms²⁻⁴. Current management of SBM focuses on optimizing a patient's quality of life by providing effective pain relief and preserving or restoring neurological function². In addition, spinal instability is a third indication for treatment, as it can lead to the aforementioned symptoms. Whereas patients with stable spines can be treated using non-invasive procedures such as radiotherapy, patients with unstable spines potentially require surgical fixation, either through minimally invasive techniques such as percutaneous stabilization or through more invasive procedures involving open fixation.

Assessment of spinal stability is challenging and is mostly done by relying on clinical experience, in the absence of validated guidelines or an established predetermined set of risk factors. The absence of a standardized approach hinders communication between physicians of different medical specialties and can result in under- as well as overdiagnosis of spinal instability.

In 2010, the Spinal Oncology Study Group introduced the Spinal Instability Neoplastic Score (SINS); the first consensus-based guideline that aids in the assessment of a patient's risk of spinal instability in the setting of neoplastic spinal disease⁵. The SINS determines tumor-related instability based on six criteria and classifies the spinal column as stable, potentially unstable or unstable. Surgical consultation is recommended for patients with a spinal column classified as either potentially unstable or unstable. As such, the SINS facilitates interdisciplinary communication, assesses and categorizes spinal instability and optimizes treatment decision making.

Previous studies have already shown that the SINS has a substantial to excellent inter-observer and intra-observer reliability⁶⁻⁹. Nevertheless, for it to be useful in clinical practice, it should also be evaluated whether the score is indeed predictive of progressive spinal instability when applied to longitudinal patient cohorts. Studies have shown that the total SINS score is not predictive for new or progressive vertebral compression fractures (VCF) in patients receiving high dose

stereotactic radiotherapy¹⁰⁻¹². Therefore, the role of SINS in assessing this specific endpoint is debatable.

The aim of the current study was to determine the predictive value of the total and individual components of the SINS system for spinal instability in a cohort of patients with spinal bone metastases, treated with radiotherapy. Secondly, the interobserver agreement of both the total categorical SINS score and the individual components was determined.

PATIENTS AND METHODS

All consecutive patients who were treated with radiotherapy for symptomatic SBM between January 2000 and December 2010 in the Leiden University Medical Center, the Netherlands, and also had pretreatment computed tomography (CT) imaging were eligible for inclusion in this retrospective cohort study. In order to ensure accurate correlation between the clinical situation and the obtained images, the maximum accepted time between the diagnostic CT scan and start of treatment was two months. Patients who had already been stabilized were excluded, leaving the patients in whom there is clinical equipoise regarding the best treatment strategy and thus reflecting the more important clinical scenario in daily practice. Only a single metastatically affected vertebra was evaluated per patient. This selection was determined based on inclusion within the radiation field. If multiple vertebrae within the same radiation field were affected by metastatic disease, the vertebra with the highest score on the SINS components location or vertebral body collapse was selected for the analysis.

Each vertebral segment was scored according to the SINS criteria as described by Fisher et al⁵. The individual SINS components consisted of location (junctional, mobile, semi-rigid, and rigid spine), type of pain (mechanical, non-mechanical, pain-free), type of lesion (lytic, mixed, sclerotic), spinal alignment (subluxation/translation, kyphosis/scoliosis, normal), presence of baseline VCF (>50% collapse, <50% collapse, no collapse but >50% of the body involved, or none of the above), and whether the tumor involved the posterolateral elements (bilateral, unilateral, none). The radiological SINS components bone lesion, alignment, vertebral body collapse, and posterolateral involvement of spinal elements were assessed

independently by four expert observers (SD; orthopedic surgeon, YL; radiation oncologist, CR; radiologist, and WP; neurosurgeon). The observers were blinded to the patients' event status. The SINS components pain and location were assessed by one observer (LB) based on the patients' clinical files and admission forms. Based on the values for the individual SINS components, the total score was calculated and the spine was classified as being stable, potentially unstable or unstable⁵.

Patient characteristics were assessed using de Karnofsky Performance Status (KPS)¹³ and the Frankel classification¹⁴. Expected survival of each individual patient was determined using the Bollen model¹⁵. Clinical and/or radiological follow-up data for instability was collected until 12 months after initial radiotherapy. The end points of the study were considered adverse events after radiotherapy and consisted of (1) the development of a new pathologic fracture, (2) progression of an existing pathologic fracture, and (3) deterioration of alignment requiring surgical stabilization of the irradiated spinal segments. The occurrence of an adverse event was determined using patients' medical charts and/or follow-up imaging.

Statistical analysis

Interobserver agreement between all four observers was calculated using Fleiss' kappa¹⁶. The level of agreement for the obtained kappa was determined according to Landis et al.¹⁷ Survival curves were estimated by using Kaplan-Meier method and follow-up was assessed by using the reverse Kaplan-Meier method¹⁸. Survival times were calculated as the difference between start of treatment and date of death or last follow-up. Time to event was calculated as the difference between the date of treatment and date of occurrence of an adverse event or last follow-up, with death being considered a competing event. The cumulative incidence for the occurrence of an adverse event at six and twelve months was assessed by using a competing risk model¹⁹. Sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) were calculated for all observers. The results of the observer with the highest sensitivity and specificity were used to fit univariate and multivariate Fine and Gray models²⁰, in order to estimate the effect of the risk factors on the cumulative incidence of the event. In order to perform the sensitivity analysis and the Fine and Gray's regression analysis, the final SINS categories were reduced from three to two, aggregating the categories *unstable* and *potentially unstable* versus the category *stable*^{6,9}. A P-value <0.05 was considered

statistically significant. Statistical analyses were performed using SPSS version 20.0, Armonk, NY and R version 2.18.

RESULTS

A total of 997 patients were treated with radiotherapy for spinal bone metastases during the study period. Of these, 236 patients underwent a CT scan within two months before starting treatment. Patients without clinical and/or radiological follow-up were excluded and a total of 110 patients remained eligible for analysis.

