



The importance of timely treatment for quality of life and survival in patients with symptomatic spinal metastases

Floris R. van Tol¹ · Karijn P. M. Suijkerbuijk² · David Choi³ · Helena M. Verkooijen⁴ · F. Cumhur Oner¹ · Jorrit-Jan Verlaan^{1,5}

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Abstract

Purpose A major challenge in metastatic spinal disease is timely identification of patients. Left untreated, spinal metastases may lead to gross mechanical instability and/or neurological deficits, often requiring extensive invasive surgical treatment. The aim of this cohort study was to assess the correlation between delayed treatment of patients with spinal metastases and functional performance, quality of life and survival.

Methods All patients surgically treated for metastatic spinal disease at a tertiary care facility were included for analysis. Patients who underwent elective surgery were considered as timely treated, whereas patients requiring emergency surgery were considered to be treated in a delayed fashion. EQ-5D scores, KPS scores and mortality rates were compared between the two groups.

Results A total of 317 patients (215 timely treated, 102 delayed) had survivorship data available and 202 patients (147 timely treated, 55 delayed) had clinical data available. Multivariate analyses showed delayed treatment was associated with lower EQ-5D and KPS scores and higher mortality rates, independent of confounders such as baseline EQ-5D/KPS scores, neurological status, tumor prognosis and patient age.

Conclusions The results from the present study show delayed treatment of patients with symptomatic spinal metastases has both direct and indirect adverse consequences for functional performance status, quality of life and survival. Optimization of referral pattern may accelerate the time to surgical treatment, potentially leading to better quality of life and survival.

Keywords Spinal metastases · Delay · Quality of life · Survival

Introduction

Primary cancer care and systemic therapy options have improved considerably over the past few decades, leading to a significant increase in survival and the subsequent

prevalence of patients with metastatic disease [1]. One of the most debilitating complications of advanced cancer is metastatic spinal disease, which currently occurs in approximately 20% of all oncological patients [2, 3]. A major challenge in metastatic spinal disease is that presenting symptoms can be very non-specific, leading to difficulties in distinguishing between patients presenting with symptoms of metastatic spinal disease from patients with other, non-malignant causes of neck or back pain [4]. Because non-specific back pain is one of the most common conditions in middle aged people, and is generally regarded as self-limiting, patients with spinal metastases are at risk for consequential delays in diagnosis, referral and treatment [5, 6].

In the early stages of metastatic spinal disease, patients can usually be treated with non-surgical methods such as systemic anti-cancer treatment or palliative radiotherapy [7]. Left untreated, however, spinal metastases may continue to compromise bone integrity or cause intractable pain,

✉ Jorrit-Jan Verlaan
j.j.verlaan@umcutrecht.nl

¹ Department of Orthopedic Surgery, University Medical Center Utrecht, P.O. Box 85500 (G05.228), 3508 GA Utrecht, The Netherlands

² Department of Medical Oncology, University Medical Center Utrecht, Utrecht, The Netherlands

³ Department of Neurosurgery, The National Hospital for Neurology and Neurosurgery, London, UK

⁴ Imaging Division, University Medical Center Utrecht, Utrecht, The Netherlands

⁵ University of Utrecht, Utrecht, The Netherlands

requiring (stabilizing) surgical procedures [8]. At a more advanced stage, spinal metastases may also cause neurological symptoms, commonly requiring large open surgical procedures to decompress the involved neural structures [9, 10]. Consequently, the timing of treatment is considered an important factor in determining treatment outcome.

We previously reported on delayed surgical treatment of patients with spinal metastases being associated with worse surgical and postoperative outcomes, showing increased surgical duration, blood loss, length of stay (LOS) and postoperative adverse events [11]. The effects of delayed treatment on functional status, perceived quality of life and survival however remains largely unclear.

The primary aim of the present prospective study was to assess the relationship between delayed treatment (i.e., requiring emergency surgery) and functional status, QoL and survival in patients surgically treated for symptomatic spinal metastases. The secondary aim was to assess how various factors of delayed treatment (e.g. neurological deficits, emergency surgery) might have contributed to the aforementioned outcome parameters independently.

