TOWARDS BETTER PATIENT JOURNEYS IN METASTATIC SPINAL DISEASE

Floris Rudolf van Tol

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TOWARDS BETTER PATIENT JOURNEYS IN METASTATIC SPINAL DISEASE

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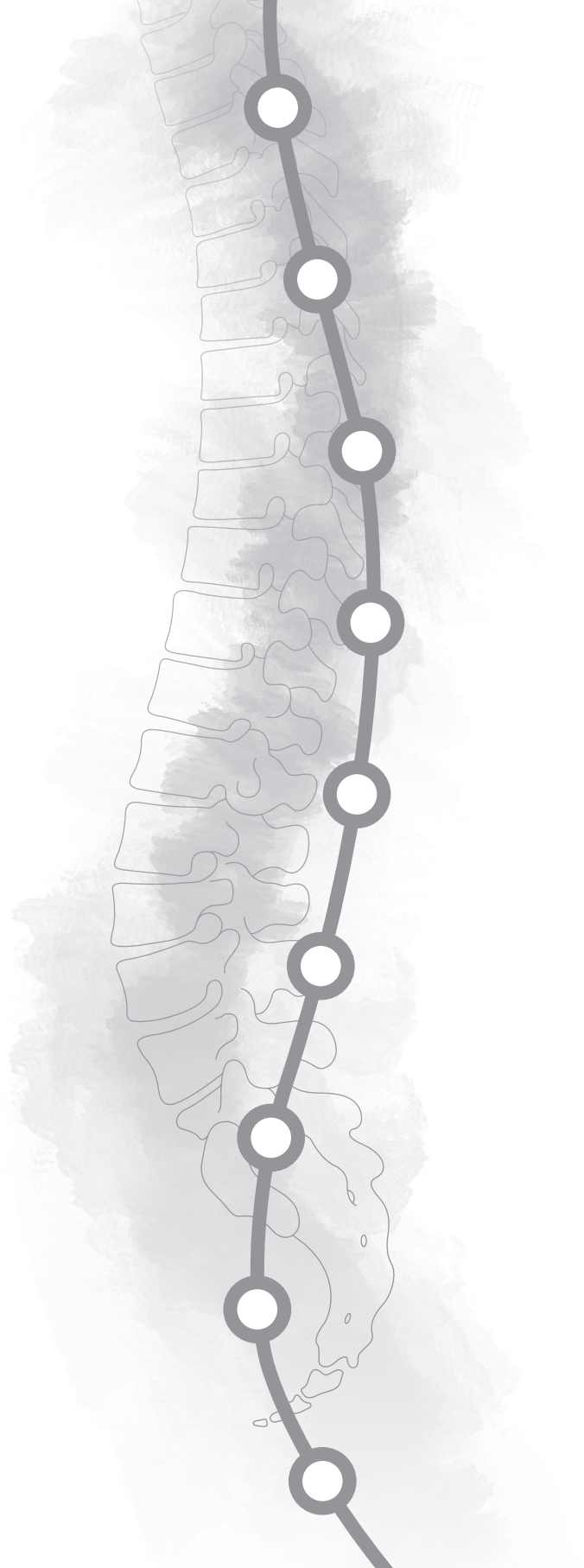

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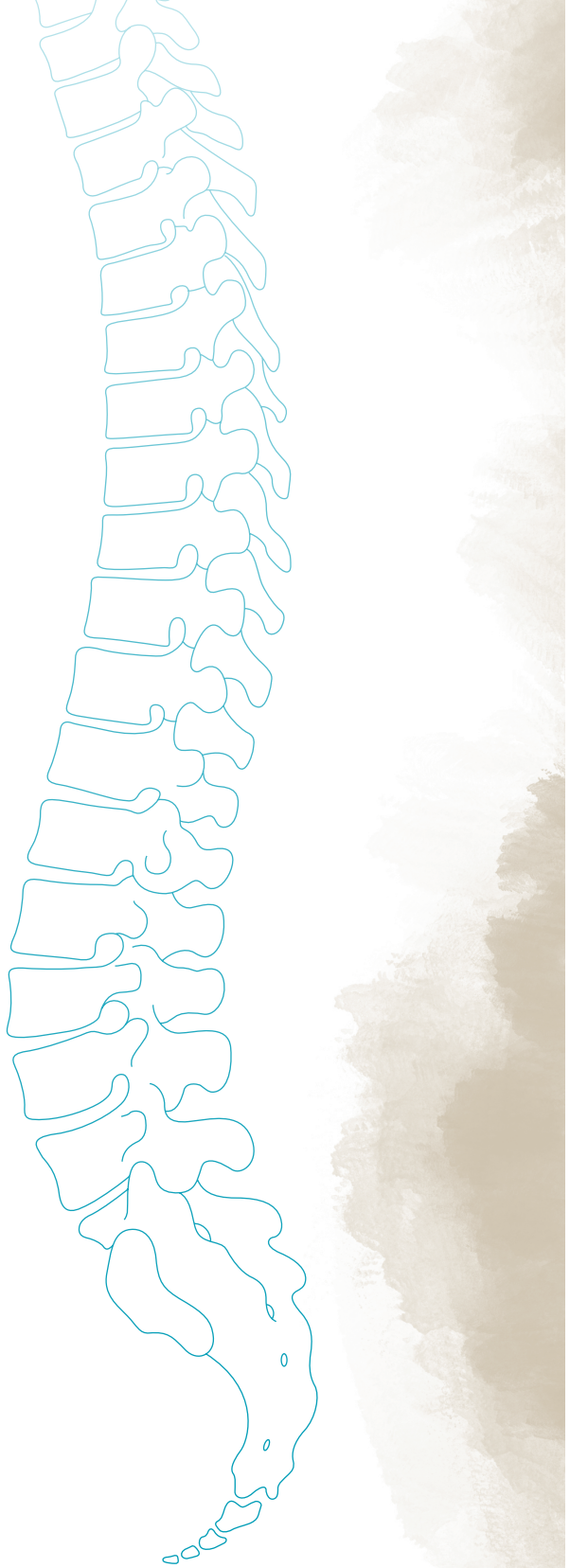

CHAPTER 1

General Introduction and Thesis Outline

BACKGROUND

Cancer is one of the largest contributors to global mortality, with approximately 10 million deaths reported in 2020 [1]. Due to an aging population, an increased exposure to environmental toxins and pollution, and improved diagnostic options, the global incidence of cancer is growing [2]. In the Netherlands, there has been a threefold increase in the annual number of patients diagnosed with cancer over the past 30 years [3]. At the same time, several groundbreaking therapies such as immunotherapy, targeted therapy, and gene therapy have significantly enhanced the survival rate of tumour types that were previously associated with a poor prognosis. New systemic anti-cancer treatments, advances in medical technology, and a better understanding of cancer biology have resulted in a 20% improvement in 5-year survival of cancer patients [2]. Nevertheless, with the increasing number of cancer patients experiencing prolonged survival, there has been a corresponding rise in individuals living with metastatic cancer. In the past, a diagnosis of cancer metastases was typically regarded as a terminal condition with limited treatment options. However, advancements in systemic therapies have enabled patients to live longer with metastatic disease. This improvement in survival for patients with metastatic cancer has created new challenges in the care for these patients. Consequently, there is a need for innovative approaches to further extend their survival and enhance their quality of life, ensuring proper care for those who were once deemed untreatable.

One of the most common sites for metastases in patients with metastatic cancer is the skeleton, with approximately 60% of deceased cancer patients having bony metastases at autopsy [4]. Although any cancer can potentially metastasize to bone, patients with metastatic renal, lung, breast, and prostate are especially at risk, with up to 89% of the patients developing bony metastases [5,6]. In the United States, there are an estimated 400,000 patients newly diagnosed with bone metastases each year [7]. With the increasing incidence and prevalence of metastatic cancer, the occurrence of bone metastases is naturally expected to rise as well [8]. Owing to its abundant blood supply and bone marrow, containing numerous growth factors and cytokines, the spinal column is the most frequent site for bone metastases, accounting for approximately 50-70% of all bone metastases [9,10]. Among oncological patients, between 10% and 20% develop symptoms related to metastatic spinal disease [11,12]. Upon the clinical suspicion of spinal metastases, it's recommended to perform Magnetic Resonance Imaging (MRI) or Computed Tomography (CT) scans to confirm or refute the presence of metastatic spinal disease. In the Netherlands, approximately 25,000 patients are diagnosed with spinal metastases every year [13].

SYMPTOMS

Patients with bone metastases often experience debilitating pain, which impairs their physical functioning and quality of life [14]. The pathophysiology of metastatic bone pain is multifactorial and complex. All bone compartments, in particular the periosteum, are densely packed with sensory neurons [15]. Mechanical stress induced by the growing tumour and neuronal irritation or damage due to inflammatory mediators both have the potential to induce severe pain in patients suffering from bone metastases [16,17].

Moreover, metastatic spinal lesions can jeopardize the spine's mechanical stability. Cytokine and growth factor secretion by tumour cells may disrupt the process of bone homeostasis, which is a balance between bone formation by osteoblasts and bone resorption by osteoclasts [18]. When there is an imbalance in bone remodelling that leads to increased osteoclast activity, the resulting bone lesions are referred to as 'lytic'. This type of lesion is characterized by the destruction of bone tissue, ultimately leading to impaired structural integrity of bone. Conversely, when there is an imbalance that leads to increased osteoblast activity, 'blastic' lesions are formed. These lesions are associated with areas of thickened or 'sclerotic' bone. However, the newly formed bone tissue may be disorganized and not as strong as native bone. As a result, both lytic and blastic lesions can interfere with the mechanical integrity of the bone and increase the risk of pathological fractures [14].

Finally, spinal metastases can give rise to neurological symptoms. A distinctive feature of bone metastases in the spinal column, as compared to the appendicular skeleton, is the proximity to vital neural structures such as the spinal cord, cauda equina and/or exiting nerve roots which can be compressed by a metastatic tumour. The subsequent disruption of signal transmission can result in a range of neurological symptoms, depending on the location and severity of the compression. Symptoms may include radiculopathy, muscle weakness, numbness or tingling as well as an ataxic gait or autonomic symptoms, including sexual, bladder or bowel dysfunction.

TREATMENT

Despite considerable improvements in survival for metastatic cancer, patients with metastatic (spinal) disease are considered in the incurable stages of disease, where treatment resolves primarily around improving a patient's quality of life and functional status through alleviating pain and other symptoms. Management of spinal metastases may occur through any combination of systemic treatment, radiotherapy, surgery and/or active surveillance. Systemic therapies, such as chemotherapy, immunotherapy, hormone therapy, or targeted therapy, act

on cancer cells throughout the entire body, irrespective of their location. In this way systemic therapy can also control the growth of widespread metastatic spinal disease and limit further spread into the spinal column. Radiation therapy is a local treatment that employs high-energy radiation to damage the DNA of cancer cells, leading to a reduction in tumour size thereby relieving the associated symptoms. When localised tumour control is needed, this is often the preferred method of treatment. Surgery may serve one of three distinct purposes: First, it may be utilized to debulk the tumour as a form of local tumour control. However, given the invasiveness of such procedures and advances in radiation therapy techniques, this is now a less favoured surgical indication. Second, surgery may be used to stabilize the spinal column in the case of mechanical compromise. Finally, surgery may be used to decompress neural structures, either in response to neurological symptoms arising from tumour compression or as a pre-emptive measure to establish physical separation between the tumour and radiosensitive structures at risk of radiotoxicity due to tumour-targeted radiation A systematic approach to select the adequate (combination of) treatment(s) is the so-called NOMS-framework [19]. The four pillars of the acronym NOMS (Neurologic, Oncologic, Mechanical and Systemic) each represent patient or disease characteristics dictating the subsequent preferred treatment modality. Through tools such as the NOMS algorithm, healthcare providers and patients can make informed, shared decisions about treatment considering the patient's individual needs and circumstances.

First, the neurologic (N) pillar concerns restoring or maintaining neurological functionality and assesses the degree to which the spinal metastases have invaded the spinal canal and/or epidural space. In clinical practice, neurological deficits are typically evaluated using the American Spinal Injury Association (ASIA) impairment scale. This scale ranges from E, representing fully intact neurological function, to A, indicating complete sensory and motor block [20]. To identify impending neurological deficits, radiological assessment of the degree of Metastatic Spinal Cord Compression (MSCC) is also important and can be expressed using the Bilsky classification on MRI. A score of 0 indicates bone-only disease without epidural compression, while a score of 3 indicates that the spinal cord is compressed to such an extent that there is no more cerebrospinal fluid visible surrounding the spinal cord [21]. In the case of clinically diagnosed neurological deficits or high grade MSCC, urgent surgical decompression of neural structures is often indicated to reverse or prevent further progression of neurological deficits [19,22–24].

Second, the oncologic (O) pillar revolves around inducing (local) tumour control, thereby preventing further tumour growth and its associated complications. To this end, the sensitivity of the tumour to radiation therapy (radiosensitivity) is determined based on the primary tumour histology. When a tumour is considered radiosensitive, conventional External Beam Radiation Therapy (EBRT) is often sufficient [25,26]. In contrast, when a tumour's susceptibility to ionizing radiation is considered limited, Stereotactic Body Radiation Therapy (SBRT) may be more suitable [27]. With this technique, the radiation is high-dosed and highly conformal, leading to ablative doses to the tumour at the focal point of radiation whilst limiting the dose to neighbouring anatomic structures [28,29].

Third, the mechanical (M) pillar revolves around restoring and/or maintaining mechanical integrity and assesses any mechanical compromise and subsequent risk of vertebral collapse of the spinal column. To aid clinicians in the diagnosis of spinal instability, an 18-point Spinal Instability Neoplastic Score (SINS) has been introduced where a score of 0-6 indicates a stable lesion, a score of 7-12 a potentially unstable lesion and a score of 13-18 an unstable lesion [30]. In the case of a (potentially) unstable lesion, surgical treatment aimed at maintaining or restoring spinal stability and preventing (further) vertebral deformation is often indicated. Posterior stabilization surgery is commonly performed to exempt mechanical weak spots from further weight bearing, thereby mitigating the risk of secondary neurological damage due to (pending) pathological fractures [31,32].

Lastly, the systemic (S) pillar assesses to which extent patients can tolerate the proposed (surgical) treatment. Relatively straight forward instruments such as the Karnofsky Performance Scale (KPS), or more advanced prognostic models such as the Skeletal Oncology Research Group (SORG) machine learning algorithm, may be used to help select appropriate surgical candidates [33,34]. Historically, a minimum life expectancy of at least three months is indicated for surgical treatment to ensure that the benefits of surgery outweigh the considerable risks of morbidity and mortality [35,36]. However, recent literature indicates that the pre-operative performance status is the most critical determinant of postoperative outcome and should be the primary consideration [37].

TIMING OF TREATMENT

Metastatic spinal disease is a progressive condition and will often lead to complications if left untreated. In the early stages of disease, metastases may not cause significant damage to the spine and symptoms may be mild or absent. At this point, the neurological and mechanical pillars are usually unaffected, and in case of symptoms, patients can thus be treated with less invasive methods such as systemic anti-cancer treatment or palliative radiotherapy [38]. However, if early metastatic spinal disease is not recognized and subsequently treated, it may lead to intractable mechanical pain, not responsive to radiation or systemic therapy, or it may compromise the mechanical integrity of the spine. In such cases, low demand stabilizing surgical procedures, typically using minimally invasive surgical approaches, are often sufficient to alleviate these symptoms [39]. When spinal metastases have progressed even further and are now affecting neurogenic structures and causing neurological deficits (either through

direct compression or as a result of vertebral collapse or deformity), more extensive surgical procedures are required to decompress and stabilize the involved neural structures [19,40]. However, even with urgent surgical intervention, complete resolution of neurologic symptoms only occurs in only 20-40% of MSCC patients [41–43]. As neurological deficits have a profound negative effect on the overall condition, quality of life and survival of cancer patients, preventing their occurrence is crucial for favourable patient outcome [44]. Furthermore, given that greater invasiveness of treatment is associated with higher morbidity and mortality, timely diagnosis, referral, and treatment are essential to obtain a positive treatment outcome in metastatic spinal disease.

CURRENT CHALLENGES

Although timely treatment of metastatic spinal disease is widely recognised as important and has been endorsed in the literature and various national guidelines, MSCC is estimated to occur in around 25-50% of patients with spinal metastases, and this number is slowly increasing [45–49]. There are several challenging aspects in expediting diagnosis, referral, and treatment for metastatic spinal disease. First, patients often present with symptoms resembling non-cancer-related back or neck pain. Non-specific back pain is one of the most common conditions in the middle-aged population and is generally regarded as self-limiting [50,51]. More alarming symptoms (e.g., neurological deficits) may only develop later in the disease process. Especially in patients where metastatic spinal disease is the first clinical manifestation of malignant disease (synchronous metastasis), there is considerable risk of potentially detrimental supervised neglect policies, which are often used in self-limiting pathologies. Even in patients with known malignancies, not recognizing symptoms associated with metastatic spinal disease can result in significant delays in diagnosis. Second, the multidisciplinary nature of metastatic spinal disease treatment can make it challenging to select the appropriate treatment modality, and this relies heavily on good communication between different medical specialties. Uncertainty about the appropriate line of treatment puts patients at risk of delayed referrals to their definitive caregiver. Finally, since virtually any primary tumour can metastasise to the spine, a wide array of healthcare providers must, by necessity, be involved in the care for patients with spinal metastases. Not all these healthcare providers may have the expertise or experience for the more detailed aspects of metastatic spinal disease. As an example, an older study among Dutch health-care providers showed that more than 80% of general practitioners believed that stand-alone palliative radiotherapy is effective treatment for MSCC [52]. Lastly, the care for spinal metastases requires specialized expertise and resources that are often only available at specialized care centres. This means that patients who present with spinal metastases at regional hospitals must be referred to these specialized centres for treatment. As the transfer

of medical records and coordination of care can take time, coordination between healthcare centres is a critical step in promoting timely treatment. To reverse the upward trend in the incidence of MSCC, it is imperative to provide healthcare providers involved in the care of patients with metastatic spinal disease the proper tools and guidance to expedite diagnosis, referral, and definitive treatment of these patients.

MITIGATING DELAY

In primary cancer care, delays in the diagnosis, referral and treatment of cancer have also been inseparably linked with poorer overall survival. Especially delays in the diagnosis inevitably lead to a higher proportion of end-stage cancers and have been shown to reduce 5-year survival by up to 20% [53]. The first step towards designing adequate strategies to tackle delays in oncological care is to fully analyse and understand patient journeys from the onset of symptoms until definitive treatment. A lack of consensus on the definitions and terms, as well as the time intervals which are measured have induced the development of several theoretical frameworks to systematically appraise patient journeys [54]. Applying such a theoretical framework to study different types of delay in the diagnosis, referral and treatment may serve to guide future interventions more successfully [55].

The most cited of such models was originally proposed by Safer et al. in 1979, and subsequently developed by Andersen et al in 1995 to separate the patient journey into 5 different delay intervals: Appraisal delay (i.e. the time it takes for a patient to notice bodily changes), illness delay (i.e. the time it takes to decide to seek medical attention), behavioural delay (i.e. the time it takes to act on the decision by making an appointment with a medical caregiver), scheduling delay (i.e. the time it takes to actually receive medical attention) and treatment delay (i.e. the time it takes to receive actual treatment) [56,57]. A more recent study reviewed the literature on the application of this 'Andersen Model' and from its findings, proposed several refinements to the model [54]. First, there was little evidence for illness delay as a separate entity to appraisal delay and behavioural delay as a separate entity to scheduling delay. Moreover, treatment delay was split into two separate intervals prior to, and after the diagnosis was made. This refined version of the Andersen model was later endorsed by an international consensus work group in 2012 [58].