Table 1 summarizes the characteristics of the study population. Fifty-nine patients (54%) were male and the mean age at the start of treatment was 60.4 years (SD $\pm$ 13.8 years). The Karnofsky Performance Status was normal (100%-80%) in 59 patients (54%) and 107 patients (97%) had no, or only minor motor and sensory deficit. The prognostic category for survival according to the Bollen model was good in six patients (5%), moderate in 28 patients (26%), poor in 57 patients (52%) and very poor in 14 patients (13%). Thirty-six patients (33%) were treated with a single fraction of 8 Gy, 26 patients (24%) with two fractions of 8 Gy and 48 patients (43%) were treated with more than two fractions, totaling a dose of 24 Gy or more.

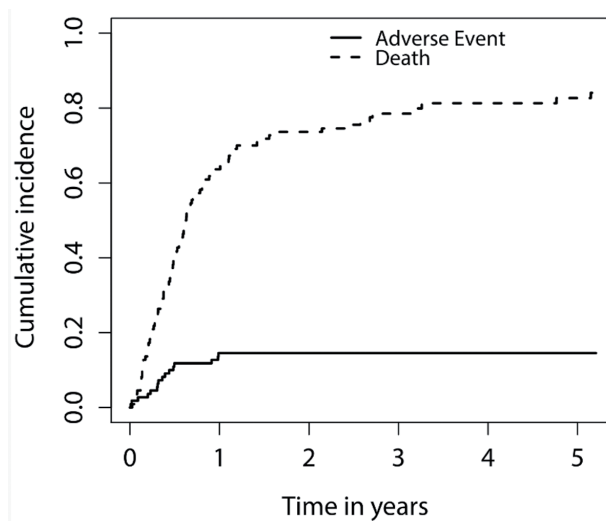


Figure 1. Cumulative incidence of adverse events and death for the entire cohort

Table 1. Patient characteristics.

Characteristic	N (%)
Gender	
Male	59 (54)
Female	51 (46)
Age (years, mean $\pm$ SD)	60.4 $\pm$ 13.8
Primary tumor	
Lung	25 (23)
Breast	18 (16)
Kidney	17 (16)
Colon	14 (13)
Esophagus	9 (8)
Prostate	8 (7)
Other	19 (17)
Karnofsky performance status	
Normal (100-80%)	59 (54)
Impaired (70-10%)	46 (42)
Missing	5 (4)
Frankel classification	
No deficit (E)	67 (61)
Minor motor or sensory deficit (D)	40 (36)
Major motor or sensory deficit (A,B,C)	3 (3)
Expected survival	
A - Good	6 (5)
B - Moderate	28 (26)
C - Poor	57 (52)
D - Very poor	14 (13)
Missing	5 (4)
Total radiotherapy dose	
8 Gy	36 (33)
16 Gy	26 (24)
≥ 24 Gy	48 (43)

The overall median survival was 6.6 months (95%CI 5.5-7.7) with a median follow-up of 5.2 years. Seventy-nine patients (72%) died within 12 months after starting treatment. A total of 16 patients (15%) experienced an adverse event during follow-up. Among them, eight patients (50%) experienced a deterioration of spinal alignment for which they were surgically stabilized and eight patients (50%) experienced a pathologic fracture, or progression of their existing fracture. In figure 1 the cumulative incidence of the two competing events is illustrated. The cumulative incidences for the occurrence of an adverse event at 6 and 12 months were 11.8% (95%CI 5.1%-24.0%) and 14.5% (95%CI 6.9%-22.2%), respectively.

Table 2 shows the SINS scores for each individual observer. The level of agreement between all four observers for the final SINS score was moderate ($\kappa=0.536$, $p<0.001$). The level of agreement was fair for the components bone lesion ($\kappa=0.299$, $p<0.001$) and spinal alignment ($\kappa=0.358$, $p<0.001$), whereas the components vertebral body collapse ($\kappa=0.453$, $p<0.001$) and posterolateral element involvement ($\kappa=0.436$, $p<0.001$) had a moderate level of agreement.

Table 2. Individual Spinal Instability Neoplastic Score and Fleiss' kappa. *) Variables location and pain were determined separately and therefore identical among all four observers.

SINS	Kappa	Observer 1 N (%)	Observer 2 N (%)	Observer 3 N (%)	Observer 4 N (%)
Bone lesion	0.299				
Lytic		88 (80)	70 (64)	80 (73)	51 (46)
Mixed		17 (16)	29 (26)	19 (17)	45 (41)
Blastic		5 (4)	11 (10)	11 (10)	14 (13)
Spinal alignment	0.358				
Subluxation/translation		1 (1)	3 (3)	4 (4)	1 (1)
Kyphosis/scoliosis		12 (11)	8 (7)	7 (6)	20 (18)
Normal alignment		97 (88)	99 (90)	99 (90)	89 (91)
Vertebral body collapse	0.453				
>50% Collapse		14 (13)	15 (14)	16 (15)	14 (13)
<50% Collapse		27 (24)	41 (37)	28 (25)	49 (44)
None, >50% involvement		22 (20)	14 (13)	39 (36)	23 (21)
None of the above		47 (43)	40 (36)	27 (24)	24 (22)
Posterolateral elements	0.436				
Bilateral		12 (11)	27 (25)	43 (39)	23 (21)
Unilateral		28 (25)	43 (40)	36 (33)	24 (22)
None		70 (64)	40 (36)	31 (28)	63 (57)
Location*	-				
Junctional		50 (55)	50 (55)	50 (55)	50 (55)
Mobile spine		25 (23)	25 (23)	25 (23)	25 (23)
Semi-rigid		35 (32)	35 (32)	35 (32)	35 (32)
Rigid		0 (0)	0 (0)	0 (0)	0 (0)
Pain*	-				
Yes; mechanical pain		24 (22)	24 (22)	24 (22)	24 (22)
Yes; non-mechanical pain		80 (73)	80 (73)	80 (73)	80 (73)
No		6 (5)	6 (5)	6 (5)	6 (5)
Total SINS score	0.536				
Stable (0-6 points)		50 (46)	41 (37)	31 (28)	37 (34)
Uncertain (7-12 points)		55 (50)	63 (57)	70 (64)	70 (63)
Unstable (13-18 points)		5 (4)	6 (6)	9 (8)	3 (3)

Table 3 shows the sensitivity, specificity, positive predictive value and negative predictive value of the SINS for all four observers. Sensitivity ranged from 35%-69%, specificity from 18%-48%, positive predictive value from 6%-18% and negative predictive value from 63%-90%.