Materials and methods

All patients surgically treated between March 2009 and July 2018 for symptomatic spinal metastases or spinal localizations of hematologic malignancies at a single tertiary spine center were eligible for inclusion. A waiver of informed consent was approved for this study by the institutional review board. In cases where metastases originated from an unknown primary tumor, tumor histology was determined at a later stage from intra-operative biopsies. Based on the clinical profile of their primary tumor, patients were classified as favorable, moderate or unfavorable, in line with the median overall survival as previously described by Bollen et al. [12] If the primary tumor remained unknown postoperatively, the prognosis was classified as unfavorable. Patients were deemed eligible for surgical treatment if the estimated survival exceeded 3 months as determined by frequently cited prognostic models and preoperative clinical assessment by the treating team consisting of a spine surgeon, oncologist and radiation oncologist [13]. Mechanical pain, gross radiographic spinal instability and/or neurological deficits were the major indications for surgical treatment. The attending/treating spine surgeon decided on the surgical approach and technique for each individual case combining common scoring systems (Neurologic, Oncologic, Mechanic, Systemic (NOMS): Frankel classification for neurological status combined with Bilsky score for degree of epidural compression; Bollen classification for tumor biology; Spinal Instability and Neoplastic Score (SINS) for spinal stability and KPS for general patient condition) [14] into a uniform treatment

strategy [10, 13]. During the study period, there were no major changes in treatment policy in this center.

Demographic data including age and sex were recorded into the dataset. The American Society of Anesthesiologists (ASA)-classification, Frankel grade, mobility score, Karnofsky Performance Score (KPS) and EQ-5D scores were extracted from patient's medical records. The surgical urgency was assessed and recorded by the treating spine surgeon preoperatively in accordance with internationally established guidelines [15]. KPS scores and EQ-5D scores were obtained at 3 and 6 months follow-up. Based on the preferred timing of surgery after initial presentation at the spine unit, patients were categorized into 'timely treatment' or 'delayed treatment', to account for the full unfavorable chain of events accompanying emergency surgery. 'Delayed treatment' was defined as requiring surgical treatment within 3 days. 'Timely treatment' was defined as being eligible for planned intervention more than 3 days after initial surgical presentation. The three-day cutoff was chosen in accordance with the protocol used by the Global Spine Tumor Study Group [16].

Statistical analysis

For continuous data, means, standard deviations (SD), medians and interquartile range (IQR) were used. For categorical data frequencies were used. In our multivariate models, KPS and EQ-5D were treated as a continuous variable in accordance with previous literature stating ordinal data with 5 or more categories does not compromise the integrity of linear models [17–19]. To compare the two patient groups at baseline unpaired *t* tests were used for continuous data and Chi-squared tests for categorical data. To assess the relationship between delayed treatment and EQ-5D and KPS scores at the two follow-up moments, independent of known prognostics, generalized estimating equations (GEE's) were used duplicating cases based on the two follow-up moments. Due to multicollinearity the authors favored the 3-point mobility score over the Frankel grade since it better reflects the functional status of the patient. Any interaction between timely or delayed treatment and the first or second follow-up moment were assessed by adding an interaction term to the GEE models. To assess the effect of loss to follow-up between 3 and 6 months on outcome parameters at 6 months, we compared KPS and EQ-5D scores at three months between patients available for analysis at 6 months and those lost to follow-up between 3 and 6 months. Kaplan–Meier curves were created to analyze 1 year survival in both treatment groups. Log-rank tests were used to test for statistical significance. To analyze the relationship between the treatment category and survival, independent of known prognostic factors such as patient mobility, tumor prognosis and patient age,

Cox proportional hazards models were used. All analyses were performed using IBM SPSS Statistics.

Results

In total, 317 patients were eligible for inclusion of which 215 underwent timely treatment and 102 delayed treatment. Survivorship data was available for all patients and follow-up data on EQ-5D and KPS at either 3- or 6-months was available for 202 patients (147 timely treated and 55 delayed treatment patients) of the 238 patients still alive at 6 months. Baseline demographics can be found in Table 1.