There are several shortcomings in the application of the (refined) Andersen Model when aiming to study metastatic spinal disease. First, the distinction between the 'appraisal' and 'help-seeking' interval is challenging to accurately depict in a retrospective setting. It is unlikely that patient records reflect the crossover point between these two phases. For practical rea-

sons, it may be more suitable to combine these two intervals into the more well-known 'patient delay'. Second, as can be appreciated from the NOMS algorithm, definitive treatment of spinal metastases can vary greatly, depending on many patient- and disease-related factors, and may be carried out by a wide variety of health-care providers (e.g., spine surgeon, radiation oncologist, medical oncologist etc.). Due to this multidisciplinary nature of treatment for metastatic spinal disease, not all patients are directly referred to the appropriate caregiver. To this end, referral tools such as the SINS have been developed [30]. The overall aim of such tools is to guide referrals and improve communication between caregivers involved in the patient journey of patients suffering from spinal metastases. To quantify the utilization and usefulness of such referral tools it is important to separate the original treatment interval into a 'referral' and a 'treatment' interval. The subsequent theoretical framework for the appraisal of patient journeys specifically in patients suffering from spinal metastatic disease is depicted in **Figure 1**.

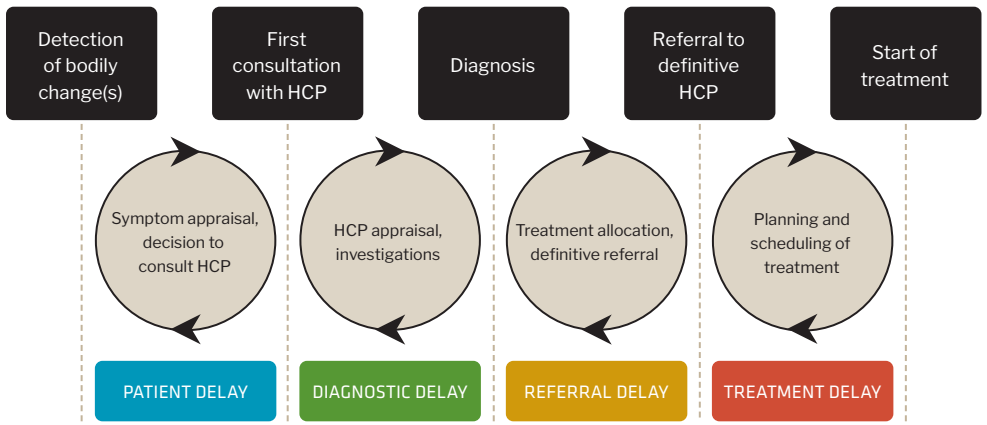

FIGURE 1. Andersen Model, adapted for studying patient journeys in metastatic spinal disease.

PURPOSE AND OUTLINE OF THIS THESIS

The current thesis focusses on identifying strategies to expedite the diagnosis, referral, and treatment of patients with metastatic spinal disease throughout the entire referral chain. As a first step towards mitigating delays, it is important to understand the implications of delays on the quality of care. In **Part I**, this thesis seeks to answer how delayed treatment impacts various short- and long-term treatment outcomes as well as treatment costs. In the first part of this thesis, delayed treatment is exemplified by patients requiring emergency surgery within 3 days of presentation, as they have likely developed irreversible damage and ideally should have been treated earlier. In **Part II**, patient journeys are analysed in depth to serve as a basis to inform future strategies aimed at reducing delays.

The following research objectives were defined:

Part I

Chapter 2 To compare surgical and clinical outcomes between patients undergoing timely treatment and patients undergoing delayed treatment.

Chapter 3 To compare physical function and quality of life up to 6 months after surgery, as well as survival between patients undergoing timely treatment and patients undergoing delayed treatment.

Chapter 4 To compare costs of treatment between patients undergoing timely treatment and patients undergoing delayed treatment.

Part II

Chapter 5 To identify and measure delay intervals in patients with metastatic spinal disease and explore factors associated with shorter or longer delays.

Chapter 6 To evaluate the duration between the onset of symptoms and the occurrence of neurological deficits and correlate this duration to several patient- and disease-related factors.

Chapter 7 To investigate the use and usefulness of alarming symptoms (red flags) as defined by the Dutch National Guideline on Metastatic Spinal Disease.

The implications of these results for clinical practice and future perspectives are further discussed in **Chapter 8**.

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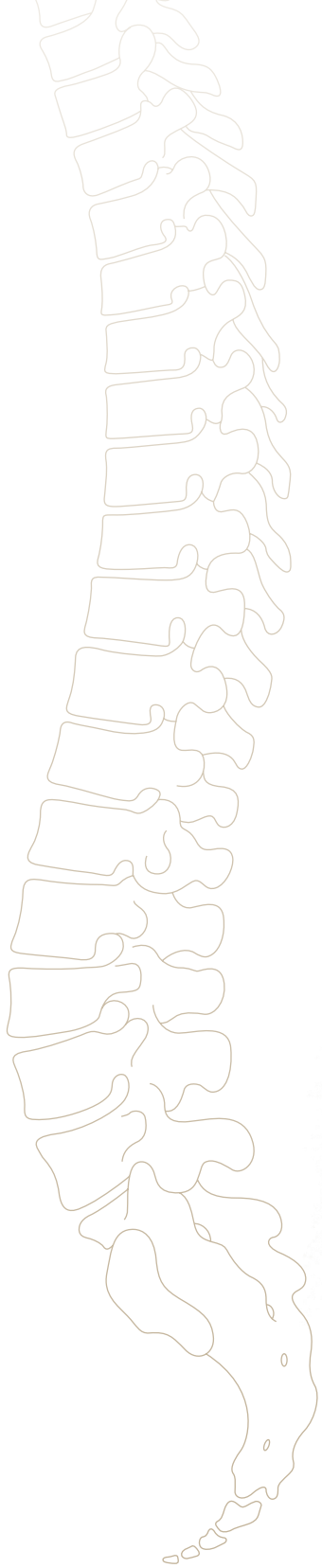
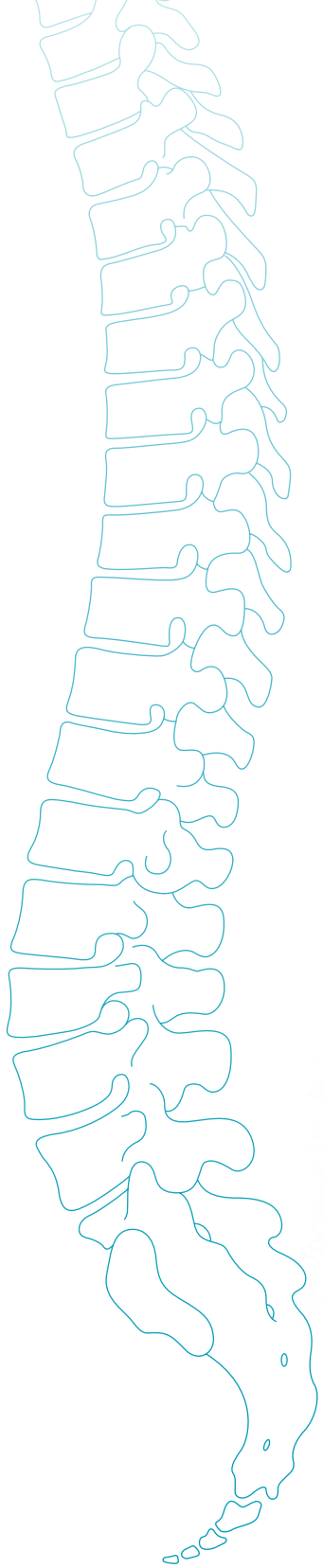
Part I



THE IMPACT OF DELAY ON TREATMENT OUTCOME



CHAPTER 2

Delayed Presentation to a Spine Surgeon is the Strongest Predictor of Poor Postoperative Outcome in Patients Surgically Treated for Symptomatic Spinal Metastases

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ABSTRACT

BACKGROUND

Symptoms associated with spinal metastases are often non-specific and resemble non-cancer related. Therefore, patients with spinal metastases are at risk for delayed referral and treatment. Delayed presentation of symptomatic spinal metastases may lead to the development of neurological deficits, often followed by emergency surgery.

OBJECTIVE

The aim of this cohort study was to analyze the effect of delayed referral and treatment of spinal metastases on clinical outcome.

METHODS

We included all patients surgically treated for spinal metastases at our tertiary care center. Based on the (in)ability to undergo elective surgery, patients were identified as timely treated or delayed. Patient- and tumor-characteristics, surgical variables, and postoperative variables such as complication rate, the ability to return home and length of hospital stay were recorded and compared between the two groups.

RESULTS

Based on the urgency of treatment at admission, 206 patients were identified as timely treated and 98 as delayed. At baseline, the two groups did not differ significantly except for the extent of neurological symptoms. Timely treated patients underwent less invasive procedures (52.9% vs 13.3% percutaneous pedicle screw fixations), less median blood loss (200cc vs 450cc), shorter median admission time (7 vs 13 days), lower complication rate (26.2% vs 48.0%) and higher chances of being discharged home immediately (82.6% vs 41.1%) compared to delayed patients. Using multivariate regression models these correlations remained present independent of tumor prognosis, preoperative mobility and ASA-score.

CONCLUSION

The delayed presentation of patients with spinal metastases to a spinal surgeon is strongly and independently associated with worse surgical and postoperative outcome parameters. Improvements in referral patterns could potentially lead to more scheduled care, negating the detrimental effects of delay.

Keywords: Spinal metastases, spine surgery, delay, emergency surgery, patient outcome

INTRODUCTION

Symptomatic spinal metastases are an increasing problem in oncology. Currently, spinal metastases occur in approximately 20% of all oncological patients [1,2]. However, due to the superior effects of new systemic anti-cancer therapies on overall survival, the prevalence of patients with spinal metastatic disease is increasing [3,4]. Unchecked growth of spinal metastases can cause mechanical instability of the spine, with or without compression on neural structures [5]. Intuitively, timely treatment of patients may be an important factor in achieving acceptable treatment outcomes.

A major challenge in the early identification of patients with spinal metastases is that patients often present with symptoms resembling non-cancer-related back pain, which is one of the most common conditions in the middle-aged population [6]. More alarming symptoms (e.g., neurological deficits) may only develop later in the disease process, putting patients at risk for delayed diagnosis, referral and treatment. As a result, symptomatic spinal cord compression occurs in 25%-50% of all patients with spinal metastases [7,8]. At this stage, patients commonly require emergency surgical intervention in an attempt to deter progression and/or reverse neurological symptoms [9–11]. The short preparation time available before emergency surgery might hamper adequate patient work-up and limit the availability of preferred spinal implants and qualified staff, potentially leading to adverse clinical outcomes [12,13]. Furthermore, an impaired neurological status has also been linked to a reduction in both postoperative clinical parameters and Quality of Life (QoL) [14–17].

The exact effects of delayed presentation and treatment of patients with spinal metastases however remains to be quantified. We hypothesized that earlier treatment of patients with spinal metastases lead to more favorable surgical and postoperative clinical outcomes. The primary aim of this study was therefore to assess the relationship between delayed presentation to a spine surgeon and surgical and postoperative parameters for patients with symptomatic spinal metastases. The secondary aim was to investigate how each aspect of delayed presentation to the spine surgeon (i.e., neurological deficits, emergency surgery, etc.) correlates to the aforementioned parameters independent of other prognostic factors.

MATERIALS AND METHODS

Our institutional review board approved a waiver of informed consent for this study. Data for all consecutive patients referred to a single tertiary spine center for surgical treatment of symptomatic spinal metastases between March 2009 and December 2017 were collected. Patients with spinal involvement of multiple myeloma were also included for analysis due to

similarities in clinical presentation and initial treatment. Tumor histology was analyzed from intra-operative transpedicular biopsies and categorized into three groups based on median overall survival as previously described by Bollen et al. and updated in consultation with our medical oncology department (<18 months: unfavorable, 18-36 months: moderate, >36 months, favorable) [18]. Unknown primary tumors were classified as unfavorable. Patients with a life expectancy of at least three months were deemed eligible for surgical treatment [19]. Indications for surgery were either mechanical pain, radiographic (imminent) spinal instability and/or neurological deficits. The surgical technique was chosen by the treating spine surgeon.

The population was split into two groups: The first, timely treated group consisted of patients who, in the absence of alarming symptoms, could be scheduled for surgery more than 3 days after initial presentation at the spinal surgery department. The second, delayed group consisted of patients who, in the presence of alarming symptoms (e.g., neurological deficits, signs of gross mechanical instability), required urgent or emergency surgery within 3 days after initial presentation at our department. The 3-day cutoff for elective or non-elective surgery was chosen in accordance with the criteria of the Global Spine Tumor Study Group (GSTSG) [20]. The delayed patient group could be further split up into patients requiring surgery within 24 hours and patients requiring surgery after 24 hours but within three days ("intermediate" patients). Sensitivity analyses were performed to assess the effect of excluding these intermediate patients from the analyses.

All parameters were extracted from medical records and included demographic data such as age, sex, ASA-classification (American Society of Anesthesiologists, a physical status classification system) [21] and tumor characteristics. Preoperative neurological status, Karnofsky Performance Score (KPS), surgical urgency, Tomita [22] scores and Tokuhashi [23] scores were assessed and recorded by the treating spine surgeon. Predefined surgical data including surgical technique, duration of surgery, blood loss and instrumented levels as well as postoperative data including duration of admission, complications, destination after discharge and postoperative neurological status were submitted to the GSTSG database for further processing [20]. All the involved surgeons adhered to the same basic principles, using SINS (Spinal Instability Neoplastic Score) [24] for spinal stability, KPS for general patient condition and ASIA/Frankel (American Spinal Injury Association) classification for neurological status, and combining these in a uniform way, similar to the NOMS-guidelines (Neurologic, Oncologic, Mechanical and Systemic) to determine the adequate type and timing of treatment for each patient [10,24].

STATISTICAL ANALYSIS

For continuous data, means, standard deviations (SD), medians and interquartile range (IQR) were used, based on their distribution. Normality was checked graphically using histograms and Q-Q plots. For categorical data frequencies were used. To compare timely treated and delayed patients at baseline, Chi-squared tests for categorical data, unpaired t-tests for normally distributed continuous data and Mann Whitney U tests for continuous data with non-normal distribution were used. Log transformation was applied in case of non-normal distribution of dependent continuous variables in regression analyses. To assess the relationship between the timing of treatment and continuous surgical/postoperative outcome measures (surgery duration, blood loss during surgery and number of days spent in the hospital), independently of potential confounders (i.e., pre-operative mobility score, KPS, preoperative ASA classification, preoperative tumor favorability and patient age), multiple linear regression analyses were used. Binary logistic regression analysis was used for dichotomous surgical/postoperative outcome variables (the occurrence of complications and the ability to return home) associations were reported using odds ratios (OR). Due to collinearity of preoperative mobility scores and the KPS, the independent parameters included in both types of regression analyses were preoperative mobility (on a 3-point Likert-scale: unassisted (reference value), assisted and unable), preoperative ASA classification (reference value: 1), preoperative tumor favorability (reference value: favorable) and patient age. Collinearity of these factors was assessed using variance inflation factors (VIF's) with a VIF exceeding 1.5 advocating in favor of collinearity. All analyses were performed using IBM SPSS Statistics for Macintosh, Version 24.0 (Armonk, NY: IBM Corp).

RESULTS

The cohort consisted of 206 timely treated and 98 delayed patients. At baseline, no significant differences between the two groups were found for age, gender, ASA-classification, tumor favorability, the number of affected levels, VAS-pain scores and mean Tomita score. Delayed patients had a higher prevalence of neurological deficits and lower outcome parameters related to neurological status such as KPS, mobility score, urinary sphincter control and Tokuhashi score (**Table 1**).

TABLE 1. BASELINE CHARACTERISTICS FOR BOTH PATIENT GROUPS

	Timely Treated n=206	Delayed n=98	*P-value*
Mean age, years (SD)	61.9 (11.7)	62.3 (11.0)	*0.789*
Gender, male (%)	106 (51.5%)	56 (57.1%)	*0.474*
ASA, n (%)			*0.122*
1	36 (17.5%)	7 (7.2%)	
2	111 (53.9%)	55 (56.7%)	
3	59 (28.6%)	35 (36.1%)	
Tumour Histology, n (%)			***0.001***
Bladder	4 (1.9%)	1 (1.0%)	
Breast	42 (20.4%)	16 (6.3%)	
Cervicouterine	4 (1.9%)	1 (1.0%)	
Gastrointestinal	11 (5.3%)	11 (11.2%)	
Lung	25 (12.1%)	17 (17.3%)	
Lymphoma	7 (3.4%)	8 (8.2%)	
Melanoma	4 (1.9%)	0 (0.0%)	
Myeloma	30 (14.4%)	13 (13.1%)	
Plasmacytoma	4 (1.9%)	5 (5.1%)	
Prostate	16 (7.8%)	13 (13.3%)	
Renal	26 (12.6%)	6 (6.1%)	
Sarcoma	2 (1.0%)	0 (0.0%)	
Thyroid	1 (0.5%)	0 (0.0%)	
Other	12 (5.8%)	2 (2.0%)	
Unknown	14 (6.8%)	3 (3.1%)	
Tumour favorability*, n (%)			*0.686*
Favorable	48 (24.0%)	27 (28.4%)	
Moderate	66 (33.0%)	30 (31.6%)	
Unfavorable	86 (43.0%)	38 (40.0%)	
KPS** (SD)	68.6 (14.5)	56.3 (16.0)	***<0.001***
Frankel on entry, n (%)			***<0.001***
A	0 (0.0%)	3 (3.1%)	
B	0 (0.0%)	7 (7.1%)	
C	4 (1.9%)	25 (25.5%)	
D	28 (13.6%)	44 (44.9%)	
E	174 (84.5%)	19 (19.4%)	

TABLE 1. BASELINE CHARACTERISTICS FOR BOTH PATIENT GROUPS

	Timely Treated n=206	Delayed n=98	*P-value*
Mobility on entry, n (%)			***<0.001***
Normal	146 (70.9%)	32 (32.7%)	
Uses one crutch	2 (1.0%)	1 (1.0%)	
Uses walker or two crutches	13 (6.3%)	7 (7.1%)	
Confined to wheelchair	13 (6.3%)	6 (6.1%)	
Confined to bed	32 (15.5%)	52 (53.1%)	
Urinary sphincter control			***<0.001***
Incontinent	1 (0.5%)	8 (8.2%)	
Impaired	11 (5.3%)	32 (32.7%)	
Normal	194 (94.2%)	58 (59.2%)	
Number of affected levels n (%)			*0.878*
1	99 (48.1%)	45 (45.9%)	
2	34 (16.5%)	15 (15.3%)	
3	27 (13.1%)	11 (11.2%)	
≥4	46 (22.3%)	27 (27.6%)	
VAS pain, mean (SD)	4,9 (2.4)	4.6 (2.5)	*0.285*
Tomita, mean (SD)	4.7 (2.7)	5.0 (2.9)	*0.363*
Tokuhashi, mean (SD)	9.5 (2.8)	8.0 (2.9)	***<0.001***

**Median survival > 36 months (favorable), 36 months ≥ 18 months (moderate) and < 18 months (unfavorable).*
***Karnofsky Performance Score.*

Delayed patients had to undergo more open surgical procedures, had a longer median surgery duration and more median blood loss during surgery than timely treated patients (**Table 2**). Six patients had an isolated vertebroplasty or vertebral body stent without further instrumentation, all in the timely treated group. None of the patients underwent multiple procedures during the same hospital admission due to multi-regional metastatic disease. Postoperatively, delayed patients spent more time in the hospital, had a higher risk of complications, fewer cases were able to return home and had more outspoken neurological symptoms (**Table 3**).