Table 3. Evaluation of SINS accuracy. PPV: positive predictive value. NPV: negative predictive value.

	Sensitivity	Specificity	PPV	NPV
Observer 1	69%	48%	18%	90%
Observer 2	35%	27%	7%	71%
Observer 3	35%	18%	6%	63%
Observer 4	41%	25%	8%	71%

Univariate Fine and Gray analysis showed that the final SINS classification, total radiotherapy dose, as well as the six individual SINS components were not significantly associated with the cumulative incidence of an event (table 4). The multivariate analysis included all six SINS components as well as total radiotherapy dose. Only the component *location* was significantly associated with the cumulative incidence of an adverse event with a hazard ratio of 0.54 (95%CI 0.30-0.96, $p=0.04$) (table 4).

Table 4. Results of the univariate and multivariate Fine and Gray models. HR: hazard ratio. CI: confidence interval.

Univariate Fine and Gray	HR	95% CI	p-value
Location	0.71	0.42-1.31	0.22
Pain	0.53	0.22-1.13	0.09
Bone lesion	1.90	0.33-10.89	0.47
Spinal alignment	1.01	0.53-1.95	0.97
Vertebral body collapse	0.96	0.61-1.51	0.85
Posterolateral elements	1.28	0.86-1.90	0.22
Total SINS score	2.01	0.73-5.62	0.19
Total dose	1.02	0.96-1.07	0.53
Multivariate Fine and Gray	HR	95% CI	p-value
Location	0.54	0.30-0.96	0.04
Pain	0.40	0.13-1.17	0.10
Bone lesion	1.32	0.25-7.02	0.75
Spinal alignment	1.06	0.46-2.40	0.90
Vertebral body collapse	0.64	0.32-1.29	0.21
Posterolateral elements	1.15	0.64-2.08	0.65
Total dose	1.01	0.95-1.08	0.79

DISCUSSION

In this single center retrospective study it is demonstrated how the Spinal Instability Neoplastic Score performs on an independent dataset consisting of 110 patients undergoing external beam radiation therapy for symptomatic spinal bone metastases. Competing risk analysis showed that the SINS classification was not

significantly associated with the cumulative incidence of an adverse event within the studied population.

The levels of agreement found in this study were obtained by calculating Fleiss' kappa based on the results of four highly experienced observers and ranged from fair to moderate. The results were comparable to those obtained in previous studies⁶⁻⁸. Especially the SINS component *bone quality*, describing the lesion as being lytic, blastic, or mixed, continues to be a challenge for observers to agree upon, ranging from only 0.21 to 0.30⁶⁻⁸.

Apparently, although seemingly objective, measures such as displacement and kyphosis, are still difficult to interpret, even for highly experienced clinicians. Previous research comparing the interobserver agreement between groups of similar specialist (e.g. orthopedic surgeons vs. no orthopedic surgeons and surgeons vs. radiation oncologists), has shown that the clinicians' background seems to affect their agreement on the total SINS score as well as different components of the SINS^{8,9}. Accordingly, a mixed group of clinicians agrees less than, for example, a group of experienced orthopedic surgeons. It has also been shown that experience affects the degree of agreement. Highly experienced spine surgeons agree more than less experienced spine surgeons⁸.

The highest levels of sensitivity and specificity found in this study (69% and 48%) differed considerably when compared to the levels found in the study performed by Fourney et al. (96% and 80%)⁶. This might be attributed to the fact that Fourney et al. used consensus opinion to *a priori* define a metastatic spine as either stable or unstable, whereas in this study actual clinical endpoints were used to define stable and unstable spines. Nonetheless, a sensitivity of 69% suggests a good capacity to identify patients with a low risk of complication due to spinal instability. In clinical practice, this could translate to fewer surgical consultations for patients who are classified as *stable* according to the SINS. On the other hand, the rather low specificity found in this study indicates that no treatment decisions should be made based on the classifications *potentially unstable* and *unstable*. In daily practice, surgical consultation is still warranted for these categories.

In line with previously reported studies^{10,11}, no predictive value of the total SINS score was observed for the occurrence of an adverse event. Total radiotherapy

dose and the individual SINS components, *pain*, *bone lesion*, *alignment*, *collapse* and *posterolateral involvement* did not show a significant association with the occurrence of an adverse event in the multivariate analysis. Even though the component *location* reached a significant level of association, a hazard ratio of less than one is indicative of a protective effect for developing spinal instability, rather than a harmful effect, as implied by the SINS. As a result, this variable might not provide any clinically relevant information when assessing spinal instability.

Similar to our study, Lam et al.²¹ retrospectively examined the relationship of the SINS and dose fractionation with the development of a spinal adverse event (SAE) in 299 patients with SBM who received radiotherapy. They found that a SINS score ≥ 11 and a single fraction of 8 Gy were independent predictors for the development of an SAE. However, the definition of an event was much broader than in the current study. For instance, hospitalization due to pain at the irradiated site was considered an SAE, constituting 37% of all events. It is unlikely that the SINS can evaluate hospitalization due to pain and including it as an adverse event could potentially obscure the results.

In contrast to our study, Cunha et al.¹¹ found an association between the components *spinal alignment* and *lesion type* on the occurrence of a VCF and Sahgal et al.¹⁰ found an association between *spinal alignment*, *lesion type* and *vertebral body collapse* on the occurrence of a VCF. The major difference is that these two studies reported on patients who underwent high-dose stereotactic radiotherapy, potentially resulting in more VCFs whereas the population in this study underwent relatively low-dose radiotherapy.

A limitation of the current study is the retrospective design. The SINS component *pain* was determined based on patient charts and intake forms, possibly resulting in inaccurate interpretation of the data. The availability of pretreatment CT scans was limited (236/1042, 23%), reducing the overall population count.

Although patients who presented with evident clinical spinal instability and were operated on are not represented in this study, our analysis reflects the more important daily clinical scenario. The main treatment for patients with painful bone metastases is radiotherapy. Since these patients have limited survival, spinal surgery must only be applied in case of a reasonable and stable clinical condition.