Figure 1 shows EQ-5D scores for both groups at baseline, three months and six months follow-up. For timely treated patients, the median (IQR) EQ-5D was 0.57 (0.24–0.73) at baseline ($n = 143$), 0.73 (0.57–0.81) at 3 months ($n = 125$) and 0.78 (0.57–0.89) at 6 months ($n = 51$). For delayed treatment patients, the median (IQR) EQ-5D was 0.24 (0.1–0.33) at baseline ($n = 50$), 0.48 (0.26–0.74) at 3 months ($n = 36$) and 0.73 (0.37–0.85) at 6 months ($n = 20$). The difference between timely treated and delayed treated patients was statistically significant at baseline and three months. Generalized estimating equations showed a time-dependent negative effect of delayed treatment on the follow-up EQ-5D scores, where delayed patients had lower EQ-5D scores at 3 months, but not at 6 months, independent of the preoperative EQ-5D score, mobility score, tumor prognosis and patient age (Table 2).

Figure 2 shows KPS scores for both groups at baseline, three months and six months follow-up. For timely treated patients, the median (IQR) KPS was 70 (60–80) at baseline ($n = 147$), 80 (80–80) at 3 months ($n = 135$) and 80 (70–90) at 6 months ($n = 53$). For delayed treatment patients, the median (SD) KPS was 60 (50–70) at baseline ($n = 55$), 70 (60–70) at 3 months ($n = 49$) and 70 (60–80) at 6 months ($n = 27$). The difference between timely treated and delayed treatment patients was statistically significant for all three time points. Generalized estimating equations showed a time-independent negative effect of delayed treatment on the follow-up KPS scores, independent of the preoperative KPS score, mobility score, tumor prognosis and patient age (Table 3). Sensitivity analyses showed no significant differences in KPS and EQ-5D scores at 3 months between patients available for analysis at 6 months and those lost to follow-up or deceased.

Out of all patients, 44 (13.9%) died within 3 months, and 119 (37.5%) within 1 year. One-year survival was 70.1% in the timely treated group versus 50.9% in the delayed treatment group ($p = 0.001$, Fig. 3). Cox

proportional hazards analysis showed that delayed treatment was associated with lower survival rates independent of the preoperative mobility score, tumor prognosis and patient age (Table 4).

Discussion

In the current study, 215 patients underwent timely treatment (i.e., were able to undergo planned surgery) and 102 underwent delayed treatment (i.e., required emergency surgery). Delayed treatment was associated with greater neurological deficits at baseline, as expected. However, no significant differences were found in patient- and disease-related parameters. These findings suggest that the largest difference between these groups lies in the timing of their surgical treatment. Multivariate analyses showed that follow-up EQ-5D, KPS and survival rates were lower in the delayed treatment group, independent of other known prognostic factors including the baseline EQ-5D/KPS, neurological status, primary tumor and patient age. Even though the lower neurological scores in the delayed treatment group are known to have a negative effect on KPS, EQ-5D and survival, these findings suggest that the resulting (delayed) treatment regimen further affected patient outcome.

Delayed treatment was associated with a median KPS of 70 compared to a median KPS of 80 in timely treated patients at both 3- and 6-months follow-up. Patients with a KPS of 80 can engage in normal activity, albeit with some difficulty, however patients with a KPS of 70 are not capable of normal activity or work. Therefore, the observed difference between the two groups can be considered highly relevant from a clinical perspective. Both treatment groups showed comparable absolute increases in KPS scores at three and six months compared to baseline scores, perpetuating the inferior KPS scores in the delayed treatment group. These findings are in line with an earlier study reporting on patients with cervical metastases either operated on through an anterior approach (in case of a single metastasis) or through a posterior approach combined with decompression [20]. Both groups had comparable absolute improvements in KPS of approximately 10 points, even though the group requiring decompressive surgery had considerably lower baseline scores. For EQ-5D scores in the present study, the differences between the two groups which were present at baseline persisted at 3 months, but not at 6 months. This is furthermore supported by a study by de Ruyter et al. [21] where patients requiring either posterior stabilization without decompression or a corpectomy did not show an increase in EQ-5D scores after 3 months. In contrast, a third group of patients requiring both posterior decompression and stabilization showed a similar increase between their baseline