TABLE 2. DIFFERENCES IN SURGICAL PARAMETERS BETWEEN TIMELY TREATED AND DELAYED PATIENTS

	Timely Treated n=206	Delayed n=98	*P-value*
Surgial technique, n (%)			*<0.001*
Open surgery	97 (47.1%)	85 (86.7%)	
Percutaneous surgery	109 (52.9%)	13 (13.3%)	
Surgical approach			*<0.001*
Anterior	1 (0.5%)	0 (0.0%)	
Combined	8 (3.9%)	2 (2.0%)	
Posterior	197 (95.6%)	96 (98.0%)	
Median surgery duration, hours (IQR)	2.0 (1.0-2.0)	2.0 (2.0-3.0)	*<0.001*
Median blood loss, ml (IQR)	200 (50-500)	450 (200-800)	*<0.001*
Level of instrumentation			*<0.001*
Cervical	19 (9.2%)	1 (1.0%)	
Cervicothoracic	26 (12.6%)	10 (10.2%)	
Thoracic	78 (37.9%)	57 (58.2%)	
Thoracolumbar	34 (16.5%)	17 (17.3%)	
Lumbar	34 (16.5%)	7 (7.1%)	
Lumbosacral	5 (2.4%)	0 (0.0%)	

TABLE 3. DIFFERENCES IN POSTOPERATIVE PARAMETERS BETWEEN TIMELY TREATED AND DELAYED PATIENTS

	Timely Treated n=206	Delayed n=98	*P-value*
Median hospital time, days (IQR)	7 (5-12)	13 (7-20)	*<0.001*
Occurrence of complications, n (%)			*0.001*
Yes	54 (26.2%)	47 (48.0%)	
No	152 (73.8%)	51 (52.0%)	
Discharge to, n (%)			*<0.001*
Home	166 (82.6%)	39 (41.1%)	
Other institution	19 (9.5%)	26 (27.4%)	
Different hospital/ward	16 (8.0%)	30 (31.6%)	
Mobility at discharge, n (%)			*<0.001*
Normal	122 (60.7%)	11 (11.8%)	
Assisted	75 (37.3%)	71 (76.3%)	
Confined to bed	4 (2.0%)	11 (11.8%)	
Frankel at discharge, n (%)			*<0.001*
A	0 (0.0%)	2 (2.0%)	
B	3 (1.5%)	3 (3.1%)	
C	1 (0.5%)	17 (17.3%)	
D	26 (12.6%)	42 (42.9%)	
E	171 (83.0%)	31 (31.6%)	

Adjusted multivariate analysis was used to estimate the association between delayed treatment and five different outcome parameters, adjusted for potential confounders (i.e., pre-operative mobility score, ASA-score, tumor favorability and age). None of these remaining potential confounders showed collinearity. The analyses showed that delayed treatment was associated with an increase in duration of hospital stay (+ 2.93 days, $p<0.001$), blood loss (+ 628 ml, $p<0.001$) and surgery duration (+ 0.46 hours, $p<0.001$) independent of preoperative mobility, ASA-score, tumor prognosis and patient age. Delayed treatment was also independently associated with a lower probability to return home with an OR of 0.203 (0.110 to 0.376, $p<0.001$) and a higher risk of complications with an OR of 2.094 (1.156 to 3.795, $p<0.001$) (**Table 4**).

TABLE 4. MULTIVARIATE ANALYSES of the association between the treatment category and hospital stay, blood loss, surgery duration, the ability to return home and the occurrence of complications independent of the preoperative mobility score, ASA-score, tumor type favorability and patient age

	Multiple linear regression					
	Hospital stay* n=293		Blood loss* n=283		Surgery duration* n=294	
	Days (CI)	*P-value*	ml (CI)	*P-value*	Hours (CI)	*P-value*
Intercept	7.01 (4.33 to 11.37)	***<0.001***	566 (266 to 1207)	***<0.001***	2.25 (1.71 to 2.96)	***<0.001***
Treatment category						
Timely treated	Reference		Reference		Reference	
Delayed	2.93 (1.24 to 4.98)	***<0.001***	628 (324 to 1034)	***<0.001***	0.46 (0.19 to 0.77)	***0.001***
Mobiliy score						
Unassisted	Reference		Reference		Reference	
Assisted	1.52 (-0.29 to 3.85)	*0.105*	-109 (-253 to 102)	*0.269*	-0.03 (-0.32 to 0.29)	*0.826*
Unable	3.19 (1.23 to 5.61)	***0.001***	6 (-155 to 231)	*0.950*	0.14 (-0.13 to 0.45)	*0.328*
ASA						
1	Reference		Reference		Reference	
2	-0.78 (-2.14 to 0.96)	*0.352*	-235 (-340 to -79)	***0.006***	-0.29 (-0.55 to 0.01)	*0.054*
≥3	-0.438 (-2.01 to 1.64)	*0.649*	-268 (-372 to -121)	***0.003***	-0.40 (-0.67 to -0.08)	***0.015***
Tumor prognosis						
Favorable	Reference		Reference		Reference	
Moderate	-0.72 (-1.94 to 0.78)	*0.321*	-102 (234 to 82)	*0.242*	-0.09 (-0.34 to 0.19)	*0.504*
Unfavorable	-0.93 (-2.05 to 0.45)	*0.175*	-168 (-276 to -20)	***0.029***	-0.10 (-0.34 to 0.16)	*0.443*
Age (per year)	0.02 (-0.03 to 0.07)	*0.410*	-3 (-9 to 4)	*0.426*	0 (-0.01 to 0.01)	*0.858*

**Statistics were performed on log-transformed dependent variables due to non-normal distribution*

TABLE 4. MULTIVARIATE ANALYSES of the association between the treatment category and hospital stay, blood loss, surgery duration, the ability to return home and the occurrence of complications independent of the preoperative mobility score, ASA-score, tumor type favorability and patient age

	Binary logistic regression			
	Return home n=294		Complications n=294	
	Odds ratio	*P-value*	Odds ratio	*P-value*
Intercept	N/A	*N/A*	N/A	*N/A*
Treatment category				
Timely treated	Reference		Reference	
Delayed	0.203 (0.110 to 0.376)	***<0.001***	2.094 (1.156 to 3.795)	***0.015***
Mobiliy score				
Unassisted	Reference		Reference	
Assisted	0.683 (0.298 to 1.568)	*0.369*	2.037 (0.961 to 4.316)	*0.063*
Unable	0.285 (0.143 to 0.568)	***<0.001***	1.787 (0.921 to 3.465)	*0.086*
ASA				
1	Reference		Reference	
2	0.888 (0.320 to 2.461)	*0.819*	0.844 (0.364 to 2.144)	*0.785*
≥3	0.708 (0.240 to 2.093)	*0.533*	2.731 (1.082 to 6.895)	***0.033***
Tumor prognosis				
Favorable	Reference		Reference	
Moderate	1.529 (0.702 to 3.330)	*285*	0.716 (0.349 to 1.470)	*0.716*
Unfavorable	1.155 (0.567 to 2.355)	*0.691*	1.033 (0.532 to 2.008)	*0.923*
Age (per year)	0.970 (0.943 to 0.998)	***0.034***	1.017 (0.992 to 1.043)	*0.174*

**Statistics were performed on log-transformed dependent variables due to non-normal distribution*

Sensitivity analysis of the influence of "intermediate" patients requiring surgery after 24 hours but within 3 days after presentation showed differences in terms of surgery duration and blood loss during surgery. Omitting the "intermediate" patients from the delayed patients led to a slightly higher risk of complications (63.8% vs 48%) and a slightly lower probability of returning home (31.1% vs 41.1%). In the multivariate analyses, the association between delayed treatment and hospital stay, surgery duration and the probability of returning home showed no meaningful differences. The added effect on blood loss was higher (1623 ml vs 628 ml) and the effect on the risk for the occurrence of complications was higher (OR of 3.526 vs 2.094) after omitting the "intermediate" patients from the analyses. (**Supplementary materials, online only**).

DISCUSSION

In this study, 304 patients were included, of which 206 received timely treatment and 98 delayed treatment for symptomatic spinal metastases. The results show worse surgical and postoperative outcome for delayed patients compared to timely treated patients. Considering the two groups did not differ in demographic characteristics such as age, gender, primary tumor type and ASA-classification, the observed differences in patient outcome are presumably caused by delayed recognition of the presence and (often) relentless progression of spinal metastatic disease. Although delayed patients had much more extensive neurological deficits, the negative impact of delayed treatment remained present after correction for other potential confounding factors such as postoperative mobility scores, comorbidities, tumor histology and KPS.

In patients with advanced cancer, the spinal column is the preferred skeletal location for the formation of metastases [9]. In these patients, QoL is frequently used as an outcome parameter for the assessment of treatments. One previous study showed that emergency surgery in patients with spinal metastases was associated with lower postoperative EQ-5D scores, as well as lower survival rates [25]. Because of these lower survival rates, less postoperative QoL data are available for analysis in this patient category. This could mean that the negative effect of emergency surgery on postoperative QoL is underestimated. Therefore, to properly assess the direct effects of delayed treatment on patient outcome, direct postoperative outcome measures available for most patients, similar to those in the current study, can be used.

An important factor to take into consideration when interpreting the differences in postoperative outcome between timely treated and delayed patients is the difference in preoperative neurological status. In the timely treated patients, 84,5% scored Frankel E (no sensorimotor deficit), as opposed to 19.4% in delayed patients. A study by Lo et al. showed that surgery within 48 hours showed a trend towards better neurological recovery than after 48 hours [26]. These findings justify the need for rapid surgical intervention when patients present with neurological deficits, but further compromise the ability of health-care providers to perform a comprehensive patient work-up in the emergency setting. Several studies however show a direct correlation between neurological deficit and reduced postoperative outcome, QoL and survival [14–17,27]. Indirectly, one study also found that patients requiring decompressive surgery and fixation of the spine experienced a smaller increase in EQ-5D scores at three months postoperatively compared to patients only requiring spinal fixation [15]. More extensive, open decompressive surgical techniques are generally preferred over percutaneous techniques in the case of compression on neural structures. This is also reflected in the current population, where open decompressive surgical procedures were utilized in 47.1% of the timely treated patients as opposed to 86.7% of the delayed patients, potentially contributing to a reduction in postoperative outcome [16]. Surgery duration was significantly longer in delayed patients and median intraoperative blood loss was more than twice that compared to patients treated in a timely fashion, likely to be due to the extent of open surgical procedures in both groups [28,29]. As a result, delayed patients had a higher chance of requiring a blood transfusion compared to timely treated patients. Previous research suggested postoperative blood transfusions have a negative impact on survival rates, especially in oncological patients, independent of other factors affecting survival and this effect is directly correlated with the number of units transfused [30]. The study by Pereira et al. did not detect a similar effect specifically in patients with spinal metastases, however, as the authors readily concurred, this study was at risk for a type 2 statistical error [31]. To assess the effect of the total tumor load on the results, sub-analyses were performed for patients with four or more affected levels between timely treated and delayed patients. However, these results did not differ from the overall study for any of the outcome measures both in significance levels and effect sizes.

In this study a 48.0% complication rate was found among delayed patients, compared to a 26.2% complication rate in timely treated patients. A previous study by Dea et al. on serious adverse events (SAEs) in emergency oncological spine surgery reported a much higher complication rate of 76.2% [14]. This discrepancy can be partly explained by differences in baseline characteristics (e.g., 58.4% neurological deficits compared to 36.5% in our population) but is more likely caused by the robust, prospective design of their study specifically aimed at assessing (all) complication rates through daily rounds by a dedicated research nurse. They identified several factors contributing to the number of SAEs such as a higher patient age, lower surgeon caseload and myelopathy or radiculopathy as the presenting complaint. Timely treated patients were almost exclusively operated on by spinal surgeons dedicated to spinal

oncological procedures. In contrast, delayed patients often presented outside office hours and would undergo surgical intervention by the spinal surgeon on-call, potentially leading to differences in indications, surgical technique and/or approach. Another potential reason for more complications in delayed patients is the fact that they spend more time in the hospital, which is known to also increase the risk of complications [32].

Symptomatic spinal metastases require specialized care, mostly available in tertiary care centers. Consequently, health-care providers familiar with the management of spinal metastatic disease are often involved late in the decision making. For timely patient presentation (particularly before the onset of neurological deficits), tertiary care centers and specialized health-care providers have to rely on efficient referral patterns within the primary and secondary health-care centers in their respective catchment area. The mean time between the onset of any symptoms and the onset of neurological deficits has been noted to be as little as seven weeks [33]. Although these neurological deficits may be the first presenting symptom of cancer, for the majority of patients a history of malignancy is known and preceding symptoms indicative of pending neurological deficits such as atypical back pain aggravated by movement, radicular pain or ataxia, may have been present for some time. Few studies have previously looked into delay for spinal metastatic patients. Husband et al. described a median total delay (time from onset of complaints until treatment) of 73,5 days [34]. Levack et al. found a slightly higher median total delay of 90 days [35]. Several factors were identified placing patients at risk for delayed treatment such as initial presentation at a general practitioner or the absence of a prior cancer diagnosis. Both studies claim that in order to improve patient outcome, earlier diagnosis is required [34,35]. Our results confirm the negative consequences of delays in identification and referral of patients with neurological deficits on short-term clinical outcome. With the overall prevalence of spinal metastatic disease increasing, referral patterns for patients with spinal metastases need to be addressed as neurological damage resulting from spinal cord and cauda equina compression can be irreversible and may have great impact on the further course of the disease.

The current study has some limitations. First, the process of deciding if a patient requires treatment within or after three days may be subject to some variability. In the authors institution all spine surgeons are member of a formal "spine unit" and adhere to basic principles. Examples are: refrain from operative intervention if life expectancy is less than three months; practice shared decision making with the goal of optimizing QoL; practice expeditious intervention in case of rapid progression of neurological deficits. Furthermore, we use a common and appropriate technical language (SINS for spinal stability, KPS for general patient condition and

ASIA/Frankel classification for neurological status)18 when tasked with the care for patients with symptomatic spinal metastases. As a result, the decision process is evidence-based, while simultaneously reflecting the realistic day-to-day practice at a tertiary referral center [19]. Second, the definition of "delayed presentation" in this study is not a resultant of actual timing of the referral, but rather of patients' surgical urgency. The authors argue that this is a suitable proxy for the timing of their presentation, however ideally actual time since the onset of symptoms should be utilized. Third, some patients might have experienced so much delay that their condition has declined to a point where they are now deemed unfit for surgery. This may result in an underestimation of the negative effects of delayed presentation on outcome parameters.

CONCLUSION

In conclusion, the results from our study show that delayed referral and treatment of patients with symptomatic spinal metastases reduces short term clinical outcome. We 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 surgery in the future.

Funding: The current work was funded with an educational grant from DePuy Synthes.

SUPPLEMENTARY TABLES

SUPPLEMENTARY TABLE 1.
BASELINE CHARACTERISTICS OF PATIENTS FOR BOTH PATIENT GROUPS

	Timely Treated n=206	Delayed n=47	*P-value*
Mean age, years (SD)	61.9 (11.7)	63.3 (11.7)	*0.455*
Gender, male (%)	106 (51.5%)	30 (63.8%)	*0.307*
ASA, n (%)			***0.021***
1	36 (17.5%)	5 (10.9%)	
2	111 (53.9%)	21 (45.7%)	
3	59 (28.6%)	20 (43.5%)	
Tumour Histology, n (%)			*0.299*
Bladder	4 (1.9%)	0 (0.0%)	
Breast	42 (20.4%)	6 (12.8%)	
Cervicouterine	4 (1.9%)	0 (0.0%)	
Gastrointestinal	11 (5.3%)	5 (10.6%)	
Lung	25 (12.1%)	7 (14.9%)	
Lymphoma	7 (3.4%)	5 (10.6%)	
Melanoma	4 (1.9%)	0 (0.0%)	
Myeloma	30 (14.4%)	5 (10.6%)	
Plasmacytoma	4 (1.9%)	4 (8.5%)	
Prostate	16 (7.8%)	7 (14.9%)	
Renal	26 (12.6%)	4 (8.5%)	
Sarcoma	2 (1.0%)	0 (0.0%)	
Thyroid	1 (0.5%)	0 (0.0%)	
Other	12 (5.8%)	1 (2.1%)	
Unknown	14 (6.8%)	3 (6.4%)	
Tumour favourability, n (%)			*0.832*
Favourable	48 (24.0%)	14 (32.1%)	
Moderate	66 (33.0%)	13 (28.9%)	
Unfavourable	86 (43.0%)	18 (40.0%)	
KPS* (SD)	68.6 (14.5)	52.3 (15.9)	***<0.001***

SUPPLEMENTARY TABLE 1.
BASELINE CHARACTERISTICS OF PATIENTS FOR BOTH PATIENT GROUPS

	Timely Treated n=206	Delayed n=47	*P-value*
Frankel on entry, n (%)			***<0.001***
A	0 (0.0%)	3 (6.4%)	
B	0 (0.0%)	6 (12.8%)	
C	4 (1.9%)	17 (36.2%)	
D	28 (13.6%)	18 (38.3%)	
E	174 (84.5%)	3 (6.4%)	
Mobility on entry, n (%)			***<0.001***
Normal	146 (70.9%)	10 (21.3%)	
Uses one crutch	2 (1.0%)	0 (0.0%)	
Uses walker or two crutches	13 (6.3%)	1 (2.1%)	
Confined to wheelchair	13 (6.3%)	3 (6.4%)	
Confined to bed	32 (15.5%)	33 (70.2%)	
Urinary sphincter control			***<0.001***
Incontinent	1 (0.5%)	21 (44.7%)	
Impaired	11 (5.3%)	20 (42.6%)	
Normal	194 (94.2%)	6 (12.8%)	
Number of affected levels n (%)			*0.71*
1	99 (48.1%)	18 (38.3%)	
2	34 (16.5%)	9 (19.150	
3	27 (13.1%)	6 (12.8%)	
≥4	46 (22.3%)	14 (29.8%)	
VAS pain, mean (SD)	4,9 (2.4)	4.9 (2.4)	***0.013***
Tomita, mean (SD)	4.7 (2.7)	5.0 (3.1)	*0.569*
Tokuhashi, mean (SD)	9.5 (2.8)	7.2 (2.9)	***<0.001***

**Median survival > 36 months (favorable), 36 months ≥ 18 months (moderate) and < 18 months (unfavorable).*
***Karnofsky Performance Score.*

SUPPLEMENTARY TABLE 2.
DIFFERENCES IN SURGICAL PARAMETERS BETWEEN TIMELY TREATED AND DELAYED PATIENTS

	Timely Treated n=206	Delayed n=47	*P-value*
Surgial technique, n (%)			*<0.001*
Open surgery	97 (47.1%)	47 (100.0%)	
Percutaneous surgery	109 (52.9%)	0 (0.0%)	
Surgical approach			
Anterior	1 (0.5%)	0 (0.0%)	
Combined	8 (3.9%)	1 (2.1%)	
Posterior	197 (95.6%)	46 (97.9%)	
Median surgery duration, hours (IQR)	2.0 (1.0-2.0)	2.0 (2.0-3.0)	*<0.001*
Median blood loss, ml (IQR)	200 (50-500)	500 (300-1000)	*<0.001*
Level of instrumentation			*0.016*
Cervical	19 (9.2%)	0 (0.0%)	
Cervicothoracic	26 (12.6%)	5 (10.6%)	
Thoracic	78 (37.9%)	30 (63.8%)	
Thoracolumbar	34 (16.5%)	7 (14.9%)	
Lumbar	34 (16.5%)	2 (4.3%)	
Lumbosacral	5 (2.4%)	0 (0.0%)	

