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REVIEW

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 to avoid over- and under-treatment. 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 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.

Conclusions 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.

Keywords Spinal bone metastases · Prognostication · Systematic review

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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%) [3–5] 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 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 optimistic [9] 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

This study was conducted according to the guidelines provided by the PRISMA statement.

Search strategy

The review protocol for this study was prospectively registered online at PROSPERO under registration number CRD42014006706 (http://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 to 18, with a cut-off set at a maximum of 50% ($\leq$ 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 score [15] or the Eastern Cooperative Oncology Group score [16]. Other combined prognostic factors were Neurologic deficit; consisting of the Frankel score [17] 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.
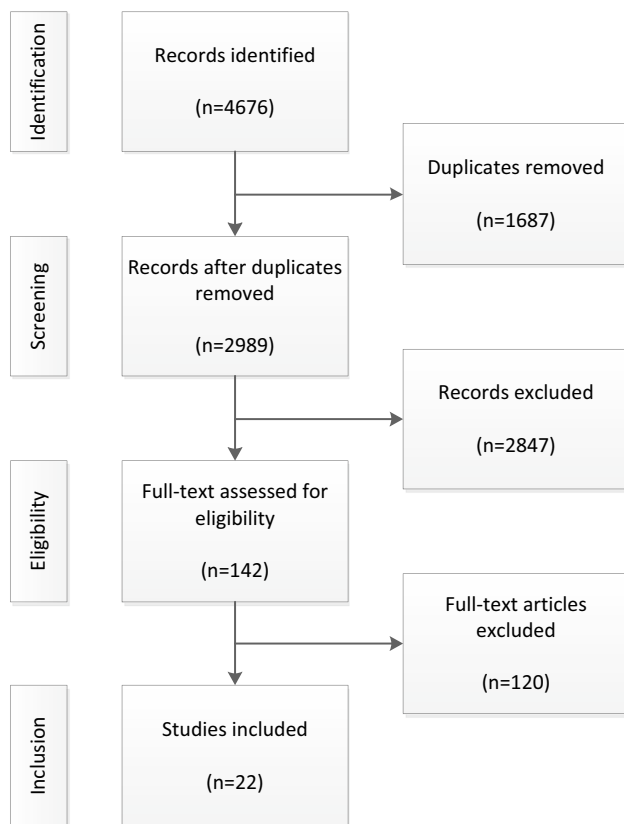
Fig. 1 Flowchart study selection process

- Inconclusive: inconsistent findings (< 75%) irrespective of study quality.

Inter-observer agreement for the risk of bias assessment was determined by the kappa-statistic [20]. 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 $n = 1092$; Cochrance $n = 145$; 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 (Fig. 1) [3–6, 8, 21–37]. During the selection process, the reviewers

disagreed on seven inclusions. Consensus was reached for all studies.

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 15 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.

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. Because the level of evidence for these factors by definition could not exceed the category '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

Table 1 Characteristics of the 22 included studies

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

SUR patients treated with surgery; *RTC* patients treated with radiotherapy or conservative therapy; *NR* not reported

Table 2 Level of evidence for investigated prognostic factors. Numbers refer to study identification from Table 1

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%

Studies with a low risk of bias are in bold

ASA American Society of Anesthesiologists; *SBM* spinal bone metastases

SBM, the presence of extraspinal bone metastases, total number of bone metastases, pain, sphincter function, weight loss and cardiovascular disease.

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 likely 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 categories [4]. 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.

A recently published meta-analysis by Luksanapruksa et al. [39] aimed to assess prognostic factors in patients with spinal bone metastases. Seventeen poor prognostic factors were identified, including the primary tumor classification and performance score. Contrary to the current study, however, Luksanapruksa et al. also found items such as number of SBM, presence of other bone metastases and ambulatory status important prognostic factors. This is most likely due to the fact that all studies by Rades et al. were included in the analysis. Since the same cohort was used repeatedly, the effects were somewhat amplified. Also, the large measure of heterogeneity found in most of the pooled risk factors indicate that a meta-analysis might not be the most ideal approach to addressing this topic.

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.

Compliance with ethical standards

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