Table 1 Demographics for patients in both treatment groups

	Timely Treated <i>n</i> = 147	Delayed <i>n</i> = 55	<i>p</i> value
Mean age, years (SD)	61.7 (11.7)	61.8 (11.6)	0.976
Gender, male (%)	75 (51.0%)	26 (47.3%)	0.758
ASA, <i>n</i> (%)			0.402
1	32 (21.8%)	6 (10.9%)	
2	84 (57.1%)	37 (67.3%)	
3	31 (21.1%)	12 (21.8%)	
Tumor Histology, <i>n</i> (%)			0.787
Bladder	2 (1.4%)	0 (0.0%)	
Breast	38 (26.0%)	14 (25.5%)	
Cervicouterine	3 (2.1%)	1 (1.8%)	
Gastrointestinal	6 (4.1%)	4 (7.3%)	
Lung	12 (8.2%)	7 (12.7%)	
Lymphoma	6 (4.1%)	5 (9.1%)	
Melanoma	2 (1.4%)	0 (0.0%)	
Myeloma	25 (17.1%)	10 (18.2%)	
Plasmacytoma	5 (3.4%)	4 (7.3%)	
Prostate	11 (7.5%)	6 (10.9%)	
Renal	19 (3.0%)	2 (3.6%)	
Sarcoma	2 (1.4%)	0 (0.0%)	
Thyroid	1 (0.7%)	0 (0.0%)	
Other	9 (6.2%)	1 (1.8%)	
Unknown	5 (3.4%)	1 (1.8%)	
Tumor favourability, <i>n</i> (%)			0.830
Favorable	42 (29.0%)	20 (36.4%)	
Moderate	55 (37.9%)	21 (38.2%)	
Unfavorable	48 (33.1%)	14 (25.5%)	
Chemotherapy past year, <i>n</i> (%)			0.010
Yes	14 (9.7%)	3 (5.6%)	
No	130 (90.3%)	51 (94.4%)	
Radiotherapy past year, <i>n</i> (%)			0.754
Yes	23 (15.9%)	7 (13.2%)	
No	122 (84.1%)	46 (86.8%)	
EQ5D, median (IQR)	0.57 (0.24–0.73)	0.24 (0.12–0.33)	<0.001
KPS*, median (IQR)	70 (60–80)	60 (50–70)	<0.001
VAS pain, mean (SD)	4.7 (2.3)	4.7 (2.4)	0.928
Frankel on entry, <i>n</i> (%)			<0.001
A	0 (0.0%)	2 (3.6%)	
B	0 (0.0%)	2 (3.6%)	
C	2 (1.4%)	13 (23.6%)	
D	20 (13.6%)	26 (47.3%)	
E	125 (85.0%)	12 (21.8%)	
Mobility on entry, <i>n</i> (%)			0.001
Normal	112 (76.2%)	22 (15.05)	
Uses one crutch	1 (0.7%)	0 (0.0%)	
Uses walker or two crutches	8 (5.4%)	4 (2.7%)	
Confined to wheelchair	6 (4.1%)	5 (3.4%)	
Confined to bed	20 (13.6%)	24 (16.3%)	
Other metastases, <i>n</i> (%)			0.761
Yes	42 (28.6%)	13 (23.6%)	
No	105 (71.4%)	42 (76.4%)	
Number of affected levels <i>n</i> (%)			0.337

Table 1 (continued)

	Timely Treated <i>n</i> = 147	Delayed <i>n</i> = 55	<i>p</i> value
1	71 (48.3%)	23 (41.8%)	
2	26 (17.7%)	6 (10.9%)	
3	17 (11.6%)	9 (16.4%)	
≥4	33 (22.4%)	17 (30.9%)	
Surgical procedure			< 0.001
Cement augmentation	4 (2.7%)	0 (0.0%)	
Decompression	0 (0.0%)	1 (1.9%)	
Percutaneous fixation	69 (47.3%)	6 (11.1%)	
Open spondylodesis without decompression	34 (23.3%)	5 (9.3%)	
Open spondylodesis with decompression	22 (15.1%)	38 (70.4%)	
Tumor resection	17 (11.6%)	4 (7.4%)	