One aims to prevent that patients treated with radiotherapy will undergo an adverse event in their follow up. Thus, especially in this heterogenous patient group in terms of amongst others primary tumor, physical condition and referring physician, in which a limited risk of spinal instability is expected, it is of utmost importance to identify those patients who, after radiotherapy, underwent an event and perhaps would have gained more in terms of sustaining quality of life if a surgical stabilizing procedure had been performed instead of radiotherapy. By including only patients treated with radiotherapy, we focused on this clinically important group in which there is some clinical equipoise. Therefore, leaving out patients who were primary stabilized did not result in major selection bias.

Strengths of the study are the number of observers and the fact that highly experienced clinicians of four different medical disciplines involved with treatment of SBM were represented. Although there was limited agreement between the four observers, our panel's constitution reflects clinical practice as in everyday reality spinal instability is often assessed separately by individual clinicians. Although a multidisciplinary meeting would seem most fitting to discuss instability and agree on appropriate treatment, due to the often swift course of disease and symptoms, such weekly meetings take place too late. Also, the endpoints used are clinically relevant. Whereas other validation studies compared the SINS outcome to predetermined consensus-based cases of stable and unstable spines, in the current study, actual clinical data were used as outcome measure.

Even though the authors agree that the components constituting the SINS classification are potentially important factors to consider when assessing spinal instability, in its current form, clinical applicability seems limited. As a tool for streamlining communication between physicians of different medical specialties and facilitating the decision making concerning surgical consultation, the SINS could be useful.

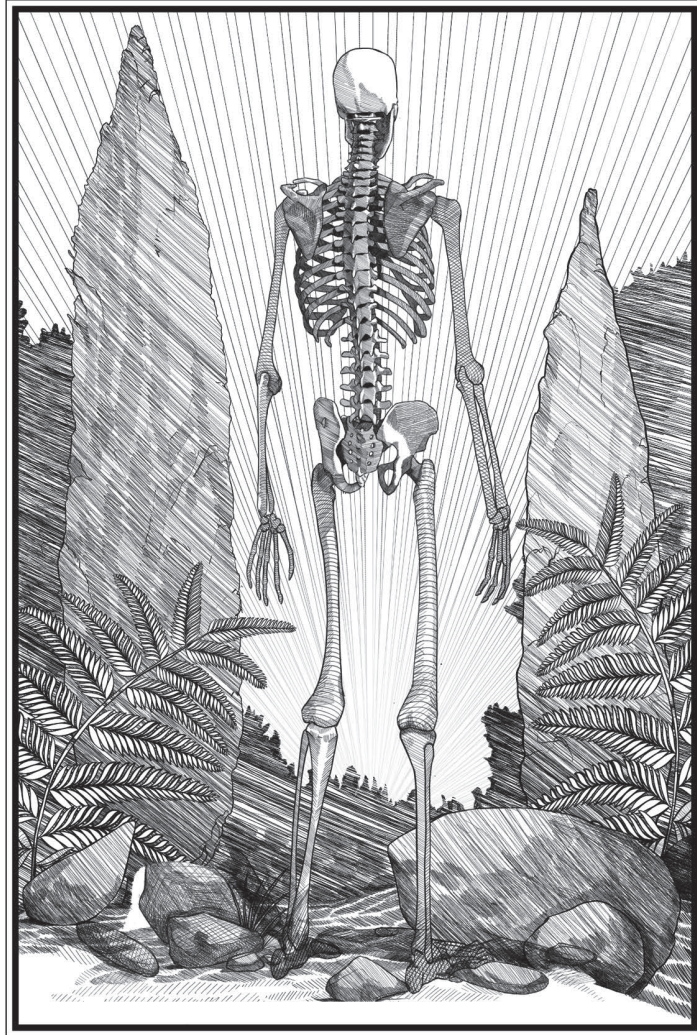
A prospective CT-based study with clear clinical endpoints might help determine the relative importance of each component in predicting complications resulting from spinal instability and could result in an adjustment of the points allocated to each component, as well as the grouping of each variable. As this study and the study performed by Teixeira et al.⁸ have shown, panels consisting of reviewers from different medical specialties can result in lower levels of agreement, whereas

a panel consisting of observers from one specialty can result in very high levels of agreement.⁹ Therefore, the optimal reviewing panel for such a study remains to be determined, but it seems observers from a surgical specialty generally have the highest level of agreement.

In conclusion, this study provides an insight into the ability of the SINS to assess spinal instability in patients undergoing external beam radiation therapy for spinal bone metastases. Based on these results, the clinical applicability of the SINS as a tool to assess spinal instability seems limited.

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CHAPTER VIII

General summary

Spinal bone metastases (SBM) are a multifactorial and multidisciplinary clinical entity. Patient-specific symptoms, life expectancy, spinal stability and patient preference all need to be evaluated, in order to provide a balanced treatment.

Chapter II described a systematic review of risk factors associated with estimating survival in patients with SBM. In the 22 included studies, the prognostic factors most frequently associated with survival were the primary tumor and the performance status. The prognostic factors most frequently not associated with survival were age, gender, number and location of the SBM and the presence of a pathologic fracture. Models aiming to provide a prognosis for patients with SBM should be based on an accurate primary tumor classification, combined with a performance score. The benefit of adding other prognostic factors was considered uncertain.

Chapter III evaluated risk factors for survival in a surgical cohort of 106 patients operated for SBM. Even though the study was performed prior to the systematic review of chapter II, the results are almost identical.