SUPPLEMENTARY TABLE 3.
DIFFERENCES IN POSTOPERATIVE PARAMETERS BETWEEN TIMELY TREATED AND DELAYED PATIENTS

	Timely Treated n=206	Delayed n=47	*P-value*
Median hospital time, days (IQR)	7 (5-12)	15 (8-22)	*<0.001*
Occurrence of complications, n (%)			*<0.001*
Yes	54 (26.2%)	3 (63.8%)	
No	152 (73.8%)	17 (36.2%)	
Discharge to, n (%)			*<0.001*
Home	166 (82.6%)	14 (31.1%)	
Other institution	19 (9.5%)	17 (37.8%)	
Different hospital/ward	16 (8.0%)	14 (31.1%)	
Mobility at discharge, n (%)			*<0.001*
Normal	122 (60.7%)	3 (6.7%)	
Assisted	75 (37.3%)	34 (75.6%)	
Confined to bed	4 (2.0%)	8 (17.8%)	
Frankel at discharge, n (%)			*<0.001*
A	0 (0.0%)	1 (2.1%)	
B	3 (1.5%)	3 (6.4%)	
C	1 (0.5%)	12 (25.5%)	
D	26 (12.6%)	21 (44.7%)	
E	171 (83.0%)	9 (19.1%)	

SUPPLEMENTARY TABLE 4.
MULTIVARIATE ANALYSES of the association between the tretment category and hospital stay, blood loss, surgery duration, the ability to return home and the occurrence of complications independent of the preoperative mobility score, ASA-score, tumor type favorability and patient age

	Multiple linear regression					
	Hospital stay* n=244		Blood loss* n=237		Surgery duration* n=244	
	Days (CI)	*P-value*	ml (CI)	*P-value*	Hours (CI)	*P-value*
Intercept	6.34	***<0.001***	766	***<0.001***	2.23	***<0.001***
Treatment category						
Timely treated	Reference		Reference		Reference	
Delayed	2.71	***0.009***	1623	***<0.001***	0.68	***0.001***
Mobiliy score						
Unassisted	Reference		Reference		Reference	
Assisted	1.75	*0.092*	-135	*0.884*	0.04	*0.837*
Unable	3.43	***0.001***	-24	*0.329*	0.05	*0.774*
ASA						
1	Reference		Reference		Reference	
2	-0.66	*0.415*	-255	***0.046***	-0.27	*0.090*
≥3	-0.45	*0.629*	-315	***0.021***	-0.39	***0.028***
Tumor prognosis						
Favourable	Reference		Reference		Reference	
Moderate	-0.37	*0.623*	-167	*0.196*	-0.12	*0.421*
Unfavourable	-0.87	*0.215*	-172	*0.152*	-0.11	*0.448*
Age (per year)	0.02	*0.316*	-9	*0.070*	0	*0.946*

**Statistics were performed on log-transformed dependent variables due to non-normal distribution*

SUPPLEMENTARY TABLE 4.
MULTIVARIATE ANALYSES of the association between the tretment category and hospital stay, blood loss, surgery duration, the ability to return home and the occurrence of complications independent of the preoperative mobility score, ASA-score, tumor type favorability and patient age

	Binary logistic regression			
	Return home n=244		Complications *n=244*	
	Odds ratio	*P-value*	Odds ratio	*P-value*
Intercept	N/A	*N/A*	N/A	*N/A*
Treatment category				
Timely treated	Reference		Reference	
Delayed	0.177	***<0.001***	3.526	***0.002***
Mobiliy score				
Unassisted	Reference		Reference	
Assisted	0.442	*0.094*	2.023	*0.111*
Unable	0.223	***<0.001***	1.870	*0.112*
ASA				
1	Reference		Reference	
2	0.858	*0.779*	1.046	*0.924*
≥3	0.705	*0.553*	2.583	*0.058*
Tumor prognosis				
Favourable	Reference		Reference	
Moderate	1.876	*0.171*	0.688	*0.372*
Unfavourable	1.823	*0.151*	1.116	*0.771*
Age (per year)	0.979	*0.182*	1.011	*0.409*

**Statistics were performed on log-transformed dependent variables due to non-normal distribution*

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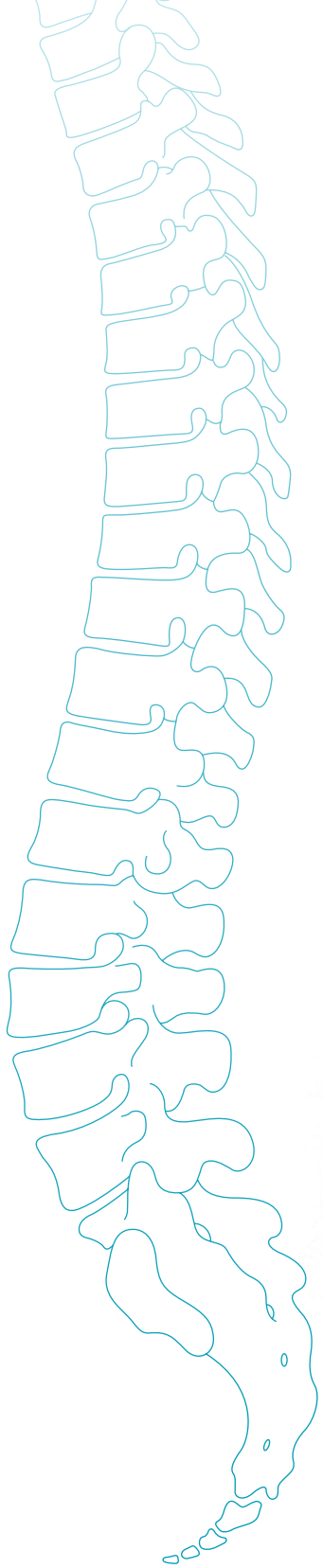

CHAPTER 3

The Importance of Timely Treatment for Quality of Life and Survival in Patients with Symptomatic Spinal Metastases.

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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, 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 three 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 three- and six-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 three days. 'Timely treatment' was defined as being eligible for planned intervention more than three 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 three and six months on outcome parameters at six months, we compared KPS and EQ-5D scores at three months between patients available for analysis at six months and those lost to follow-up between three and six months. Kaplan-Meier curves were created to analyze one-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 three- or six-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**.

TABLE 1. DEMOGRAPHICS FOR PATIENTS IN BOTH TREATMENT GROUPS

	Timely Treated n=147	Delayed n=55	*P-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, n (%)			*0.402*
1	32 (21.8%)	6 (10.9%)	
2	84 (57.1%)	37 (67.3%)	
3	31 (21.1%)	12 (21.8%)	
Tumour Histology, n (%)			*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%)	
Tumour favourability, n (%)			*0.830*
Favourable	42 (29.0%)	20 (36.4%)	
Moderate	55 (37.9%)	21 (38.2%)	
Unfavourable	48 (33.1%)	14 (25.5%)	
Chemotherapy past year, n (%)			***0.010***
Yes	14 (9.7%)	3 (5.6%)	
No	130 (90.3%)	51 (94.4%)	
Radiotherapy past year, n (%)			*0.754*
Yes	23 (15.9%)	7 (13.2%)	
No	122 (84.1%)	46 (86.8%)	

TABLE 1. DEMOGRAPHICS FOR PATIENTS IN BOTH TREATMENT GROUPS

	Timely Treated n=147	Delayed n=55	*P-value*
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, n (%)			***<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, n (%)			***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, n (%)			*0.761*
Yes	42 (28.6%)	13 (23.6%)	
No	105 (71.4%)	42 (76.4%)	
Number of affected levels, n (%)			*0.337*
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*

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 three months (n=125) and 0.78 (0.57-0.89) at six months (n=51). For delayed treatment patients the median (IQR) EQ-5D was 0.24 (0.12-0.33) at baseline (n=50), 0.48 (0.26-0.74) at three months (n=36) and 0.73 (0.37-0.85) at six months (n=20). The difference between timely treated and delayed treated patients was statistically significant at baseline and three months.

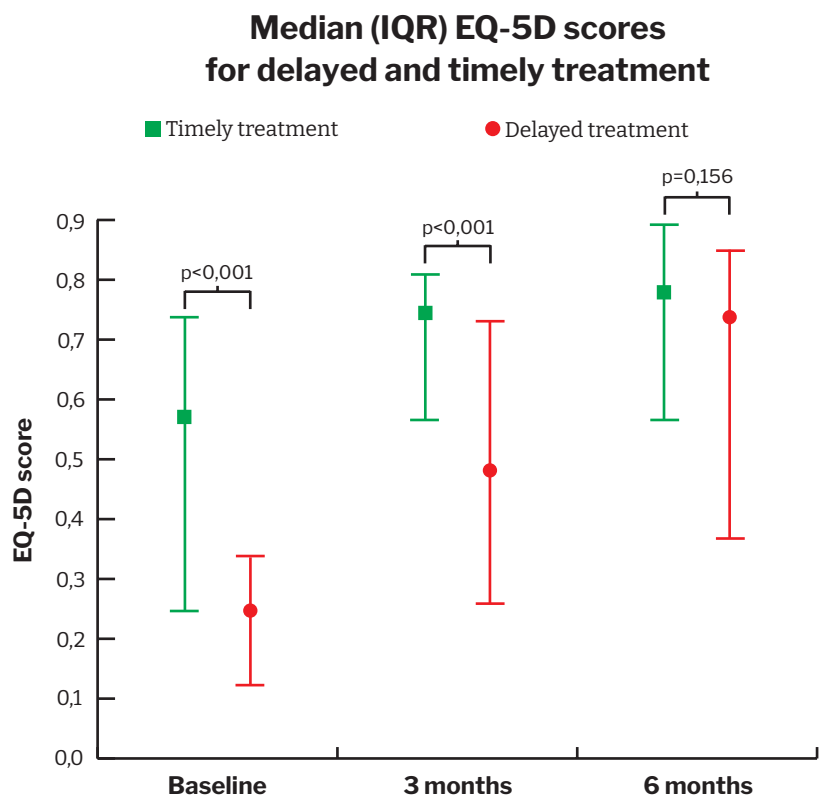

FIGURE 1. Medan (IQR) EQ-5D scores for timely treated patients and delayed patients at baseline, 3 months and 6 months follow-up.

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**).

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

	Without interaction term	
	EQ-5D *n=166*	
	Utility score (CI)	*P-value*
Intercept	0.88 (0.65 to 1.00)*	***<0.001***
Follow-up moment		
3 months	Reference	
6 months	0.05 (0.00 to 0.11)	*0.065*
Pre-operative EQ-5D	0.19 (0.05 to 0.33)	***0.008***
Treatment category		
Timely treated	Reference	
Delayed	-0.08 (-0.18 to 0.01)	*0.078*
Mobility score		
Unassisted	Reference	
Assisted	-0.03 (-0.16 to 0.09)	*0.615*
Unable	-0.07 (-0.18 to 0.05)	*0.260*
Tumor prognosis		
Favorable	Reference	
Moderate	-0.03 (-0.12 to 0.06)	*0.646*
Unfavorable	-0.12 (-0.21 to -0,03)	***0.013***
Age (per year)	0.00 (-0.01 to 0.00)	***0.013***

**Rounded down to clinically appropriate values*

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

With interaction term		
	EQ-5D *n=166*	
	Utility score (CI)	*P-value*
Intercept	0.9 (0.66 to 1.00)*	***<0.001***
Follow-up moment		
3 months	Reference	
6 months	0.01 (-0.05 to 0.08)	*0.709*
Pre-operative EQ-5D	0.19 (0.05 to 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 to 0.10)	*0.658*
Unable	-0.06 (-0.18 to 0.05)	*0.274*
Tumor prognosis		
Favorable	Reference	
Moderate	-0.04 (-0.13 to 0.05)	*0.418*
Unfavorable	-0.13 (-0.22 to -0,03)	***0.009***
Age (per year)	0.00 (-0.01 to 0.00)	***0.012***
Interaction term		
6 months + delayed treatment	0.15 (0.03 to 0.28)	***0.016***

**Rounded down to clinically appropriate values*

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 three months (n=135) and 80 (70-90) at six months (n=53). For delayed treatment patients the median (SD) KPS was 60 (50-70) at baseline (n=55), 70 (60-70) at three months (n=49) and 70 (60-80) at six months (n=27). The difference between timely treated and delayed treatment patients was statistically significant for all three timepoints.

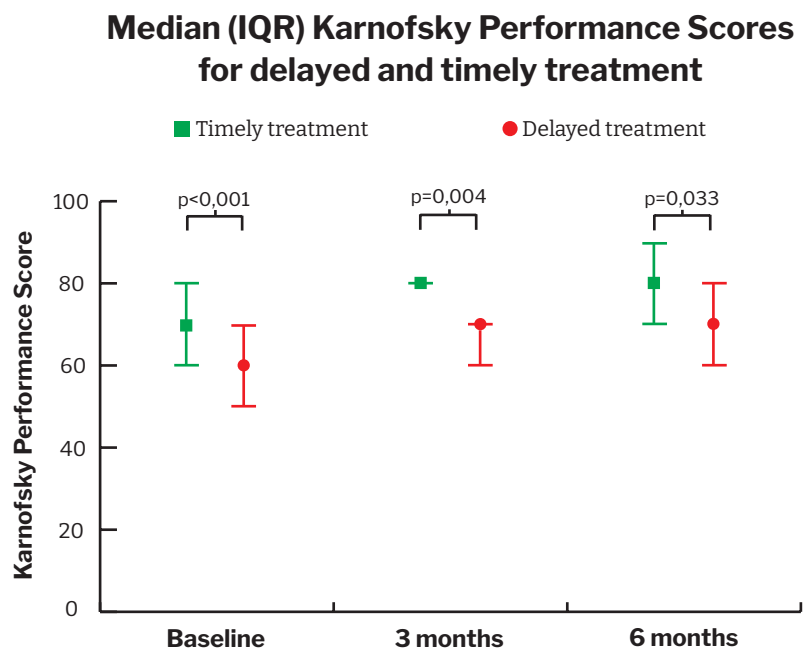

FIGURE 2. Median (IQR) KPS scores for timely treated patients and delayed patients at baseline, 3 months and 6 months follow-up.

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 2**). Sensitivity analyses showed no significant differences in KPS and EQ-5D scores at three months between patients available for analysis at six months and those lost to follow-up or deceased.

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

Without interaction term

	KPS *n=192*	
	Score (CI)	***P-value***
Intercept	75.7 (60.1 to 89.3)	***<0.001***
Follow-up moment		
3 months	Reference	
6 months	4.6 (2.3 to 6.9)	***<0.001***
Pre-operative KPS	0.2 (0.0 to 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 to 2.6)	*0.318*
Unable	-2.1 (-7.2 to 3.0)	*0.412*
Tumor prognosis		
Favorable	Reference	
Moderate	0.3 (-3.2 to 3.9)	*0.851*
Unfavorable	-2.6 (-6.4 to 1.1)	*0.168*
Age (per year)	-0.2 (-0.3 to -0.0)	***0.012***

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

With interaction term

	KPS *n=192*	
	Score (CI)	***P-value***
Intercept	74.7 (60.1 to 89.3)	***<0.001***
Follow-up moment		
3 months	Reference	
6 months	3.3 (0.6 to 6.0)	***0.017***
Pre-operative KPS	0.2 (0.0 to 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 to 2.7)	*0.345*
Unable	-2.2 (-7.3 to 3.0)	*0.405*
Tumor prognosis		
Favorable	Reference	
Moderate	0.2 (-3.4 to 3.8)	*0.917*
Unfavorable	-2.9 (-6.7 to 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 to 8.6)	*0.113*

Out of all patients, 44 (13.9%) died within three months, and 119 (37.5%) within one year. One-year survival was 70.1% in the timely treated group vs 50.9% in the delayed treatment group (p=0.001, **Figure 3**).

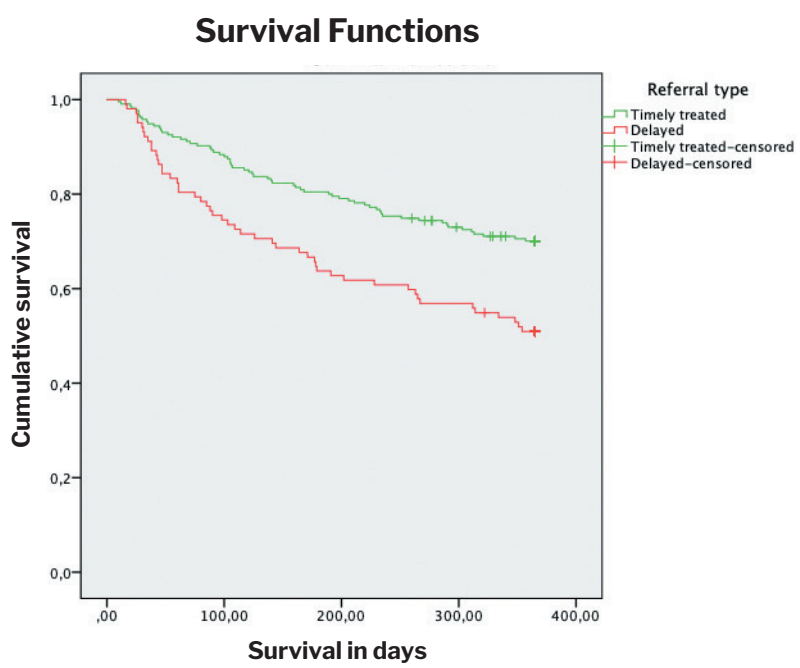

FIGURE 3. Survival curves for timely treated (n=215) and delayed patients (n=102) patients. One-year survival was 70.1% for timely treated patients vs 50.9% for delayed patients (log rank test: p = 0.001).

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**).

TABLE 4. COX PROPORTIONAL HAZARDS MODEL INVESTIGATING FACTORS ASSOCIATED WITH ONE-YEAR MORTALITY

	Hazard Ratio (CI)	*P-value*
Treatment category		
Timely treated	Reference	
Delayed	0.65 (0.43 to 0.99)	**0.043**
Mobiliy score		
Unassisted	Reference	
Assisted	0.45 (0.28 to 0.70)	**<0.001**
Unable	1.00 (0.59 to 1.72)	*0.975*
Tumor prognosis		
Favorable	Reference	
Moderate	0.17 (0.09 to 0.31)	***<0.001***
Unfavorable	0.29 (0.18 to 0.47)	***<0.001***
Age (per year)	1.00 (0.98 to 1.02)	*0.842*

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 three- and six-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 three months, but not at six months. This is furthermore supported by a study by de Ruiter et al. where patients requiring either posterior stabilization without decompression or a corpectomy did not show an increase in EQ-5D scores after three months. In contrast, a third group of patients requiring both posterior decompression and stabilization showed a similar increase between their baseline and three-month scores, but also a slight increase between three and six month scores [21]. 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 one-year survival of 70.1% compared with a one-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 one-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 effect 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, 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 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 three- and six-months follow-up points, partially caused by loss to follow-up and partially by mortality. Sensitivity analyses comparing KPS and EQ-5D at three months between patients with and without data available at six months showed no significant differences, therefore an effect of bias due to of loss to follow-up on our results is likely limited.