*Karnofsky Performance Score

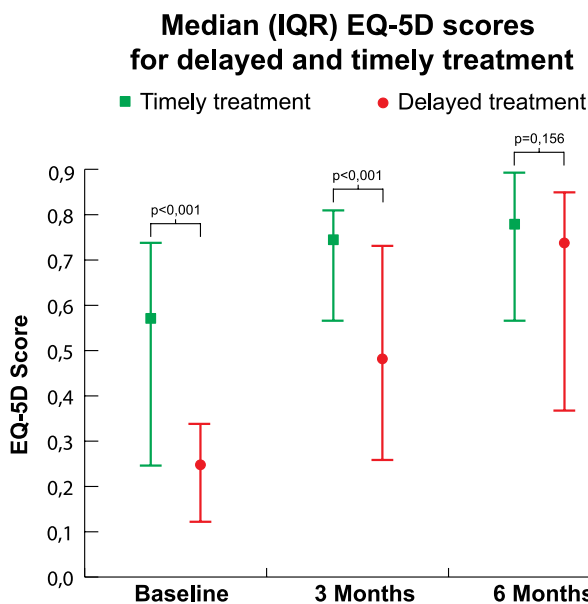


Fig. 1 Median (IQR) EQ-5D scores for timely treated patients and delayed patients at baseline, 3 months and 6 months follow-up

and 3 month scores, but also a slight increase between 3 and 6 month scores. This may be partially attributed to a ceiling effect in the timely treated group, not allowing for more improvement in their utility scores and/or performance status. Another common phenomenon in patients with neurological deficits is a so-called response shift, which is also frequently observed in patients with traumatic spinal cord injury [22]. In these cases, patients show adaptation to their neurological condition and report increases in perceived QoL despite limited improvements in objective functioning. This is also reflected in the current study, where generalized estimating equations showed that delayed treatment was independently correlated with follow-up KPS and EQ-5D scores after correction for confounding factors, however for EQ-5D this was a time-dependent correlation not persisting

at 6 months follow-up. This may also partly explain why the differences in EQ-5D scores between the two treatment groups became non-significant over time.

Timely treatment was associated with a 1 year survival of 70.1% compared with a 1 year survival of 50.9% for delayed treatment. A Cox proportional hazards model showed that the negative effects of delayed treatment on survival remained present independent of known prognostic factors such as preoperative mobility, tumor prognosis and patient age. Lower pre-operative mobility scores were also independently associated with worse 1 year survival, which is in line with previous literature [23, 24]. Since both neurological symptoms, as well as the subsequent emergency surgery, are often caused by delays, this suggests a considerable effect of delays on patient survival.

Symptomatic spinal metastases occur in approximately 10% of all oncological patients, but not all oncological health-care providers are fully familiar with the management of metastatic spinal disease. Nonetheless, for the timely treatment of patients, specialized care-centers rely heavily on the efficiency of referral patterns within primary and secondary care. Even though treatment for metastatic spinal disease is becoming increasingly effective, an important factor in determining treatment outcome is the patient's pre-treatment condition. Consequently, it is imperative to combat the negative effects of delay on the quality of life and survival of patients.

Delayed recognition of metastatic spinal disease often leads to a chain of unfavorable events which may negatively influence patient outcome. Firstly, the epidural spinal cord compression has a direct negative effects on patient outcome and survival [8, 21, 25, 26]. Furthermore, the subsequent emergent surgical procedures required to decompress the neural structures are more invasive than simple (for example, percutaneous) stabilizing procedures, used in patients without symptomatic spinal cord compression, as is also reflected in the current study. Due to their more demanding nature,

Table 2 Generalized Estimating Equations for follow-up EQ-5D scores independent of preoperative EQ-5D score, mobility score, tumor prognosis and patient age. To assess if the correlation between delayed treatment and EQ-5D scores differed at 3 and 6 months follow-up, a second analysis was performed with an interaction term between the follow-up moment and the treatment category