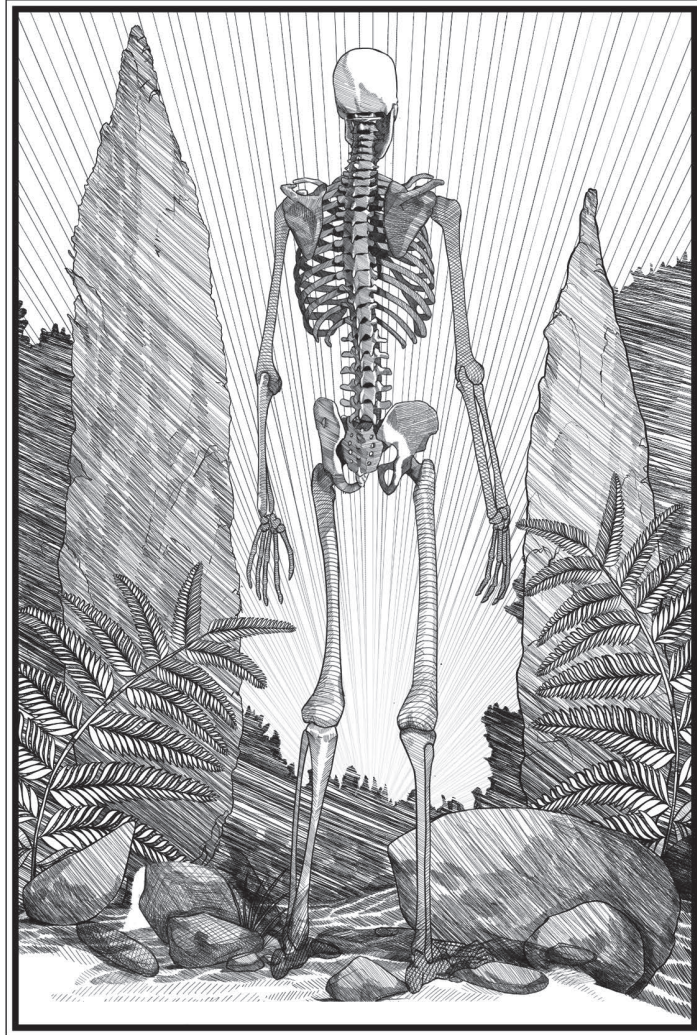
The large retrospective cohort study described in **Chapter IV** was the basis of this thesis and described the creation of our own predictive model for life expectancy in SBM. By using the presented flowchart and assessing the primary tumor type, functional status and the presence of visceral metastases, a patient is stratified to a risk category. This risk category corresponds with a median overall survival and provides a decent measure of certainty when assessing life expectancy.

Chapter V aimed to further fine-tune the most important variable in estimating survival, namely the primary tumor type. Along with lung and prostate cancer, breast cancer is the most common cause of SBM. Predictive models do not take breast cancer phenotypes based on estrogen (ER), progesterone (PR) and human epidermal growth factor 2 (HER2) receptors into account. The aim of this study was to ascertain whether receptors are associated with survival, when the disease has progressed up to the point of SBM. Patients with SBM from breast cancer with a triple negative phenotype have a shorter survival time than patients with a receptor positive phenotype, showing that models estimating survival should be adjusted accordingly.

Chapter VI assessed the performance of six predictive models, including our own, on an independent dataset. The Tokuhashi, Bauer, Tomita and Van der Linden models performed similar with a c-statistic of 0.64-0.66 and a 4-month accuracy of 62-65%. The Rades model (c-statistic 0.44) and Bollen model (c-statistic 0.70) had a 4-month accuracy of 69% and 75%, respectively. We therefore concluded that the model created in Chapter IV outperformed the models created prior to this thesis.

Chapter VII aimed to determine the predictive value of the Spinal Instability Neoplastic Score (SINS) in a cohort of patients treated with radiotherapy for SBM. Assessment of spinal stability in metastatic disease is challenging and is mostly done by relying on clinical experience, in the absence of validated guidelines or an established predetermined set of risk factors. The SINS provides clinicians with a tool to assess tumor-related spinal instability. However, as was shown in this chapter, clinical applicability of the SINS as a tool to assess spinal instability seems limited.

Finally, **Chapter IX** draws the conclusions and clinical implications of this thesis and future perspectives for the treatment of SBM are also discussed.



CHAPTER IX

**General discussion and
future perspectives**

Metastases to the spinal column in patients with end-stage malignant disease are a frequently observed complication of. Depending on their extent and localization, they cause a variety of clinical symptoms ranging from pain to neurological deficits and even paraplegia. Due to improvements in systemic treatment options for the primary tumor, overall survival times in patients suffering from metastatic disease are on the rise.^{1,2} Most likely, this will result in a prolonged palliative phase in which the incidence of patients presenting with symptomatic spinal bone metastases (SBM) will increase. Treatment with radiotherapy and/or surgery can be beneficial to patients presenting with pain, neurological deficit or both.³⁻⁵ However, the most optimal treatment algorithm for individual patients has not yet been established. In practice, the treating physician will match extent and type of treatment not only to a patient's clinical presentation, but also to the expected survival time, thus balancing the increase in morbidity and mortality associated with more extensive treatment to the expected gain in quality of life.

Survival

Prediction of survival has become an integral part of selecting the appropriate treatment for patients suffering from SBM. Depending on the symptoms, patients with a short expected survival are most likely to benefit from short radiotherapy regimens, best supportive care or minimally invasive surgery. Patients with a relatively long expected survival could potentially benefit from high dose radiotherapy or – in the case of radioresistant tumors and (impending) biomechanical instability – more extensive surgical interventions. Several studies have shown that the estimation of survival by clinicians in terminally ill patients is inaccurate⁶ and have suggested the use of prognostic models in order to prevent exposure of patients to unnecessarily extensive treatments. Models that can be used in the decision making process have been developed by Tokuhashi, Bauer, Tomita, Van der Linden, Rades and several others.⁷⁻¹¹ These models include prognostic factors such as primary tumor type, amount and location of spinal metastases, presence of visceral, brain and extraspinal bone metastases, functional status and neurological status.

However, clinical applicability seems limited due to over- or undertreatment and especially when predicting short survival the existing models fall short. Therefore, after an assessment of risk factors in a surgical cohort of patients described in **Chapter III**, we decided to create a new model. In the study described in

Chapter IV, 1043 patients who were treated for symptomatic SBM were evaluated. Overall median survival of the entire cohort was short, with just 4.8 months (95%-CI 4.3-5.4). Patients were stratified according to the clinical profile of their primary tumor: favorable (e.g. breast), moderate (e.g. prostate) or unfavorable (e.g. lung), after which all risk factors that might be associated with survival were evaluated with a multivariate analysis. It was shown that survival in patients with SBM from a favorable clinical profile was influenced by the presence of visceral metastases and brain metastases, as well as the performance status. In patients with a moderate or unfavorable clinical profile, only performance status was associated with survival. Based on these results a flowchart was created, stratifying patients into four categories (A-D) with significantly different survival. Patients in category A had a median overall survival of 31.2 months (95%CI 25.2-37.3), compared to 15.4 months (95%CI 11.9-18.2) for patients in category B, 4.8 months (95%CI 4.1-5.4) for patients in category C and 1.6 months (95%CI 1.4-1.9) for patients in category D. Predictive accuracy of the model was assessed by using Harrell's C-statistic,¹² which was equal to 0.71, indicating reasonable discriminative accuracy. A C-index equal to one means that the model has perfect discrimination and a C-index equal to 0.5 means that the model predicts just as well as flipping a coin.