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.

DECLARATIONS

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Conflicts of interest: None

Availability of data and material: Not applicable

Code availability: Not applicable

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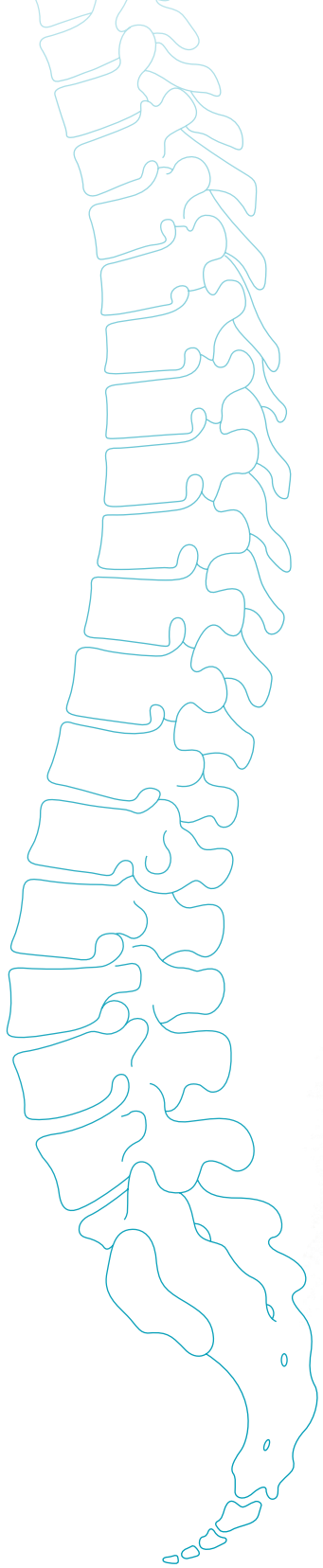

CHAPTER 4

Costs Associated with Timely and Delayed Surgical Treatment of Spinal Metastases.

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ABSTRACT

STUDY DESIGN

Retrospective cohort study.

OBJECTIVES

Symptoms caused by spinal metastases are often difficult to distinguish from symptoms caused by non-malignant spinal disease, complicating timely diagnosis, referral and treatment. The ensuing delays may promote the risk of neurological deficits or severe mechanical instability and consequent emergency surgery, leading to poorer prognosis. Presumably, treatment delay may subsequently lead to more health-care consumption and therefore increased average costs of treatment.

METHODS

All patients surgically treated for spinal metastases were included in the current study. Based on the presence of alarming symptoms and urgency of the required intervention, patients were categorized as having received timely or delayed treatment. Pre-surgical, in-hospital, aftercare and total costs were analyzed and compared between the two groups.

RESULTS

In total, 299 patients were included, of which 205 underwent timely and 94 delayed treatment. There was no significant difference in pre-surigcal costs (€3.229,13 in the timely treated group vs. €2.528,70 in the delayed treatment group, p=0,849). The in-hospital costs (€16.738,49 vs. €13.108,81, p<0,001) and the aftercare costs (€13.950,37 vs. 3.981,93, p<0,001) were significantly higher for delayed treatment vs. timely treatment, respectively. The total costs were €33.741,71 for delayed treatment and €20.318,52 for timely treatment (p<0,001).

CONCLUSIONS

The total costs for timely treated patients with spinal metastases are significantly lower compared with patients receiving delayed treatment. Investing in the optimization of referral patterns may therefore reduce the overall pretreatment delay and subsequently increase patient outcome, leading to better clinical outcomes at lower costs.

INTRODUCTION

Spinal metastases occur in approximately 20% of all oncological patients [1,2]. Due to an increase in overall cancer survival rates, this number is expected to rise considerably over the next few decades [3,4]. Because symptoms caused by spinal metastases are commonly non-specific, patients with spinal metastases are at-risk for delayed diagnosis, referral and treatment [5–7]. Problematically, untreated spinal metastases can eventually cause mechanical instability of the spine and/or neurological deficits due to compression of neural structures, requiring emergency surgery [8–13]. It is well studied that emergency surgery leads to considerably worse patient outcome compared with timely interventions [14,15].

The optimization of referral patterns for patients with spinal metastases may reduce overall delay, preventing the negative effects associated with delayed treatment. A subsequent potential cost increase of more extensive diagnostics and referrals may, however, discourage health-care providers and insurance companies in pursuing this practice. Nonetheless, a potential decrease in clinical and aftercare costs is rarely considered and may outweigh the increase in upfront costs. Until now, no study has investigated the difference in costs between patients undergoing timely and delayed treatment for symptomatic spinal metastases.

The purpose of this study was to assess the difference in costs between timely and delayed surgical treatment for symptomatic spinal metastases. It was hypothesized that delayed treatment is associated with higher costs than timely treatment.

METHODS

STUDY DESIGN

The ethics review board (METC Utrecht, protocol no. 18-841-C) approved a waiver of informed consent for this observational, retrospective cohort study. Patient and treatment data has been prospectively collected for all patients referred to a single tertiary spine center for surgical treatment of radiographic or histologically proven symptomatic spinal metastases between March 2009 and January 2019. Age, sex, primary tumor type, EQ-5D-5L scores, Karnofsky Performance Scores (KPS), Visual Analog Scale (VAS) scores for pain, neurological status and date of death were extracted from medical records.

Patients were categorized into ‘timely’ or ‘delayed’ treatment. Delayed treatment was defined as requiring surgical treatment within three days, either due to (progressive) neuro-

logical deficits and/or gross mechanical instability. It indicates limited time during work-up, potential surgery during after-hours and preclusion of elective intervention. Timely treatment was defined as the ability to undergo elective surgery more than three days after initial presentation. It suggests sufficient time left for work-up until planned treatment. The three-day cutoff was chosen in accordance with the protocol used by the Global Spine Tumor Study Group [16].

All treating spine surgeons adhered to generally accepted principles for surgical treatment of patients with spinal metastases, combining common scoring systems (currently NOMS: ASIA/Frankel classification for neurological status combined with Bilsky score for degree of epidural compression; Bollen classification for prognosis; SINS for spinal stability and KPS for general patient condition) [17–19]. Furthermore, a uniform treatment strategy was achieved by a weekly plenary multidisciplinary 'spine meeting'.

The referral chain for each individual patient was analyzed using medical records and all relevant correspondence with other health-care providers. In the Netherlands, all health-care providers send a summary of consultation to the patient's general practitioner. Therefore, the medical record possessed by the general practitioner can be used for, near complete, reconstruction of the timeline of referral, diagnosis and treatment.

Health-care costs were calculated in Euros. Costs were analyzed separately for three different stages: Pre-surgical costs (from the first medical consultation for spinal metastases related symptoms until admission to our spine unit), in-hospital costs (from admission to our spine unit until discharge) and initial aftercare costs (from discharge until three months postoperatively).

PRE-SURGICAL COSTS

The pre-surgical costs consisted of outpatient care, general practitioner visits, diagnostics and previous admission days (related to metastatic spinal disease) at a different ward or hospital. Because only the involvement of a health-care provider (outpatient clinic or general practitioner) was available, and not the number of visits, one visit per health-care provider involved was assumed. The national average prices for outpatient visits, diagnostics and admission days were used [20]. For SPECT-scans and conventional spinal radiographs, no nationwide average reference costs were available. Therefore, internal prices of our institution were used (**Table 1**). Costs for one admission day were multiplied by the LOS (in days) for each individual patient.

TABLE 1. PRICES USED FOR COST-ANALYSIS

General		In-hospital costs	
Admission day		Operating Room*	
Peripheral	€ 443,00	Per session	€ 295,35
Academic	€ 642,00	Per hour	€ 266,45
ICU	€ 1.186,00	Hourly wage surgeon	
Pre-surgical costs		Academic	€ 113,00
Diagnostics		Blood Products	
MRI	€ 444,00	Packed cells	€ 216,00
CT	€ 285,00	Platelets	€ 522,00
SPECT*	€ 512,00	Plasma	€ 186,00
X-Ray*	€ 16,00	Instrumentation	
Outpatient visit		Open Thoracolumbar Screw	€ 401,11
Peripheral	€ 80,00	Open Thoracolumbar Rod	€ 123,24
Academic	€ 163,00	Open Thoracolumbar Nut	€ 66,45
General practitioner	€ 33,00	Cervical Screw	€ 416,38
		Cervical Rod	€ 123,24
		Cervical Locking Screw	€ 48,03
		Percutaneous Screw	€ 534,86
		Percutaneous Rod	€ 311,94
		Percutaneous Set Screw	€ 93,40
		Vertebral Augmentation Stent	€ 934,39
		Vertebral Augmentation Cement	€ 486,34
		Vertebral Augmentation Cement Syringe	€ 294,83
		Vertebral Augmentation Inflator	€ 117,43
		Vertebral Augmentation Acces Kit	€ 261,14
		Follow-up costs	
		Clinical rehabilitation per day**	€ 821,43
		Geriatric rehabilitation per day***	€ 348,22
		Nursing home per day	€ 18,00
		Home care (per hour)	€ 73,00
		Geriatric rehabilitation per day***	€ 348,22
		Nursing home per day	€ 18,00
		Home care (per hour)	€ 73,00

**Internal prices (2012-2018)*
*** Price in local rehabilitation center*
**** Price in local geriatric rehailitation center*

IN-HOSPITAL COSTS

The in-hospital costs consisted of surgical and hospital admission costs. To calculate the surgical costs, the following data were extracted from the patients' medical records; the implants used, time in operating room (OR) and surgeon operating time. Nationwide average prices were available for the surgeon's salary. For the costs associated with the surgical implants and the OR utilization (including associated costs such as OR staff salary, logistics, cleaning etc..), internal prices were used. To calculate the hospital admission costs, the number of admission days and use of blood products were extracted from medical records and nationwide average prices were used (**Table 1**) [21].

AFTERCARE COSTS

After discharge, patients went to either a (geriatric) rehabilitation clinic; a nursing home; a different hospital; a different ward in the same hospital; or their own home with or without homecare assistance. Nationwide average prices for stay in a nursing home (per day), homecare (per hour) and a hospital admission day were used (**Table 1**). In the Netherlands, a stay in a nursing home generally means limited perspective on returning home. Therefore, the daily price was multiplied by the days left until the three months follow-up.

For a rehabilitation clinic, the average daily price was calculated by using the average reimbursement price for a stay of 6 weeks with 99-223 treatment hours, divided by 42. For geriatric rehabilitation, the average daily price was calculated using the reimbursement price of a standard stay of 29 to 56 days with more than 59 treatment hours, divided by 42. In case the duration of (geriatric) rehabilitation could not be extracted from the medical record, the standard rehabilitation period for patients with metastatic spinal disease of 6 weeks was assumed.

After (geriatric) rehabilitation, data about homecare assistance was extracted from medical records up to three months postoperatively. Data on re-admissions, including reoperations, were extracted from patients' medical records up to three months postoperatively.

STATISTICAL ANALYSIS

For continuous data, means and standard deviations (SD) were used in case of normally distributed data. Medians and interquartile range (IQR) were calculated in case of non-normally distributed data. For categorical data frequencies were used. In case of normally distributed data, unpaired T-tests were used to compare continuous parameters and Chi-squared tests to compare categorical parameters. Normality was assessed visually using Q-Q plots and in the case of non-normal distribution, the data was log-transformed for statistical analysis. All analyses were performed using IBM SPSS Statistics for Macintosh, Version 24.0 (Armonk, NY: IBM Corp).

RESULTS

In total, 299 patients were included of which 205 underwent timely treatment and 94 delayed treatment. No significant differences were found in terms of patient age, sex, tumor histology, VAS-pain scores and median survival in months. As expected, timely patients had higher baseline EQ-5D-5L and KPS scores and a lower percentage of neurological deficits, compared with delayed patients (**Table 2**).

TABLE 2. PATIENT CHARACTERISTICS FOR PATIENTS IN BOTH SURGERY GROUPS

	Timely Treatment n=205	**Delayed Treatment** n=94	***P-value***
Mean age, years (SD)	61.8 (118)	62.8 (11.0)	*0.482*
Gender, male (%)	106 (51,7%)	99 (48,3%)	*0.452*
Tumour Histology, n (%)			*0.130*
Bladder	3 (1.5%)	1 (1.1%)	
Breast	42 (21,5%)	15 (16.0%)	
Cervicouterine	4 (2.0%)	1 (1.1%)	
Gastrointestinal	10 (5.0%)	11 (11.7%)	
Lung	25 (12.5%)	16 (17.0%)	
Hematological tumors	41 (20.5%)	26 (27.7%)	
Melanoma	4 (2.0%)	0 (0.0%)	
Prostate	17 (8.3%)	13 (13.9%)	
Renal	27 (13.2%)	6 (6.4%)	
Other	14 (6.8%)	1 (1.1%)	
Unknown	14 (6.8%)	2 (2.1%)	
EQ5D, mean (SD)	0.43 (0.32)	0.25 (0.25)	***<0.001***
KPS, median* (IQR)	70 (60-80)	50 (50-70)	***<0.001***
VAS pain, mean (SD)	5.0 (2.4)	4.6 (2.6)	*0.261*
Frankel on entry, n (%)			***<0.001***
A	0 (0.0%)	2 (2.1%)	
B	0 (0.0%)	7 (7.4%)	
C	3 (1.5%)	24 (25.5%)	
D	33 (16.1%)	43 (45.7%)	
E	169 (82.4%)	18 (19.1%)	
Median survival, months (IQR)	23,7 (6,8-70,9)	14,2 (3,0-65,6)	*0.145*

**Karnofsky Performance Score*

The results of the cost-analyses are listed in **Table 3**. The exact duration of could not be found in 19% of patients requiring clinical rehabilitation and 43% of patients requiring geriatric rehabilitation. The mean total costs for timely treated patients were significantly lower compared with patients undergoing delayed treatment (€20.318,52 vs. €33.741,71, p<0,001). Pre-surgical costs were higher in the timely treated group (€3.229,13 vs. €2.528,70, p=0,849).

TABLE 3. MEAN TOTAL, PRE-SURGICAL, IN-HOSPITAL AND AFTERCARE COSTS FOR TIMELY AND DELAYED TREATMENT PATIENTS

	Timely Treatment (€)		Delayed Treatment (€)		*P-value*
	n=205	SD	n=94	SD	
Total costs	**€ 20.318,52**	**€ 12.773,54**	**€ 33.741,71**	**€ 20.874,34**	**<0.001**
Pre-surgical costs	€ 3.229,13	€ 4.019,63	€ 2.528,70	€ 2.246,30	0.849
Outpatient visits	*€ 189,29*	*€ 97,90*	*€ 194,37*	*€ 103,49*	*0,564*
Diagnostics	*€ 884,97*	*€ 361,48*	*€ 841,69*	*€ 369,75*	*0,341*
X-rays	€ 16,47	€ 11,95	€ 12,77	€ 12,54	***0.015***
CT's	€ 304,46	€ 172,86	€ 312,29	€ 167,54	*0.714*
MRI's	€ 426,67	€ 214,67	€ 467,62	€ 219,52	*0.129*
SPECT	€ 137,37	€ 238,44	€ 49,02	€ 151,46	***0.001***
Preclinical admission days	*€ 2.154,87*	*€ 4.006,02*	*€ 1.492,64*	*€ 2.275,90*	***<0.001***
In-hospital costs	€ 13.108,81	€ 7.441,31	€ 16.738,49	€ 9.699,15	***<0.001***
Admission days	€ 6.514,88	€ 6.656,79	€ 10.420,15	€ 8.223,88	***<0.001***
ICU stay	€ 104,14	€ 623,71	€ 37,85	€ 209,59	*0,678*
OR costs	€ 1.167,98	€ 334,67	€ 1.281,22	€ 363,35	***0.002***
Surgeon	€ 296,17	€ 124,99	€ 363,08	€ 283,22	***0.003***
Implants	€ 4.842,26	€ 2.110,03	€ 4.161,35	€ 2.131,34	***0,010***
Blood products	€ 68,05	€ 487,26	€ 31,85	€ 308,81	*0,509*
Reoperations	€ 30,98	€ 184,69	€ 136,43	€ 539,46	***0,013***
Admission days other ward	€ 56,37	€ 547,60	€ 109,27	€ 774,29	*0,499*
Aftecare costs	€ 3.981,93	€ 6.896,11	€ 13.950,37	€ 17.803,82	***<0.001***
Admission days other hospital	€ 179,36	€ 981,50	€ 928,41	€ 2.057,51	***<0.001***
Readmissions	€ 563,52	€ 1.953,40	€ 983,49	€ 3.558,60	*0,314*
Reoperations readmission	€ 57,97	€ 245,20	€ 73,52	€ 303,84	*0,638*
Blood products readmission	€ -	€ -	€ 13,78	€ 99,20	***0,036***
Clinical rehabilitation	€ 1.121,37	€ 5.764,67	€ 9.240,62	€ 18.139,65	***<0.001***
Geriatric rehabilitation	€ 441,65	€ 2.604,04	€ 1.411,40	€ 4.224,68	***0,003***
Nursing home	€ 576,94	€ 2.517,59	€ 489,70	€ 2.200,91	*0,773*
Home care	€ 1.041,13	€ 1.858,86	€ 809,44	€ 1.873,96	*0,319*

The mean outpatient costs for conventional radiograph, SPECT-scans and costs associated with pre-surgical admission days in a different hospital were significantly higher in timely treatment. The in-hospital costs were significantly lower in the timely treated group (€13.108,81 vs. €16.738,49, p<0,001). The in-hospital cost differences were mainly caused by differences in the costs of admission days. Timely treated patients averaged €6.514,88 for 10 days LOS vs. €10.420,15 for 16 days LOS in patients undergoing delayed treatment (p<0,001). In contrast, the implants used in timely treated patients were significantly more expensive compared with the implants used in delayed treated patients (€4.842,26 vs. €4.161,35, p=0,010). The aftercare costs were significantly lower in timely treated patients (€3.981,93 vs. €13.950,37, p<0,001). The largest difference was found in the clinical rehabilitation, which averaged €1.121,37 in timely treated patients and €9.240,62 in delayed treated patients (p<0,001).

DISCUSSION

This cost-analysis study is the first to compare costs for delayed versus timely surgical treatment of patients with symptomatic spinal metastases. The current study shows that costs associated with timely treatment are significantly lower compared with costs of delayed treatment, confirming our hypothesis of the multiple benefits of timely treatment in patients with symptomatic spinal metastases. The results from this study can serve as encouragement for investing in referral patterns, thereby increasing patient outcome without necessarily increasing the associated costs.

Costs for emergency treatment compared with elective treatment has been previously studied outside the field of spinal surgery [22,23]. In a study by Haider et al., the mean costs for emergency surgery in several different procedures (i.e., abdominal aortic aneurysm repair and coronary artery bypass graft) were on average € 6.756,71 higher than costs for the same elective procedures (using US Dollars to Euro exchange rate of € 0.91508 in June 2015) [22]. Similarly, Jestin et al. showed a relative cost increase of 50% for patients undergoing emergency surgery compared with elective surgery for colonic cancer [23]. In line with our findings, the biggest contributor to the cost difference observed by Jestin et al. was increased LOS.