	EQ-5D Utility score (CI)	<i>n</i> = 166 <i>p</i> value
<i>Without interaction term</i>		
Intercept	0.88 (0.65–1.00)*	< 0.001
Follow-up moment		
3 months	Reference	
6 months	0.05 (0.00–0.11)	0.065
Pre-operative EQ-5D		
Per point	0.19 (0.05–0.33)	0.008
Treatment category		
Timely treated	Reference	
Delayed	–0.08 (–0.18–0.01)	0.078
Mobility score		
Unassisted	Reference	
Assisted	–0.03 (–0.16–0.09)	0.615
Unable	–0.07 (–0.18–0.05)	0.260
Tumor prognosis		
Favorable	Reference	
Moderate	–0.03 (–0.12–0.06)	0.646
Unfavorable	–0.12 (–0.21 to –0.03)	0.013
Age		
Per year	0.00 (–0.01–0.00)	0.013
<i>With interaction term</i>		
Intercept	0.9 (0.66–1.00)*	< 0.001
Follow-up moment		
3 months	Reference	
6 months	0.01 (–0.05–0.08)	0.709
Pre-operative EQ-5D		
Per point	0.19 (0.05–0.33)	0.008
Treatment category		
Timely treated	Reference	
Delayed	–0.14 (–0.24 to –0.03)	0.012
Mobility score		
Unassisted	Reference	
Assisted	–0.03 (–0.15–0.10)	0.658
Unable	–0.06 (–0.18 to 0.05)	0.274
Tumor prognosis		
Favorable	Reference	
Moderate	–0.04 (–0.13–0.05)	0.418
Unfavorable	–0.13 (–0.22 to –0.03)	0.009
Age		
Per year	0.00 (–0.01–0.00)	0.012
Interaction term		
6 months + delayed treatment	0.15 (0.03–0.28)	0.016

*Rounded down to clinically appropriate values

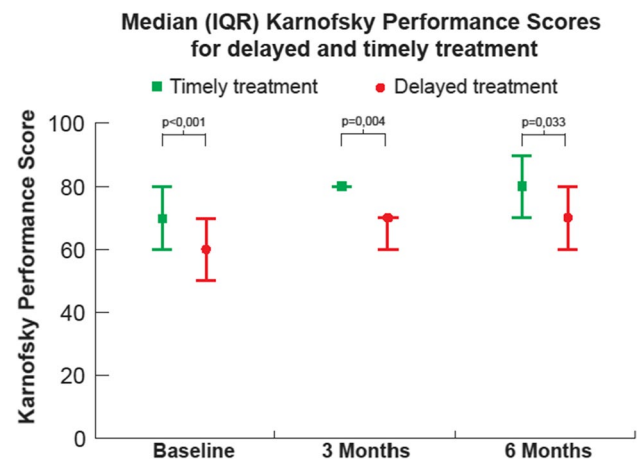


Fig. 2 Median (IQR) KPS scores for timely treated patients and delayed patients at baseline, 3 months and 6 months follow-up

these decompressive surgical procedures can also lead to inferior patient outcomes [21]. In addition to neurological deficit and the subsequent invasive surgical treatment necessary, other factors associated with emergency treatment, such as a more limited window for adequate patient work-up and/or having to perform surgery outside office hours with a potentially less experienced team, may further negatively influence patient outcome [27, 28].

Several limitations apply to this study. First, even though no differences between the two groups were found in terms of primary tumor types, no further details on the molecular subtype and clinical characteristics of tumors were available. We cannot fully exclude that patients presenting with an indication for emergency surgery had more aggressive tumor biology. However, because differences in prognoses will be more outspoken between different primary tumor types than differences within a single tumor type, the authors believe that the results adequately represent the effect of delayed treatment. Second, because the timing of the surgery was left to the discretion of the attending surgeon, this process may be subject to some variability. However, all surgeons involved in this study are part of the same spinal unit and adhere to the same basic principles in the treatment of patients with spinal metastases (the NOMS-framework) [10]. Finally, there was some drop-out between the 3- and 6-months follow-up points, partially caused by loss to follow-up and partially by mortality. Sensitivity analyses comparing KPS and EQ-5D at 3 months between patients with and without data available at 6 months showed no significant differences, therefore an effect of bias due to loss to follow-up on our results is likely limited.