It has been shown that the primary tumor causing the SBM is the strongest predictor of survival. Patients with symptomatic SBM from breast cancer tend to live longer than patients with SBM from, for instance, lung cancer. This is reflected in all predictive models, where breast cancer is considered a favorable prognostic factor, compared to other primary cancers.

Based on estrogen receptor status (ER), progesterone receptor status (PR) and human epidermal growth factor receptor 2 status (HER2), several molecular phenotypes of breast cancer can be distinguished.^{13,14} It is known that these phenotypes are associated with survival when measured from the time of diagnosis of the primary tumor, however, it is unclear whether this effect remains when the disease has progressed up to the point of symptomatic SBM. If so, the manner in which our predictive model stratifies patients needs to be adjusted, distinguishing between different breast cancer phenotypes. In **Chapter V** we examined this effect by combining all breast cancer patients from our database, with all breast cancer patients from two external databases from Graz, Austria and Aarhus, Denmark. Based on the ER, PR and HER2 expression, tumors were further subdivided into

four categories; luminal A, luminal B, HER2 and triple negative. The luminal A subtype is ER positive and/or PR positive without HER2 overexpression. The luminal B subtype is ER positive and/or PR positive with HER2 overexpression. The HER2 subtype is ER and PR negative, with HER2 overexpression. Finally, the triple negative subtype is negative for all three receptors. Median survival times in the luminal A, luminal B and HER2 categories were not significantly different, whereas the median survival time in the triple negative category was much shorter. Median survival in the triple negative category was 5.5 months (95%CI 2.0-9.0), whereas survival in the other three combined receptor positive phenotypes was 23.4 months (95%CI 19.0-27.8) (log-rank test $p < 0.001$). Based on this information we changed our primary tumor classification, by moving triple negative breast cancer patients into the 'moderate' clinical profile. All receptor positive phenotypes remained in the 'favorable' clinical profile. The adjustment resulted in an increase of 5% of the c-statistic calculated for this specific cohort.

Analogous to the study described above, Willeumier et al. studied the effect of epidermal growth factor receptor (EGFR) mutations in patients presenting with bone metastases from non-small cell lung cancer.¹⁵ It was shown that survival in patients with EGFR-positive tumors was much longer, due to the advent of new systemic treatment options.

As stated above, the aim was to develop a more accurate model than the ones available at the time. In order to ascertain whether we had achieved this, in **Chapter VI** we compared our own model to the ones created by Tokuhashi, Bauer, Tomita, Van der Linden and Rades.⁷⁻¹¹ A database containing 1379 patients was created by combining our own data with data from Graz, Austria. All models were fitted with the available patient information and survival times and c-statistics were calculated for each model. Results showed that all models performed within a similar range (c-statistic 0.64-0.69), with our own model slightly outperforming the older models. A recently published study by Nater et al. evaluated a total of eight predictive models based on prospectively collected data in 142 surgically treated patients.¹⁶ C- statistics found in this study ranged from 0.61 to 0.68, similar to our own study.

In 2015, the Dutch national guideline on spinal metastases was updated and one of the topics addressed was the estimation of survival. In order to investigate which

risk factors are associated with survival, a systematic review was performed, which is described in **Chapter II**. After screening 2989 abstracts, 142 full-text papers were evaluated for eligibility. In total 22 studies were included, describing a total of 43 different prognostic factors, of which 17 were relevant to pre-treatment survival estimation. The prognostic factors most frequently associated with survival were the primary tumor and the performance status. The prognostic factors most frequently *not* associated with survival were age, gender, number and location of the SBM and the presence of a pathologic fracture. The evidence was inconclusive for the presence of visceral metastases and the presence of neurologic deficit. Therefore, prognosis of survival for patients with SBM should be based on an accurate primary tumor classification, combined with a performance score. The benefit of adding other prognostic factors was considered doubtful.

Stability

Next to life expectancy, spinal stability is one of the key factors to examine when deciding on treatment. Whereas patients with stable spines can be treated using non-invasive procedures such as radiotherapy, patients with unstable spines potentially require surgical fixation, either through minimally invasive techniques such as percutaneous stabilization or through more invasive procedures involving open fixation.

Assessment of spinal stability is challenging and in the absence of validated guidelines or an established predetermined set of risk factors, is mostly done by relying on clinical experience and radiological imaging. The absence of a standardized approach hinders communication between physicians of different medical specialties and can result in under- as well as overdiagnosis of spinal instability.

In 2010, the Spinal Oncology Study Group introduced the Spinal Instability Neoplastic Score (SINS); the first consensus-based guideline that aids in the assessment of a patient's risk of spinal instability in the setting of neoplastic spinal disease.¹⁷ The SINS determines tumor-related instability based on six criteria and classifies the spinal column as stable, potentially unstable or unstable. Surgical consultation is recommended for patients with a spinal column classified as either potentially unstable or unstable. As such, the SINS facilitates interdisciplinary communication, assesses and categorizes spinal instability and assists in treatment

decision making. In **Chapter VII** we aimed to evaluate the SINS in a clinical setting, based on an analysis of 110 patients who were treated for SBM. Even though previous studies by the original authors have shown that the SINS has a substantial to excellent inter-observer and intra-observer reliability, the kappa-values found in this paper and several others^{18,19} differed considerably when compared to the levels found in the studies performed by Fourney et al. and Fisher et al.^{20,21} Also, the multivariate competing risk analysis showed that only the component *location* was significantly associated with the cumulative incidence of an adverse event, however a hazard ratio of 0.54 (95%CI 0.30-0.96, $p=0.04$) for this item indicates a protective effect for developing an adverse event. Even though the components constituting the SINS classification are important factors to consider when assessing spinal instability, in its current form, clinical applicability in predicting for the occurrence of a vertebral compression fracture seems limited.^{22,23} As a tool for streamlining communication between physicians of different medical specialties and facilitating the decision making concerning surgical consultation, the SINS could be useful.²⁴