Several previous studies investigating costs specifically in metastatic spinal disease show that overall, the in-hospital costs are the biggest contributor to total costs [24,25]. Likewise, in the current study the in-hospital costs account for approximately half the total costs (54% in timely treatment, 45% in delayed treatment). A previous study by Turner et al., investigating costs associated with surgical treatment for spinal metastases, has shown that the mean in-hospital costs for treatment in patients with confirmed symptomatic spinal metasta-

ses was €23.669,39 (using UK pounds to Euro exchange rate of € 1.3866 in June 2015) [25]. In our study, the mean in-hospital costs for all patients were considerably lower at €14.249,91. The biggest difference between the current study and the study by Turner et al. can be found in OR-costs (€1.203,58 vs. €5.804,85). Furthermore, Turner et al. investigated several factors not included in the current study, such as imaging during admission, pathology and pharmacy costs. However, the authors of this study assumed that such factors would not be unequally distributed between timely and delayed treatment and therefore would not have changed the conclusions of the current study.

The present study is the first to compare total costs of delayed versus timely treatment in patients requiring surgical treatment for spinal metastases. The results clearly show that treatment delay of patients with spinal metastases leads to considerably higher costs. In accordance with previous studies reporting on unfavorable surgical outcomes and lower Quality of Life (QOL), functional status and survival, the need to prevent delayed surgical treatment is further emphasized [14,15,26,27]. By investing in a catchment area's referral chain, for instance by introducing a 'hotline' or a multidisciplinary treatment system, the proportion of patients undergoing delayed treatment may decrease, thereby reducing the in-hospital and aftercare costs [28,29]. In the current study, the pre-clinical costs were higher (albeit non-significant) for timely treated patients, strengthening the idea that a relatively limited investment at the beginning of the referral chain will lead to considerably lower in-hospital and aftercare costs. Similarly, using more advanced surgical techniques such as percutaneous pedicle screw fixation may lead to higher initial costs, as can be seen in **Table 3**. Nonetheless, the subsequent favorable outcomes, such as decreased risk of complications, reduced LOS and a better overall patient convalescence, will reduce costs later on substantially [30]. Finally, delayed treatment is also associated with lower pre-operative EQ-5D and KPS scores, which persist after surgery [15]. If costs were to be viewed in light of the associated increase in QOL (i.e., costs per Quality Adjusted Life Year (QALY)), the combination of better QOL and lower costs would reasonably yield much lower costs per QALY than delayed treatment. In other words, relatively limited (financial) investments, used to optimize the referral patterns within a spine center's catchment area, may considerably reduce the overall pretreatment delay and increase patient outcome, leading to better clinical outcomes at lower costs.

The current study has several limitations. Firstly, due to the retrospective nature, not all aspects of treatment could be considered for the current study. For example, extra costs for the treatment of complications were not included. As increased LOS is associated with a higher complication rate, the associated costs would likely have predominantly emerged from the delayed treated group [31]. Extra costs for paramedic treatments, such as physical therapy, ergotherapy or dieticians, were not considered but expected to be equally present in both treatment groups as they are included in the treatment protocol. Radiotherapeutic treatment, which is commonly provided for most patients within our spine center, was not included in the current analyses. Because delayed treated patients generally have an inferior functional status and lower life expectancy, it may be hypothesized that the type of radiotherapeutic treatment after delayed treatment is generally less complex and therefore less expensive. In some cases, assumptions were required to estimate actual costs. For instance, only the number of involved caregivers was known and a single contact-moment per caregiver was assumed. Moreover, the duration of (geriatric) rehabilitation was not always available and, in some cases, the standard duration of 6 weeks had to be assumed. Finally, aftercare was only assessed up to three months postoperatively. Timely treatment, with higher chances of good outcome, may subsequently lead to a longer life-expectancy [32]. Costs and contributions of these patients for society in the long-term were not considered in the current study. Presumably, the societal costs incurred after this three-month period are higher for delayed treatment, but the duration of survival and its impact on societal costs may be higher in timely treatment.

A strength of the current stud is that the costs were calculated manually by separately assessing all aspects of care rather than using invoiced prices. Therefore, the data in the current study is presumably more accurate than when using reimbursement tariffs. Moreover, this means the data can be applied in different countries when costs are adjusted for local tariffs.

In conclusion, costs are significantly lower in timely treatment compared to delayed treatment for patients with spinal metastases. These findings emphasize the importance of efficient referral patterns and rapid diagnosis and treatment for patients with spinal metastases. Investing in the pre-surgical trajectory, ensuring timely referral, diagnosis and treatment, may result in better outcome at lower overall costs for treatment of spinal metastases. Further research is necessary to determine how referral patterns can be improved, (e.g., investing in early imaging in patients with back pain and a history of malignancy, setting up a multidisciplinary outpatient clinic etc.). In this way, outcome for patients with metastatic spinal disease can be improved while decreasing the associated costs.

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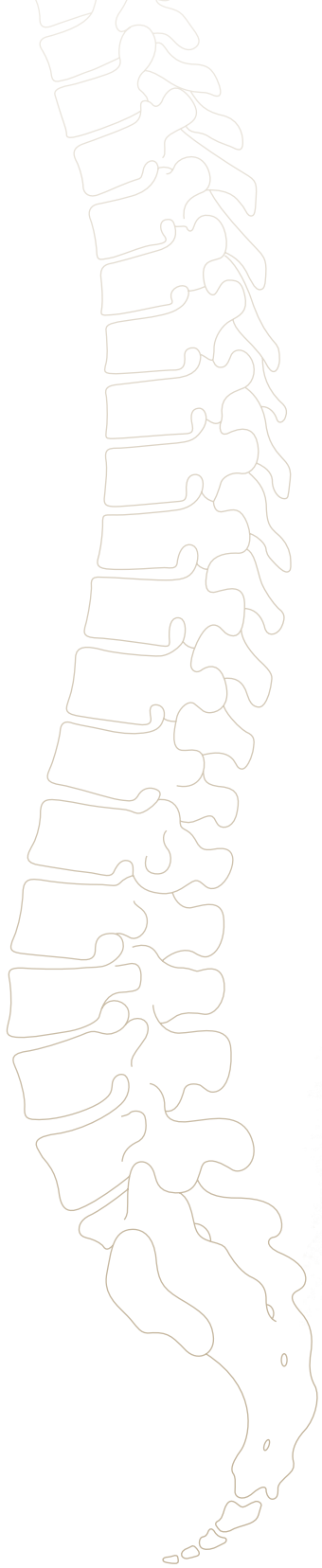
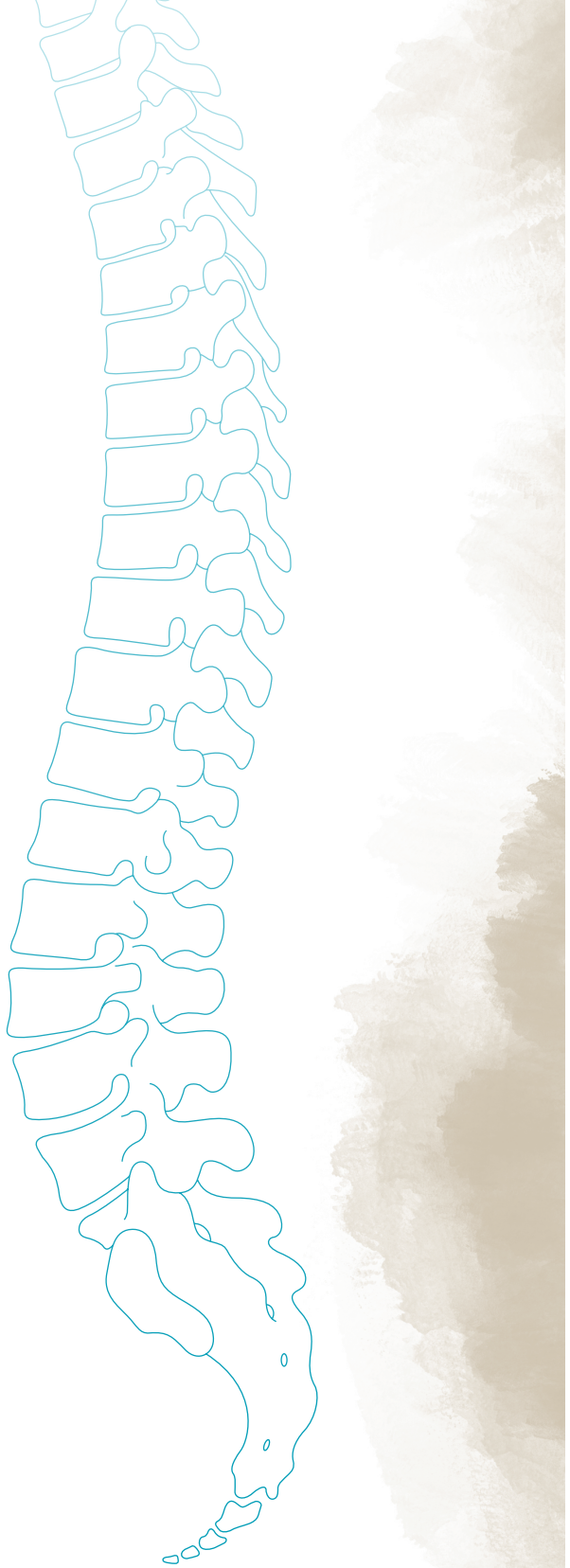
Part II



REFERRAL PATTERNS AND DELAY INTERVALS FOR METASTATIC SPINAL DISEASE



CHAPTER 5

Time to Surgical Treatment for Metastatic Spinal Disease: Identification of Delay Intervals.

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ABSTRACT

STUDY DESIGN

Retrospective cohort study

OBJECTIVES

Minimizing delays in referral, diagnosis and treatment of patients with symptomatic spinal metastases is important for optimal treatment outcomes. The primary objective of this study was to investigate several forms of delay from the onset of symptoms until surgical treatment of spinal metastases for patients with and without a known preexisting known malignancy.

METHODS

All patients receiving surgical treatment for spinal metastases in a single tertiary spine center were identified. Referral patterns were reconstructed, and the total delay was divided into four categories: patient delay (onset of symptoms until medical consultation), diagnostic delay (medical consultation until diagnosis), referral delay (diagnosis until referral to spine surgeon) and treatment delay (referral spine to surgeon until treatment). These intervals were compared between patients with and without a known preexisting malignancy.

RESULTS

The median total delay was 99 days, patient delay 19 days, diagnostic delay 21,5 days, referral delay 7 days, treatment delay 8 days and diagnosis and treatment delay combined 18,5 days. No difference in total delay was observed between patients with and without a known preexisting malignancy. Total delay was not significantly associated with patient age, sex, oncological history, tumor prognosis and spinal level of the tumor.

CONCLUSIONS

Patients with symptomatic spinal metastases experience considerable delays, even after metastatic spinal disease has been diagnosed, regardless of a preexisting malignancy. By identifying and eliminating the causes of these delays, diagnosis, referral and treatment may be expedited leading to improved patient outcome.

INTRODUCTION

Metastatic spinal disease is one of the most debilitating complications of cancer. The incidence of spinal metastases, currently affecting approximately 20% of all oncological patients, is increasing rapidly due to improvements in palliative cancer care [1–4]. One of the most important factors for achieving satisfactory treatment outcome is timely recognition of symptomatic spinal metastases [5]. Previous studies have shown that delayed treatment is associated with both unfavorable surgical outcomes, including increased amounts of blood loss, longer operating times, and a higher incidence of complications, and unfavorable long-term clinical outcomes such as poor functional performance, impaired quality of life, and reduced survival [6,7]. Reducing delays in referral, diagnosis and definitive treatment of patients with spinal metastases may therefore improve patient outcome considerably [8].

In principle all neurologic injuries caused by spinal metastases in patients with known malignancies could be viewed as potentially preventable complications. To identify targets for reducing delays in referrals of patients with spinal metastases, an understanding of the referral patterns is required. Previous studies have analyzed referral patterns in patients with spinal metastases, however these studies were limited to patients with symptomatic metastatic spinal cord compression (MSCC) [9–14]. Analyzing referral patterns in patients with MSCC may yield a skewed representation, because the onset of MSCC is generally regarded as a medical emergency accelerating the referral process substantially. Secondly, spinal metastases should preferably be identified long before the onset of MSCC. To better understand referral patterns of patients with symptomatic spinal metastases it is essential to also analyze patients without neurological symptoms who require (surgical) treatment. Moreover, the absence or presence of a preexisting malignancy will doubtlessly play a meaningful role in the risk assessment for metastatic spinal disease and the subsequent referral patterns, warranting separate analysis for these two patient groups. Lastly, no prior study has continued referral pattern analysis after the diagnosis was made. It might be possible that substantial delays still occur after the diagnosis but prior to treatment.

The primary objective of this study was to reconstruct referral patterns in patients surgically treated for symptomatic spinal metastases and to assess the total delay experienced from onset of symptoms until the initiation of treatment. As a secondary objective, we aimed to investigate the relative contribution of different types of delay to the total experienced delay and compare these separate intervals between patients with and without a known preexisting malignancy.

METHODS

All patients who received surgical treatment for spinal metastases between March 2009 and January 2019 in a single tertiary spine center (in The Netherlands) were eligible for inclusion. Patients with spinal tumors from hematological malignancies were also eligible due to the broad similarities in clinical presentation and surgical treatment compared to spinal metastases originating from solid tumors. The ethics review board (METC Utrecht, protocol no. 17-695/C) approved a waiver of informed consent for this observational, retrospective cohort study.

Indications for surgical intervention included intractable pain, mechanical instability or neurological deficits. Patients with a life expectancy of at least three months were deemed eligible for surgical treatment [15]. All treating spine surgeons adhered to generally accepted principles for surgical treatment of patients with spinal metastases, combining common scoring systems (currently NOMS: ASIA/Frankel classification for neurological status combined with Bilsky score for degree of epidural compression; Bollen classification for prognosis; SINS for spinal stability and KPS for general patient condition) [15–17]. Furthermore, a uniform treatment strategy was achieved by a weekly multidisciplinary 'spine meeting' between spine surgeons and radiation oncologists. Demographic data, tumor histology, EQ-5D score, Karnofsky Performance Score, VAS-pain score, neurological status, the presence of other metastases and the number of affected spinal levels were collected. The clinical profile of the primary tumor was classified as favorable, moderate or unfavorable, based on up-to-date median overall survival, similar to the biological tumor profile used by the Bollen classification [18].

For each patient, the referral timeline was reconstructed from the onset of first symptoms (probably) caused by the spinal metastases until definitive treatment using data from the patients' electronic medical records. For any previously diagnosed malignancy, the date of diagnosis, histological type and preexisting presence of spinal metastases were collected. Hereafter, the onset and type of the presenting symptom(s) and the date the patient first contacted any health-care provider were noted. For each health-care provider involved in the referral pattern the following parameters were extracted separately: date of consultation, medical specialty, type of care (i.e. primary, secondary or tertiary), the neurological status (Frankel-score) and ambulatory state (5-point Likert scale from fully ambulant to bedridden), date of diagnosis of spinal metastases (if applicable) and in case of a referral, the date, medical specialty and type of care (i.e. primary, secondary or tertiary) of the specialty referred to.

The overall delay throughout the referral pattern was divided into four distinct intervals: patient delay, diagnostic delay, referral delay and treatment delay. Patient delay was defined as the time between the onset of first symptoms caused by the spinal metastases (i.e., new back pain or neurological symptoms) and the first time a patient contacted any health-care provider for these symptoms. Diagnostic delay was defined as the time between the first time the patient contacted any health-care provider and the diagnosis of metastatic spinal disease. Referral delay was defined as the time between the diagnosis of metastatic spinal disease and referral to the spine surgeon. Treatment delay was defined as the time between referral to the spine surgeon and surgical treatment of the patient. The referral patterns were reconstructed using the hospital's electronic health-records. In case of missing data, the patients' general practitioners were contacted by phone to complete the referral patterns. It is mandatory for all health care providers in the Netherlands to provide the family doctor with a report of any medical consultation performed. Therefore, health records possessed by the general practitioner could be used for additional reconstruction of the referral patterns.

Due to the retrospective nature of this study, the exact date of a particular event (e.g., the onset of symptoms, a medical consultation, a referral date etc.) could not always be retrieved reliably. In the case where an approximation was written down (i.e., 'several days', 'last year' etc.) decision rules were developed to allow for consistent date approximation. These decision rules, along with other general considerations on how to interpret incomplete data, were described in a Standard Operating Procedure (SOP) to promote data consistency. The SOP provided decision rules on quantifying date approximations such as 'several days' or '3-4 months', how to handle missing data (e.g., when no onset of complaints could be found, the onset of complaints should be synchronized with the first visit to a health-care provider) and a data extraction format.

Preoperative baseline parameters were compared between patients with and without a previously known malignancy. Patient delay, diagnostic delay, referral delay, treatment delay and total delay were extracted from the reconstructed referral patterns and compared between patients with and without a known malignancy.

STATISTICAL ANALYSIS

For continuous data, means, standard deviations (SD) and, in the case of non-normally distributed data, medians and interquartile range (IQR) were used. For categorical data frequencies were used. To compare the two patient groups (presence vs absence of a known preexisting malignancy) at baseline, unpaired t-tests were used for continuous data and Chi-squared tests for categorical data. To compare the different delay intervals, unpaired t-tests were used. Because most of the intervals were left-skewed, log-transformed values were used for these

t-tests. To independently analyze prognostic factors for the total delay, a multivariable linear regression analysis was used with total experienced delay as the dependent parameter. In the case of continuous independent parameters, a regular regression coefficient was presented. In the case of categorical independent parameters, a reference category was chosen, and each non-reference category received its own coefficient in relation to the reference category. Significance for all tests was accepted at $p<0.05$. All analyses were performed using IBM SPSS Statistics for Macintosh, Version 24.0 (Armonk, NY: IBM Corp).

RESULTS

In total, 307 patients, including 175 patients without a known preexisting malignancy and 132 patients with a known malignancy were included in the analyses (**Figure 1**).

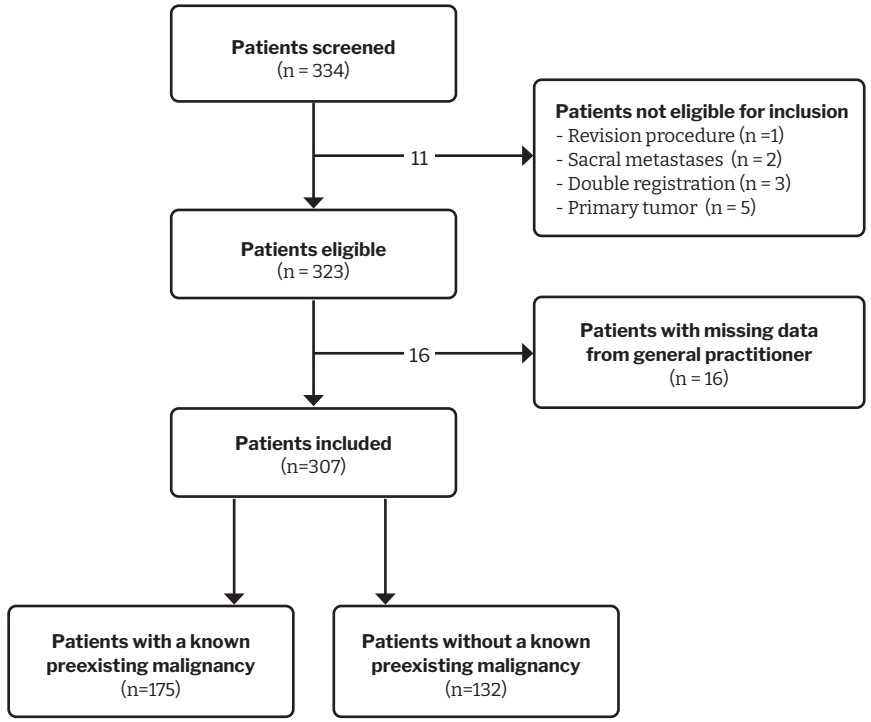


FIGURE 1. Flowchart of patient inclusion. The inclusion of all eligible patients followed by the categorization into two separate groups: 1) Patients with a known preexisting malignancy and 2) patients without a known preexisting malignancy.