Table 3 Generalized Estimating Equations for follow-up KPS scores independent of preoperative KPS score, mobility score, tumor prognosis and patient age. To assess if the correlation between delayed treatment and KPS scores differed at 3 and 6 months follow-up, a second analysis was performed with an interaction term between the follow-up moment and the treatment category

	KPS Score (CI)	n = 192 p value
<i>Without interaction term</i>		
Intercept	75.7 (60.1–89.3)	< 0.001
Follow-up moment		
3 months	Reference	
6 months	4.6 (2.3–6.9)	< 0.001
Pre-operative KPS		
Per point	0.2 (0.0–0.3)	0.012
Treatment category		
Timely treated	Reference	
Delayed	–7.7 (–11.2 to –4.2)	< 0.001
Mobility score		
Unassisted	Reference	
Assisted	–2.6 (–7.8–2.6)	0.318
Unable	–2.1 (–7.2–3.0)	0.412
Tumor prognosis		
Favorable	Reference	0.851
Moderate	0.3 (–3.2–3.9)	0.168
Unfavorable	–2.6 (–6.4–1.1)	
Age		
Per year	–0.2 (–0.3 to –0.0)	0.012
<i>With interaction term</i>		
Intercept	74.7 (60.1–89.3)	< 0.001
Follow-up moment		
3 months	Reference	
6 months	3.3 (0.6–6.0)	0.017
Pre-operative KPS		
Per point	0.2 (0.0–0.3)	0.013
Treatment category		
Timely treated	Reference	
Delayed	–8.8 (–12.6 to –5.0)	< 0.001
Mobility score		
Unassisted	Reference	
Assisted	–2.5 (–7.7–2.7)	0.345
Unable	–2.2 (–7.3–3.0)	0.405
Tumor prognosis		
Favorable	Reference	
Moderate	0.2 (–3.4–3.8)	0.917
Unfavorable	–2.9 (–6.7–0.9)	0.133
Age		
Per year	–0.2 (–0.3 to –0.0)	0.012
Interaction term		
6 months + delayed treatment	3.9 (–0.9–8.6)	0.113

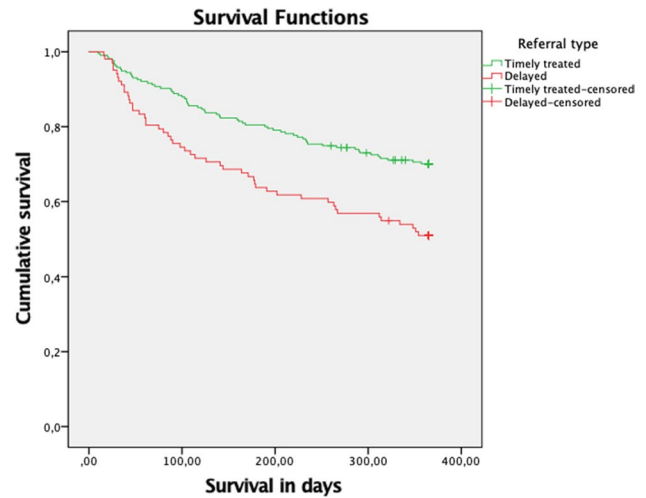


Fig. 3 Survival curves for timely treated (n=215) and delayed patients (n=102) patients. One-year survival was 70.1% for timely treated patients versus 50.9% for delayed patients (log rank test: p=0.001)

Table 4 Cox proportional hazards model investigating factors associated with 1 year mortality

n = 317	Hazard Ratio (CI)	p value
<i>Treatment category</i>		
Timely treated	Reference	
Delayed	0.65 (0.43–0.99)	0.043
<i>Mobility score</i>		
Unassisted	Reference	
Assisted	0.45 (0.28–0.70)	< 0.001
Unable	1.00 (0.59–1.72)	
<i>Tumor prognosis</i>		
Favorable	Reference	
Moderate	0.17 (0.09–0.31)	< 0.001
Unfavorable	0.29 (0.18–0.47)	< 0.001
<i>Age</i>		
Per year	1.00 (0.98–1.02)	0.842

Conclusion

In conclusion, the results from our study suggest delayed treatment of patients with symptomatic spinal metastases has both direct and indirect adverse consequences for functional performance status, quality of life and survival. Our results emphasize the need for early identification of patients with spinal metastases at risk of neurological deficits and optimization of referral patterns to prevent or minimize delayed referrals and treatment in the future.

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Data availability Not applicable.

Code availability Not applicable.

Compliance with ethical standards

Conflicts of interest None.

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