Future Perspectives

In their current form and with the current set of known risk factors, it would seem that the predictive models have reached a plateau with a c-statistic in the range of 0.6-0.7.^{16,23} By further fine-tuning the most important variable – the primary tumor – improvements can still be made,^{15,25} but it is doubtful that a value of 0.8 or higher, indicating very good predictive capability, will be reached. This by no means implies that we should abandon our attempts at improvements, as the routine use of these models does provide clinicians with useful feedback concerning survival estimations, which are generally speaking too positive.⁶

As treatments for different cancer types tend to differ considerably between countries, let alone continents, it is unlikely that a model created based on data from the Netherlands could be applied seamlessly in Japan or the United States. We experienced this during our attempts to integrate data from Austria into our own database. Even in the larger cancer-specific groups such as prostate cancer, survival times differed considerably between the two countries. This underlines the need for a more adaptive approach when evaluating the models, where the framework (i.e. the risk factors) would remain the same, but the way in which points are assigned or patients are stratified is adjusted according to regional data.

For instance, in our paper described in **Chapter VI**, we noticed early on that the Rades model would do poorly, based on its weighing of the primary tumor types. The points assigned differed greatly from the survival times in our cohort, leading to a very low c-statistic. Had we optimized this category, we would have been able to better assess whether the combination of risk factors is of value. Now we only learned that a rigid translation of the model is not applicable to our dataset. Continuous updating and fine-tuning of the predictive models is needed to ensure their clinical applicability. Considering the above, it is not unlikely that our model will require some adaptations, since it is based on data collected from patients who were treated between 2000 and 2010. This update could then be implemented in the recently released OPTIModel app for Android and iOS (available for free in the Google Play Store and the App Store). The OPTIModel is a tool to estimate survival in patients with bone metastases to the spinal column and long bones, based on the work described in this thesis and papers by Willeumier et al.²⁶

Where stability is concerned, it is unlikely that the SINS will fill the role of a predictive tool in its current form. Even as a referral tool for non-surgical clinicians, as which it is originally meant, it lacks discriminative capability, as the majority of patients end up in the intermediate category. Also, the manner in which the points are assigned across the different items seems somewhat arbitrary. For instance, patients who experience subluxation or translation of the spinal column are awarded four points. One could argue that this is *de facto* spinal instability and a patient should be referred for surgical consultation immediately, irrespective of the other items. Considering the vast clinical experience of the authors involved in creating the SINS, there is no doubt that the individual items are important in assessing the metastatic spinal column. Perhaps a re-imagining and simplification of the SINS into major criteria (misalignment, deformity, collapse) and minor criteria (location, aspect of the lesion, pain, and posterior involvement) can increase its clinical usefulness.

While the aforementioned adjustments might result in predictive models attaining a c-statistic upwards of 0.7 and an increase in the discriminative power of the SINS, it is by no means a great leap forward. All our efforts at optimizing care for a patient population as diverse as the one of spinal metastases could improve considerably with the advent of machine learning in medicine. In recent years, several abstracts have been presented at the annual meeting of the American

Society of Clinical Oncology, demonstrating the use of IBM's Watson for Oncology (WFO), a self-learning computing system that is able to provide evidence-based treatment recommendations, by processing data from medical literature, treatment guidelines, imaging, laboratory results and pathology reports, among many other sources. Studies showed a high concordance between recommendations made by tumor boards and WFO.^{27,28} Also, recent work done by Groenen et al. made use of finite element modelling to assess spinal stability.²⁹ This is a form of structural stress analysis developed in engineering mechanics and can be applied to CT-based assessments of the metastatic spine. By further developing this technique, perhaps in combination with machine learning, a more robust system for predicting spinal instability can be created.^{30,31}

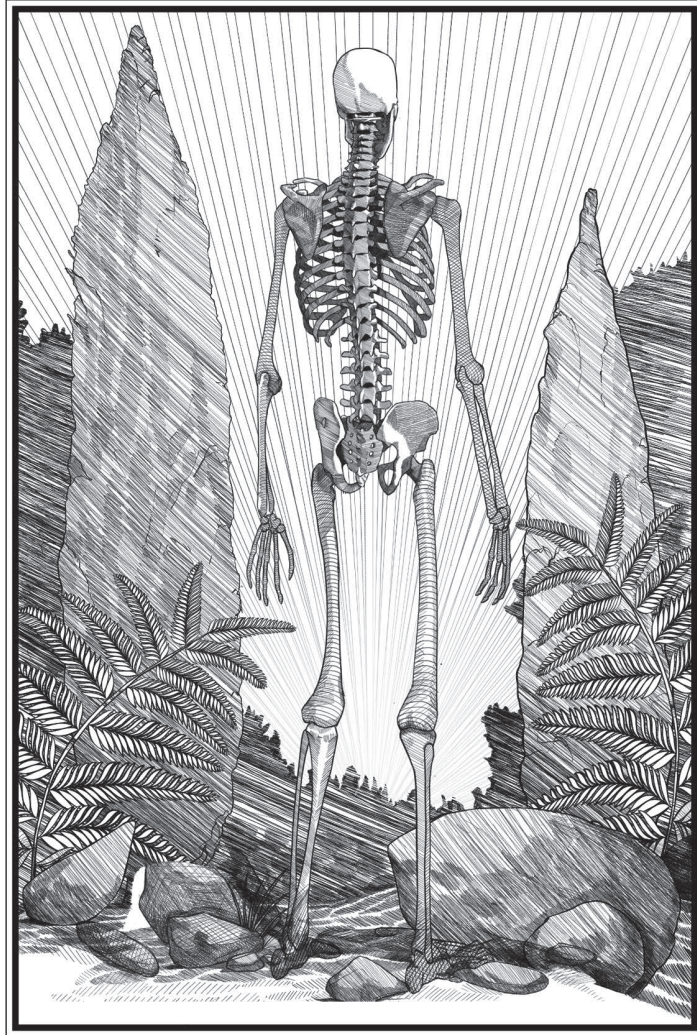
Over the past years, advances in radiotherapy planning techniques as well as advances in minimally invasive surgical techniques have opened up entire new avenues of treatment. However, in order to adequately deploy these new treatment strategies, correct assessment of spinal stability, as well as survival is essential in order to avoid overtreatment. In the case of Stereotactic Body Radiotherapy (SBRT), the benefit of a faster and longer lasting response must be offset to the higher risk of inducing vertebral compression fractures (VCFs). While this complication might be an acceptable risk in a curative or oligometastatic setting, in a palliative setting, it is not. Ideally, these treatment decisions are made in a multidisciplinary setting, including all medical specialties involved in diagnosing and treating spinal metastases.