No differences were observed between the two groups at the time of treatment in terms of mean patient age (62.0 vs 61.8 years), EQ-5D score (0.38 vs 0.36), median Karnofsky Performance Score (KPS 70 vs 70), the presence of other metastases (28.2% vs 27.9%), and the number of affected levels (one affected level in 47.1% vs 47.3%). The percentage of males was significantly lower in patients with a known preexisting malignancy (47.1% vs 62.8%). Furthermore, breast cancer was more prevalent in patients with a known malignancy (27.6% vs 7.0%) and lung cancer (9.2% vs 20.2%) and hematological malignancies (8.6% vs 41.1%) in patients without a known malignancy. Mainly due to the high prevalence of hematological malignancies, the biological tumor favorability was higher in patients without a previously known malignancy. In patients with a known malignancy, significantly less patients had sensorimotor disturbances (Frankel A-D, 31.5% vs 46.5%) (**Table 1**).

TABLE 1. PRE-TREATMENT BASELINE CHARACTERISTICS FOR PATIENTS WITH AND WITHOUT A PREEXISTING MALIGNANCY

	Known preexisting malignancy n=175	Unknown preexisting malignancy n=132	P-*value*
Mean age, years (SD)	62.0 (11.9)	61.8 (11.6)	*0.910*
Gender, male (%)	82 (47.1%)	81 (62.8%)	***0.007***
Tumour Histology, n (%)			***<0.001***
Breast	48 (27.6%)	9 (7.0%)	
Gastrointestinal	16 (9.2%)	5 (3.9%)	
Lung	16 (9.2%)	26 (20.2%)	
Hematological malignancy	15 (8.6%)	53 (41.1%)	
Prostate	17 (9.8%)	13 (10.1%)	
Renal	23 (13.3%)	10 (7.8%)	
Other	25 (14.3%)	6 (4.5%)	
Unknown	12 (6.9%)	4 (3.1%)	
Tumour favourability n (%)			***<0.001***
Favourable	23 (13.5%)	53 (42.4%)	
Moderate	74 (43.3%)	24 (19.2%)	
Unfavourable	74 (43.3%)	48 (38.4%)	
EQ5D, mean (SD)	0.38 (0.32)	0.36 (0.30)	*0.565*
KPS, median* (IQR)	70 (50-80)	70 (50-80)	*0.882*
VAS pain, mean (SD)	5.2 (2.4)	4.5 (2.5)	***0.022***

TABLE 1. PRE-TREATMENT BASELINE CHARACTERISTICS FOR PATIENTS WITH AND WITHOUT A PREEXISTING MALIGNANCY

	Known preexisting malignancy n=175	Unknown preexisting malignancy n=132	*P-value*
Frankel on entry, n (%)			*0.035*
A	0	2 (1.6%)	
B	4 (2.3%)	3 (2,3%)	
C	12 (6.9%)	15 (11.6%)	
D	37 (21.3%)	40 (31.0%)	
E	121 (69.5%)	69 (53.5%)	
Mobility on entry, n (%)			*0.062*
Normal	108 (62.1%)	68 (52.7%)	
Uses one crutch	3 (1.7%)	0	
Uses walker or two crutches	11 (6.3%)	10 (7.8%)	
Confined to wheelchair	12 (6.9%)	5 (3.4%)	
Confined to bed	40 23.0%)	46 (35.7%)	
Other metastases, n (%)			*0.961*
Yes	49 (28.2%)	36 (27.9%)	
No	125 (71.8%)	93 (72.1%)	
Spinal level, n (%)			*0.129*
Cervical	13 (8.1%)	12 (11.1%)	
Cervicothoracic	10 (6.2%)	8 (7.4%)	
Thoracic	66 (41.0%)	50 (46.3%)	
Thoracolumbar	20 (12.4%)	12 (11.1%)	
Lumbar	39 (24.2%)	16 (14.8%)	
Diffuse	13 (8.1%)	10 (9.3%)	
Number of affected levels, n (%)			*0.678*
1	82 (47.1%)	61 (47.3%)	
2	31 (1.8%)	19 (14.7%)	
3	24 (13.8%)	15 (11.6%)	
≥4	37 (21.3%)	35 (26.4%)	

**Karnofsky Performance Score*

DELAY INTERVALS

Overall, patients had a median total delay of 99 days (14 weeks) from the onset of symptoms associated with spinal metastases, until definitive treatment. Overall, median patient delay was 19 days, diagnostic delay 21,5 days, referral delay 7 days and treatment delay 8 days. The median for referral and treatment delay combined was 18,5 days (**Figure 2**). Comparing patients with and without a known malignancy, median patient delay was 14 vs 25 days (p=0.001), diagnostic delay 15 vs 34 days (p=0.002), referral delay 9,5 vs 4 days (p<0.001), treatment delay 11 vs 5 days(p<0.001), referral and treatment delay combined 21 vs 13 days (0.834) and total delay 99 vs 99,5 days (p=0.077) (**Figure 3**). Multivariable linear regression analysis showed that total delay was not significantly associated with patient age, sex, oncological history, spinal level of the tumor and tumor prognosis (**Table 2**).

TABLE 2. MULTIVARIATE LINEAR REGRESSION ANALYSIS FOR TOTAL EXPERIENCED DELAY

	Delay n=254 Days (CI)	*P-value*
Intercept	85,6 (-7,6 to 178,9)	*0,072*
Age	0,5 (-0,7 to 1,8)	*0,381*
Sex		
Female	Reference	
Male	-15,9 (-44,5 to 12,6)	*0,275*
Oncological history		
No preexisting malignancy	Reference	
Preexisting malignancy	-10,5 (-40,5 to 19,9)	*0,499*
Level spinal tumor		
Cervical	Reference	
Cervicothoracic	68,7 (-1,5 to 138,9)	*0,055*
Thoracic	-11,1 (-59,6 to 37,4)	*0,654*
Thoracolumbar	-13,5 (-72,7 to 45,8)	*0,656*
Lumbar	22,6 (-30,8 to 75,9)	*0,407*
Diffuse	19,8 (-48,3 to 88,0)	*0,568*
Tumor prognosis		
Favorable	Reference	
Moderate	27,5 (-12,3 to 67,3)	*0,175*
Unfavorable	8,7 (-27,1 to 44,4)	*0,635*

FIGURE 2. Delay intervals for all patients. Median number of days of patient delay (onset of symptoms to medical consultation), diagnostic delay (medical consultation to diagnosis), referral delay (diagnosis to referral spine surgeon), treatment delay (referral spine surgeon to treatment), referral and treatment delay combined and total delay.

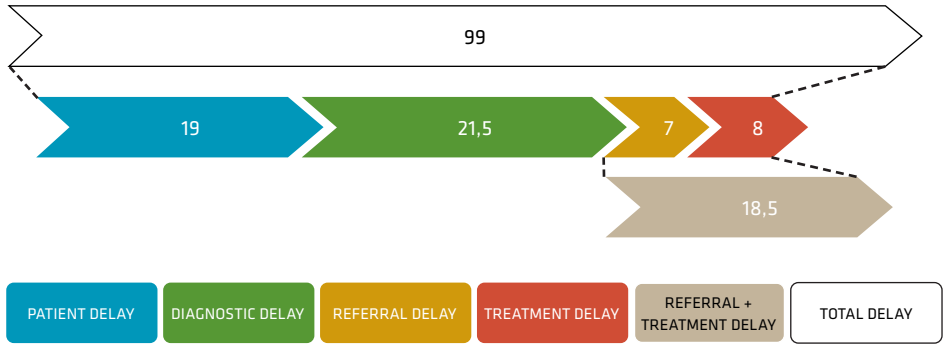
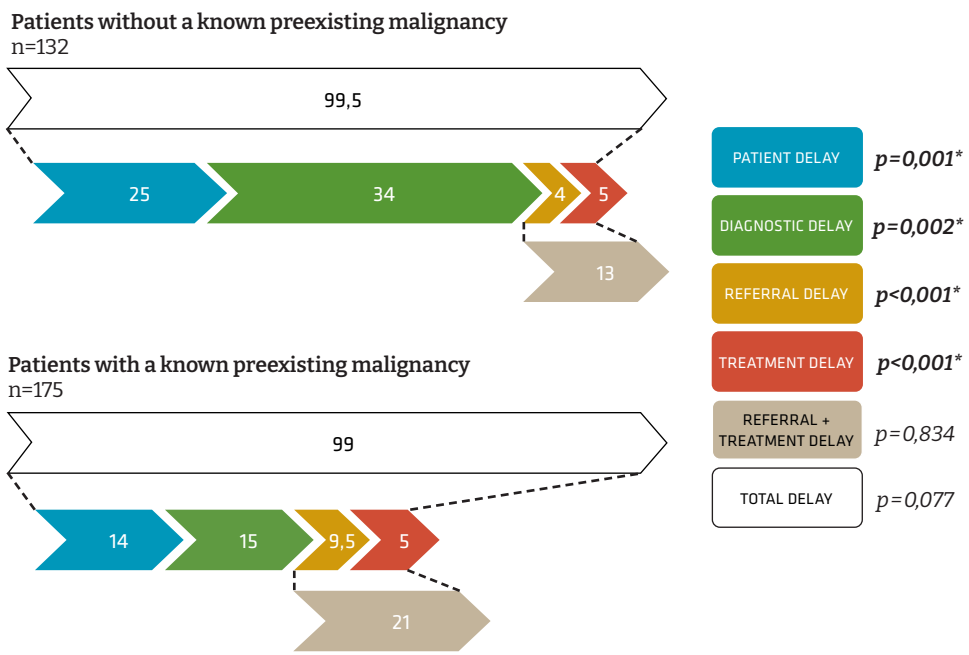


FIGURE 3. Delay intervals for patients with and without a known preexisting malignancy. Median number of days of patient delay (onset of symptoms to medical consultation), diagnostic delay (medical consultation to diagnosis), referral delay (diagnosis to referral spine surgeon), treatment delay (referral spine surgeon to treatment), referral and treatment delay combined and total delay for patients with and without a preexisting malignancy.



DISCUSSION

In the current study, referral patterns of 307 patients surgically treated for symptomatic spinal metastases were reconstructed and subsequently analyzed. The median total delay (representing the time from first symptoms until definitive treatment) for all patients was more than three months (99 days). According to our results patient delay is only the second largest contributor to total delay, as considerable delays also occur while patients are under medical attention throughout the ensuing referral chain. A previously known malignancy was associated with shorter patient and diagnostic delay, however longer referral and treatment delay, resulting in a total delay comparable to patients without a previously known malignancy. In other words, oncological patients developing new back pain do not seem to advance faster through the overall referral chain than patients without a preexisting cancer diagnosis, suggesting a paucity in awareness or sense of urgency for metastatic spinal disease in known oncological patients among Dutch health-care providers. As has been shown in previous studies, earlier treatment will likely result in patients being more fit for (surgical) intervention, ultimately leading to better patient outcome [6,19,20]. The data presented in this study provides several targets for minimizing delay in patients with spinal metastases, thereby potentially enhancing the clinical outlook for better pre- and postoperative status.

Non-malignant back pain is one of the most prevalent conditions in middle-aged people and commonly regarded as self-limiting [21]. Symptoms caused by spinal metastases are generally difficult to distinguish from symptoms caused by non-malignant back pain and are therefore often subjected to a wait-and-see policy [22]. Consequently, patients with spinal metastases are at risk for delays in their diagnosis, referral and treatment, particularly in the absence of a previously diagnosed malignancy [23,24]. The incidence of malignant spinal disease in all patients with lower back pain is described to be as low as 0.7% [25]. However, in 4.9% of all patients with compression fractures the fracture is of a pathological nature [26]. In specialized spine centers, 5.9% of patients presenting with non-mechanical back pain without movement restrictions are subsequently diagnosed with metastatic disease [27]. Specifically in oncological patients, an estimated 92.5% of pain complaints is related to tumor involvement [28]. A previous study analyzing oncological patients with new onset back pain found that 60% of patients without abnormalities on neurological examination still showed radiologic evidence of spinal metastases [29]. Consequently, even though the incidence of metastatic spinal disease in the general population is relatively low, the incidence increases as patients enter hospital care, particularly in those patients who are already known to have a malignancy. It is important for health care providers in secondary and tertiary care to acknowledge the relatively high prevalence of metastatic spinal disease among patients with back pain.

In our study, the overall delay for all patients was 99 days from the onset of symptoms until treatment, which is slightly longer than overall delays described in studies performed by Husband et al. (75 days) and Levack et al. (90 days) [9,10]. In the current study patients without MSCC at the time of treatment were also included, in contrast to Levack et al. and Husband et al., who included only patients with MSCC. The referral process is often accelerated after the onset of neurological deficits, commonly regarded as a medical emergency, explaining the longer total delay in patients presenting without neurological deficits. In our study, a median patient delay of 19 days was observed, which is similar to the median patient delay of 18 days observed by Levack et al [10]. Another study investigating time to radiotherapeutic treatment showed that patient delay was the biggest contributor (64%) to a total delay of 12 days [14]. In a study by Guzik et al., patients noticing a decline in their neurological status still showed a mean patient delay of four days from the onset of neurological deterioration [13]. Patient delay may be reduced by patient education or self-assessment tools, however this will always remain a challenge, especially in patients unaware or in repudiation of any underlying malignancy. In the current study, the largest contributor to total delay was diagnostic delay with a median of 21.5 days, slightly longer than the previously reported 15 days by Levack et al. [10]. Another study by Bach et al. showed that even after presentation with symptoms indicative of MSCC, patients still experienced a mean diagnostic delay of 23 days [30]. Timely diagnosis remains a significant challenge in patients with spinal metastases, apparently even in the presence of progressive neurological symptoms. Nonetheless, timely treatment is largely dependent on timely diagnosis, making diagnostic delay one of the most important targets for optimization and shortening of the referral chain. For example, educating general practitioners and/or other health-care providers on the importance of red flags, especially a preexisting cancer diagnosis, when assessing patients with back pain or lowering MRI/CT thresholds for oncological patients with back pain may lead to a reduction in diagnostic delay.

This is the first study to separately analyze delays in the referral chain after the diagnosis of metastatic spinal disease and treatment. After patients were diagnosed, a median of 7 days was required for the patients to be referred to their definitive caregiver (in the current study: a spine surgeon), and another 8 days from referral until the initiation of treatment. In many cases, symptomatic spinal metastases require radiotherapeutic or surgical treatment which are commonly performed in specialized, tertiary care centers. Therefore, non-specialized (oncological) health-care providers may not always be familiar with the management of metastatic spinal disease and may not be aware of the preferred treatment regimen (i.e., systemic, radiotherapeutic, or surgical interventions), resulting in delayed and/or erroneous referrals and treatment. In the past decade, the introduction of referral tools such as the Spinal Instability Neoplastic Score (SINS) have demonstrated to assist health-care providers in adequately referring patients after diagnosis of metastatic spinal disease [31,32]. Nonetheless, this study shows that further reductions in referral delay could be possible to further expedite treatment. Educational initiatives in a catchment area, aimed at increasing awareness and expertise on the treatment of metastatic spinal disease among the involved health-care providers, along with referral tools such as the SINS may play a vital role in optimizing referral chains.

In our study, 43% of the patients did not have a previously known malignancy, which is comparable to the 34% and the 40% reported by Husband et al. and Levack et al., respectively. We observed no difference in total delay between patients with and without a known malignancy. In contrast, Levack et al. and Husband et al. found a median total delay of 49 days and 60 days, respectively, for patients with a known malignancy and both studies showed a total delay of 90 days for patients without a previously diagnosed malignancy [9,10]. Similarly, in the current study, patient delay and diagnostic delay were significantly shorter if the patient already was previously diagnosed with a malignancy. This is in line with a study by Mitera et al. where median delay from the onset of symptoms until radiotherapeutic treatment was 5.5 days for patients who suspected a relationship between the symptoms and their oncological history and 17 days for those who did not [14]. As opposed to our hypothesis, median referral and treatment delay were significantly longer in patients with a known malignancy. A potential explanation for this difference can be found in previous studies showing that metachronous metastases are histologically less aggressive than synchronous metastases. As a consequence, patients with a known malignancy may be less susceptible to the occurrence of acute MSCC and subsequent acceleration of treatment [33]. Moreover, in patients with a known malignancy may be considered less alarming to be diagnosed with metastases compared with patients who were previously presumed healthy being diagnosed with malignant, metastatic disease, leading to faster referral and treatment in the latter category.

In a previous study, the mean time from the onset of symptoms until neurological deficits has been described to be as little as seven weeks [34]. This finding clearly emphasizes the need for rapid diagnosis, referral and treatment for patients with metastatic spinal disease. Delaying treatment will increase the risk for emergency surgery, which is associated with inferior outcome, however, is still preferred over postponed surgery in an emergency situation [35,36]. In case of neurological deterioration, emergency surgery is commonly preferred within 24-48 hours to maximize the chances of neurological recovery or prevent further neurological deterioration [37]. This however jeopardizes the ability for health-care providers to perform an adequate work-up of patients and may lead to overtreatment of patients with unfavorable

prognoses [19]. Previous studies have emphasized the potential improvement of patient outcome by enhancing patient pathways [8]. Health-care providers early in the referral chain are at a unique and high-leverage position to prevent complications and improve patient outcome by early detection and referral [31].

This study has several limitations. Firstly, our study included only patients who were surgically treated and not patients who underwent only radiotherapeutic or systemic tumor treatment. Because surgical patients generally have more severe or more advanced metastatic spinal disease, this may bias our results towards shorter delay intervals. Nonetheless, in the literature all previous studies have focused only on patients with MSCC. Therefore, the current study is still the best available representation of typical referral patterns in patients with spinal metastases and provides a good starting point for identifying targets in the referral chain to reduce delays with the goal to improve clinical outcome for these patients. Future studies should aim to also include non-surgically treated patients to get an even more comprehensive overview of referral patterns in patients with spinal metastases. Secondly, due to the retrospective nature of this study, not all delay intervals could be fully reconstructed without the occasional approximation of the timing of certain events throughout the referral patterns. Nonetheless, each approximation is based on the same set of decision rules as was carefully noted in an SOP. Therefore, the authors are convinced that the results from the current study were not grossly biased by the retrospective nature of this study. Lastly, the current study does not identify actual causes of the occurring delays. Future studies should use the current results as guidance to identify and address specific causes of these delay intervals, thereby expediting treatment of metastatic spinal disease.

CONCLUSION

In conclusion, patients with symptomatic spinal metastases experience considerable delays, even after the diagnosis of metastatic spinal disease is established. Educating health-care providers on the urgency of treatment for metastatic spinal disease and equipping them with efficient referral tools to stimulate appropriate referrals may lead to a reduction in referral delay. Moreover, although patients with a known malignancy experience shorter patient and diagnostic delays, they also experience longer referral and treatment delays. Therefore, no differences in total delay between patients with and without a previously known malignancy were observed. Increasing awareness on the importance of a patient's oncological history in the case of back pain may also lead to a reduction in diagnostic delay. By reducing the mean total delay experienced by all patients with metastatic spinal disease, the proportion of patients with complications such as neurological deficits should decrease, thereby promoting overall patient outcome.