This thesis provides an insight into the challenges of selecting the appropriate treatment for patients presenting with spinal metastases, by considering the estimated survival and clinical assessment of spinal instability. Hopefully this work can be used to further improve patient and treatment selection and further reduce overtreatment of patients in a palliative setting.

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ADDENDUM

Nederlandse samenvatting

List of publications

Curriculum vitae

Acknowledgements

NEDERLANDSE SAMENVATTING

Wervelmetastasen zijn een complex klinisch probleem dat een multidisciplinaire aanpak behoeft. Patiëntspecifieke symptomen, levensverwachting, stabiliteit van de wervelkolom en voorkeuren van de patiënt dienen allemaal geëvalueerd te worden om tot een gedegen behandelbesluit te komen.

In **Hoofdstuk II** wordt een systematische review beschreven van de risicofactoren die worden geassocieerd met het schatten van de overleving van patiënten met wervelmetastasen. In de 22 geïnccludeerde studies werden de risicofactoren *primaire tumor* en *conditie* het meest frequent beschreven. De risicofactoren *leeftijd*, *geslacht*, *aantal wervelmetastasen*, *locatie van de wervelmetastasen* en *aanwezigheid van een pathologische fractuur* werden het minst frequent beschreven. Derhalve werd geconcludeerd dat prognostische modellen voor het inschatten van de overleving van patiënten met wervelmetastasen gebaseerd dienen te zijn op een accurate classificatie van de primaire tumor in combinatie met een maat voor de conditie van de patiënt. Het nut van het toevoegen van andere risicofactoren aan het model is twijfelachtig.

In **Hoofdstuk III** worden de risicofactoren voor overleving beschreven in een cohort van 106 chirurgisch behandelde patiënten. Deze studie werd uitgevoerd voorafgaand aan de systematische review uit hoofdstuk II, desondanks waren de resultaten nagenoeg identiek.

De retrospectieve cohort studie in **Hoofdstuk IV** was de basis voor dit proefschrift en beschrijft de totstandkoming van ons eigen model om de levensverwachting voor patiënten met wervelmetastasen in te schatten. Door de primaire tumor, klinische status en de aanwezigheid van viscerale metastasen te evalueren en de gepresenteerde flowchart te gebruiken, kunnen patiënten gestratificeerd worden in een risicocategorie. Deze risicocategorie correspondeert met een mediane overleving en geeft een goede maat voor de verwachte overleving van de patiënt.

In **Hoofdstuk V** is getracht de belangrijkste prognostische variabele – de primaire tumor – verder uit te werken. Naast longkanker en prostaatkanker, is borstkanker de meest voorkomende oorzaak van wervelmetastasen. Tot op heden maken de verschillende voorspellende modellen geen onderscheid tussen de verschillende

fenotypen van borstkanker, gebaseerd op de aan- of afwezigheid van oestrogeen (ER), progesteron (PR), of *Human Epidermal Growth Factor 2* (HER2) receptoren. Het doel van deze studie was om vast te stellen of de verschillende fenotypen invloed hebben op de overleving, wanneer de ziekte is gevorderd tot de aanwezigheid van wervelmetastasen. Het bleek dat patiënten met wervelmetastasen uitgaande van borstkanker met het triple negatieve fenotype een kortere overleving hebben. Dit houdt in dat de voorspellende modellen een onderscheid dienen te maken tussen dit fenotype en de andere vormen van borstkanker met een aanzienlijk betere overleving.

In **Hoofdstuk VI** werden de voorspellende prestaties van zes modellen onder de loep gelegd met behulp van een onafhankelijke dataset. De modellen van Tokuhashi, Bauer, Tomita en Van der Linden presteerden gelijkwaardig met een c-score van 0.64-0.66 en een nauwkeurigheid van 62-65% na vier maanden. De modellen van Rades (c-score 0.44) en ons eigen model (c-score 0.70) hadden een nauwkeurigheid na vier maanden van respectievelijk 69% en 75%. Derhalve concludeerden wij dat het model uit hoofdstuk IV beter presteerde dan de overige voorspellende modellen.

In **Hoofdstuk VII** werd de voorspellende waarde van de *Spinal Instability Neoplastic Score* (SINS) onderzocht in een cohort patiënten met wervelmetastasen behandeld met radiotherapie. Het evalueren van de stabiliteit van de wervelkolom is bijzonder uitdagend en gebeurt voornamelijk op basis van klinische expertise in de afwezigheid van gevalideerde richtlijnen. De SINS voorziet klinici van een hulpmiddel om tumor-gerelateerde instabiliteit in te schatten. Echter, de resultaten van deze studie lieten geen klinisch nut zien van het gebruik van de SINS bij het inschatten van stabiliteit.

Tot slot worden in **Hoofdstuk IX** de conclusies en klinische impact van dit proefschrift besproken, alsmede de toekomstperspectieven aangaande de behandeling van wervelmetastasen.

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2012

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CURRICULUM VITAE

Laurens Bollen was born in Amsterdam on January 22nd 1984. In 2002 he graduated from the Barlaeus Gymnasium and, after two years of law school, started medical school at the Leiden University Medical Center in 2004. After his final internship at the department of orthopaedic surgery at the LUMC and graduating medical school in 2011, he started as a PhD-researcher on the topic of spinal metastases under supervision of prof. dr. R.G.H.H. Nelissen and prof. dr. P.D.S. Dijkstra. This resulted in several papers, which were also presented at national and international medical conferences. At the 2013 meeting of the International Society Of Limb Salvage (ISOLS) he was awarded the Alberghini award for the best oral presentation and in 2014, he received the Dutch Spine Society (DSS) annual award for the best Dutch publication related to the spinal column. In 2014 he worked as a resident in orthopaedic surgery at the Medical Center Alkmaar, before starting his specialization in radiation oncology in 2015 at the Academic Medical Center in Amsterdam, under supervision of prof. dr. L.J.A. Stalpers.

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