Nonetheless, further research is still needed to gain a more in-depth understanding of the actual causes of the delays as described in the current study. By targeting these causes, the total time to treatment can be reduced substantially, leading to improved treatment outcome for patients with symptomatic spinal metastases.

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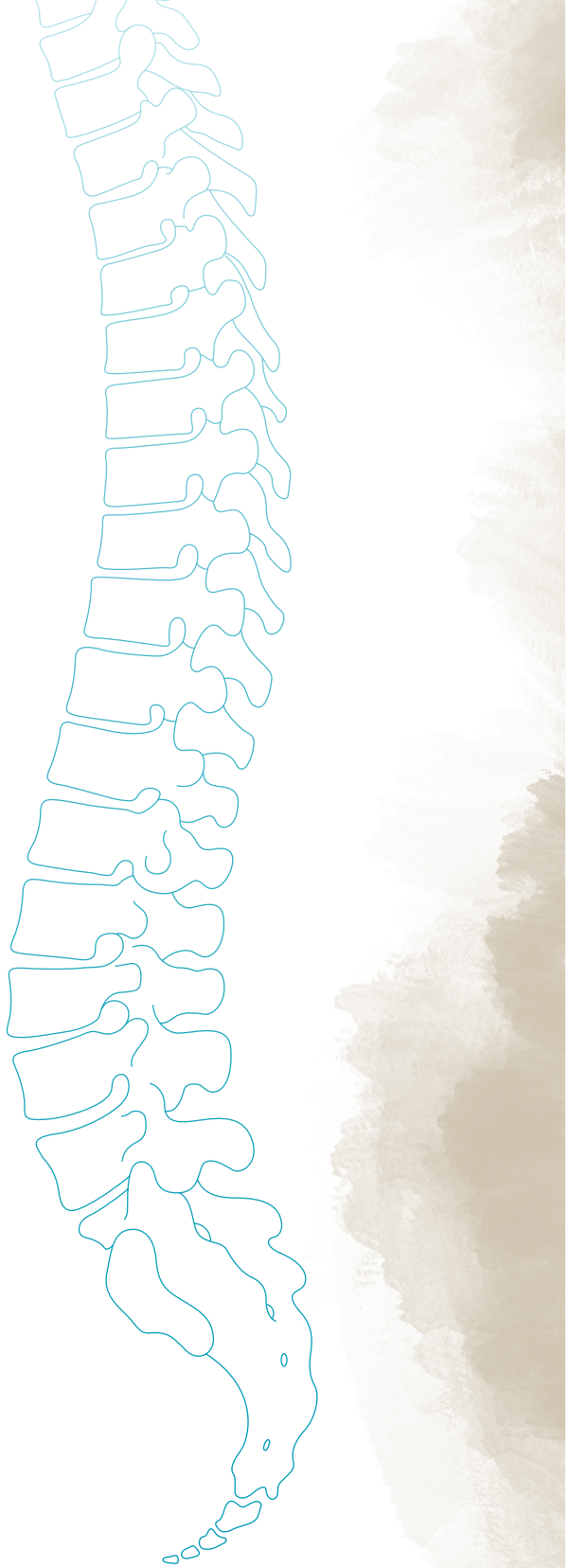

CHAPTER 6

Time between Early Symptoms caused by Metastatic Spinal Disease and The Potential Onset of Neurological Deficits

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ABSTRACT

INTRODUCTION

Spinal metastases can cause debilitating complications in cancer patients. Without timely treatment, patients may develop metastatic spinal cord compression, impairing quality of life and survival. The current study evaluates the time between first symptoms and onset of neurological deficits and which patient- and disease-related factors are associated with a more rapid onset of neurological symptoms. Moreover, the timing of neurological deficits within the patient journey was assessed.

MATERIALS AND METHODS

A retrospective review of 389 patients surgically treated for spinal metastases was conducted. In patients with neurological deficits prior to treatment, the time between the first symptom onset related to spinal metastases and deterioration in Frankel grade was calculated in days and defined as the time to neurological deficits. Regression was used to correlate the time to neurological deficits to the primary tumour, spinal localisation, and the oncological history of the patient. Patient journeys were reconstructed using electronic patient records.

RESULTS

Neurological deficits occurred in 141 patients (36.2%) with a median time to neurological deficits of 64 days. A previously established cancer diagnosis, thoracic lesions and haematological tumours showed a trend towards a more rapid onset of neurological deficits. Approximately 20% of neurological deficits occurred prior to any medical involvement, 43% during diagnostic investigation, and 38% after the diagnosis of metastatic spinal disease, but before surgical treatment was initiated.

CONCLUSION

The current study shows the limited time available for health-care providers to prevent the onset of neurological symptoms in patients with spinal metastases. These results emphasize the importance of awareness amongst oncological health-care providers on the timely identification and treatment of metastatic spinal disease.

Keywords: Spinal metastases, neurological deficits, delay

INTRODUCTION

Symptomatic spinal metastases occur frequently in malignant disease and are observed in approximately 10% of all cancer patients [1,2]. Due to a combination of rising cancer incidences and longer survival, the incidence of metastatic spinal disease is growing [3–5]. One of the most debilitating complications of metastatic spinal disease is the development of neurological deficits due to metastatic epidural spinal cord compression (MESCC) or compression of other neural structures (e.g. cauda equina, nerve roots), which is observed in 25-50% of patients with symptomatic spinal metastases [6,7].

Patients with symptomatic MESCC often require surgical decompression of neural structures in an attempt to reverse or prevent progression of neurological deficits [8]. Despite urgent surgical intervention, generally followed by radiotherapy for local tumour control, complete resolution of neurologic symptoms only occurs in only 20-40% of MESCC patients [9–11]. Previous studies have shown that delayed treatment puts patients at risk for neurological deterioration and subsequently worse surgical and clinical outcomes [12,13]. Identifying patients at risk of developing MESCC, and initiating early treatment aimed at preserving mechanical and/or neurological integrity, is therefore essential.

In previous studies, the time between first symptoms related to spinal metastases and onset of neurological deficits has been reported to be as short as 7-8 weeks [3,14]. However, these studies date back more than 30 years and oncological care has undergone considerable change since. To get a more accurate sense of urgency in metastatic spinal disease, it is furthermore important to recognize which patient- and disease-specific factors correlate to the time until onset of symptomatic MESCC. Moreover, the timing of definitive treatment relies highly on the efficiency of the preceding referral chain. To effectively prevent the onset of MESCC, it is essential to know during which stage of the patient journey neurological deficits are likely to occur. For example, if most deficits occur prior to consultation of any health-care provider (i.e., during patient delay), promoting timely treatment might benefit most from patient education.

The primary goal of this study was to evaluate the time between first symptoms related to metastatic spinal disease and onset of neurological deficits in patients surgically treated for metastatic spinal disease. As a secondary objective, this study aimed to identify specific patient- and disease related factors which could be associated with a more rapid onset of neurological symptoms. As a tertiary objective, this study assessed at which stage of the patient journey neurological deficits occur.

MATERIALS AND METHODS

A retrospective review of all patients surgically treated for metastatic spinal disease between March 2009 and September 2020 from a single tertiary spine centre was conducted. Indications for surgical treatment were mechanical pain refractory to radiotherapeutic or systemic treatment, spinal mechanical instability, or neurological deficits. The study was approved by the Research Ethics Board (REB).

Data were extracted from our hospital's electronic data record, as well as from the electronic data record from general practitioners (GP's). Patient journeys were reconstructed using data from the hospital's electronic patient records and reports that health-care providers (HCP's) in the Netherlands write to provide the GP with a summary of their medical consultation.

Data regarding age, sex, oncological medical history, tumour histology, prior systemic and/or radiotherapeutic treatment, localization and number of metastases, Karnofsky Performance Scores (KPS), EQ-5D scores and neurological status of the patient were retrieved. In the current study, neurological deficits were defined as a deterioration in Frankel grade, which is a scale of A-E where E is completely neurologically intact, and A is complete sensory and motor loss. Patient journeys from symptom onset until definitive surgical treatment were reconstructed for each individual patient. Symptom onset was defined as the first reported time point of any symptom that could retrospectively be attributed to metastatic spinal disease and included: (new) back/neck pain, sensorimotor symptoms and more subtle neurological signs and symptoms such as radiculopathy, atactic gait and autonomic symptoms such as bladder/bowel dysfunction. For each HCP involved in the patient journey related to the spinal metastases, the date of consultation, type of symptoms, neurological status (Frankel-score) and ambulatory state (5-point Likert scale from fully ambulant to bedridden) were noted. The onset of symptoms was extracted from the first involved HCP.

The time to neurological deficits was defined as the time between symptom onset and the first known date of a deteriorated Frankel grade and was calculated for each patient in days. MESCC in the current study was defined as neurological symptoms (including bladder, bowel and/or sexual dysfunction) due to metastatic compression on neural structures including the spinal cord, cauda equina and exiting nerve roots. The time to onset of neurological deficits was then correlated to the absence or presence of a pre-existing cancer diagnosis, tumour histology and tumour localization. Tumour histology was stratified into 6 categories based on the primary origin of the cancer: breast, urogenital (including bladder, cervicouterine, ovarium, prostate and renal), lung, haematological (including lymphoma, myeloma and plasmacytoma) tumours, gastro-intestinal tumours (including cholangiocarcinoma, colorectal, gastroesophageal and liver), and 'other' tumours (including melanoma, thyroid, and unknown primary tumours). For the analyses, the spinal localisation of the tumour was confined to cervical, thoracic, and lumbar localisation based on which spinal segment was affected the most.

The patient journey was divided into four intervals: Patient delay, defined as the time between onset of the first reported symptoms caused by the metastases (e.g., new back or neck pain or neurological symptoms) and the first medical consultation for these symptoms. Diagnostic delay, defined as the time elapsed between the first medical consultation and the diagnosis of (new) spinal metastases. Referral delay, defined as the time between the diagnosis and referral to the spine surgeon. Treatment delay, defined as the time between referral to the spine surgeon and surgical treatment of the patient.

Patients were divided into five groups based on the interval of the patient journey during which neurological deficits first occurred: during patient delay, during diagnostic delay, during referral delay, during treatment delay and patients who were neurologically intact at the time of surgical treatment. For each of these groups, the duration of different delay intervals (i.e., patient delay, diagnostic delay, referral delay, treatment delay and total delay) was assessed separately.

STATISTICAL ANALYSIS

For continuous data, means, standard deviations (SD) or medians and interquartile range (IQR) were used. For categorical data frequencies and percentages were used. The correlation between the time to neurological deficits and oncological history, histology type and the level(s) of the lesions was analysed by univariable and multivariable negative binomial regression since other methods (including Poisson regression) suffered from overdispersion in the data. Coefficients were exponentiated back to incidence rate ratio's and displayed along with estimated marginal means for interpretability. All analyses were performed by means of IBM SPSS Statistics for Macintosh, Version 27.0 (Armonk, NY: IBM Corp).

RESULTS

PRIMARY OBJECTIVE

A total of 389 patients met the inclusion criteria and were included into the current study (**Figure 1**). The baseline characteristics of all patients are presented in **Table 1.** A total of 141 patients had neurological deficits at the time of surgical treatment, of which 129 patients had complete data available on tumour histology, oncological history and the spinal level(s) of the lesion(s) and could therefore be included into multivariable negative binomial regression analyses. Of the 248 patients without sensorimotor deficits at treatment, 51 patients showed subtle neurological symptoms such as radicular pain or minor sensory disturbances prior to treatment. The median time to neurological deficits was 64 days (IQR 31.75-117.25).

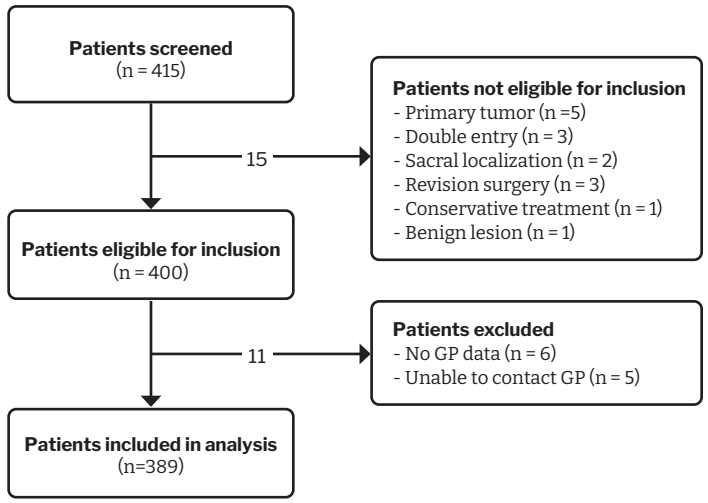


FIGURE 1. Flowchart of patient inclusion.

TABLE 1. PATIENT CHARACTERISTICS FOR PATIENTS WITH AND WITHOUT SENSORIMOTOR DEFICITS AT SURGICAL TREATMENT

	All patients n=389	No sensorimotor deficits at treatment n=248	Sensorimotor deficits at treatment n=141
Male, n (%)	218 (56.0%)	133 (53.6%)	85 (60.3%)
Age, mean (SD*)	62.4 (11.5)	61.9 (11.6)	63.1 (11.4)
Preexisting malignancy, n (%)	231 (59.4%)	160 (64.5%)	71 (50.4%)
Prior systemic treatment, n (%)	43 (11.1%)	31 (12.5%)	12 (8.5%)
Prior radiotherapeutic treatment, n (%)	66 (17.0%)	44 (17.7%)	22 (15.6%)
Histology, n (%)			
Breast	73 (18.8%)	51 (20.6%)	22 (15.6%)
Gastro-intestinal	25 (6.4%)	14 (5.6%)	11 (7.8%)
Hematological	77 (19.8%)	47 (19.0%)	30 (21.3%)
Lung	61 (15.7%)	36 (14.5%)	25 (17.7%)
Urogenital	93 (23.9%)	56 (22.6%)	37 (26.2%)
Other	37 (9.5%)	28 (11.3%)	9 (6.4%)
Unknown	23 (5.9%)	16 (6.5%)	7 (5.0%)
Number of affected levels, n (%)			
1	175 (45.0%)	110 (44.4%)	65 (46.1%)
2	64 (16.5%)	43 (17.3%)	21 (14.9%)
3	52 (13.4%)	34 (13.7%)	18 (12.8%)
4-6	58 (14.9%)	40 (16.1%)	18 (12.8%)
7-10	23 (5.9%)	11 (4.4%)	12 (8.5%)
>11	17 (4.4%)	10 (4.0%)	7 (5.0%)
Localization of metastases, n (%)			
Cervical (C1-C7)	24 (6.2%)	19 (7.7%)	5 (3.5%)
Cervicothoracic (C1-Th12)	25 (6.4%)	15 (6.0%)	10 (7.1%)
Thoracic (Th1-Th12)	186 (47.8%)	110 (44.4%)	76 (53.9%)
Thoracolumbar (Th1-L5)	64 (16.5%)	40 (16.1%)	24 (17.0%)
Lumbar (L1-L5)	62 (15.9%)	45 (18.1%)	17 (12.1%)
Diffuse (C1-L5)	28 (7.2%)	19 (7.7%)	9 (6.4%)

TABLE 1. PATIENT CHARACTERISTICS FOR PATIENTS WITH AND WITHOUT SENSORIMOTOR DEFICITS AT SURGICAL TREATMENT

	All patients n=389	No sensorimotor deficits at treatment n=248	Sensorimotor deficits at treatment n=141
Frankel, n (%)			
A	3 (0.8%)	0 (0.0%)	*3 (2.1%)*
B	8 (2.1%)	0 (0.0%)	*8 (5.7%)*
C	30 (7.7%)	0 (0.0%)	*30 (21.3%)*
D	97 (24.9%)	0 (0.0%)	*97 (68.8%)*
E	248 (63.8%)	248 (100%)	*0 (0.0%)*
EQ-5D Score, mean (SD)	0.41 (0.31)	0.46 (0.32)	*0.32 (0.27)*
KPS**, median (IQR***)	70 (50-80)	70 (60-80)	*60 (50-70)*

** Standard Deviation*
*** Karnofsky Performance Score*
**** Inter-Quartile Range*

SECONDARY OBJECTIVE

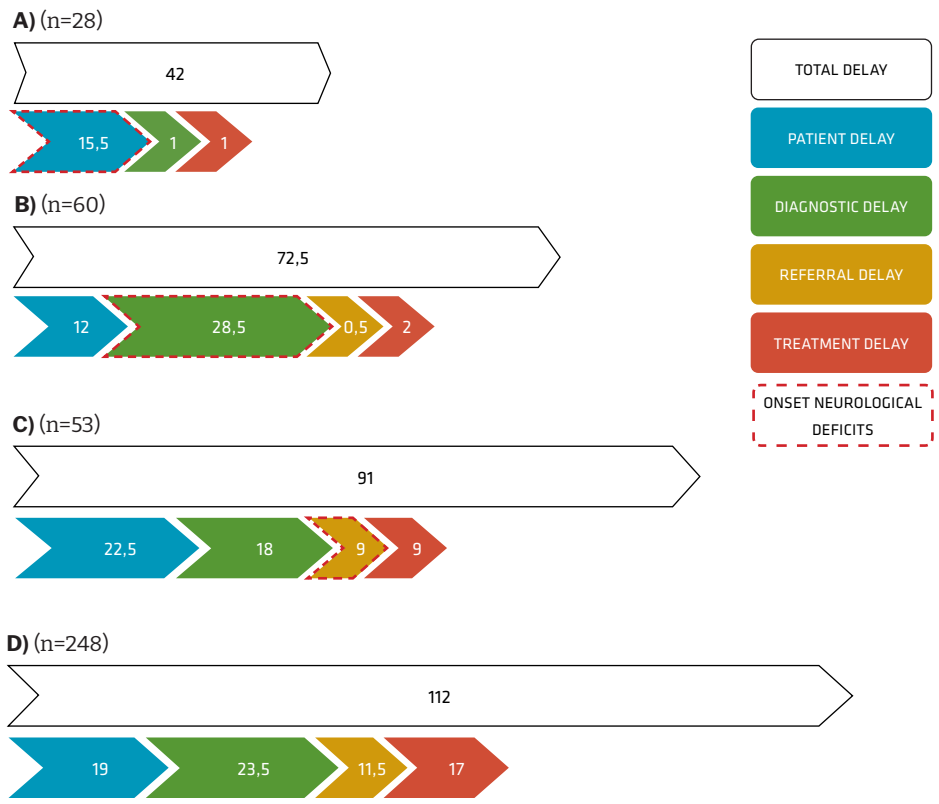
Univariable regression analyses showed no statistically significant correlation between the time to neurological deficits and a pre-existing cancer diagnosis, spinal localisation of the lesion and the primary tumour. When incorporating all factors into a multivariable regression model, haematological tumours were significantly associated with a more rapid onset of neurological deficits (p=0.032). Furthermore, a more rapid onset of neurological deficits in patients with a pre-existing cancer diagnosis (metachronous metastasis) compared with an absent pre-existing cancer diagnosis (synchronous metastasis) approached clinical significance (IRR 1.34, p=0.077). Lastly, thoracic metastases were associated with the most rapid onset of neurological deficits, however these results were also non-significant (IRR 0.52, p=0.276). These results are displayed in **Table 2**.

TABLE 2. UNIVARIABLE AND MULTIVARIABLE NEGATIVE BIOMIAL REGRESSION ANALYSIS predicting the amount of days between the onset of symptoms related to the spinal metastases and the onset of sensorimotor symptoms based on medical history, tumor type and metastasis location

	Number of patients	Estimated Marginal Means		Incidence Rate Ratio		*P-value*
	n	Absolute Value	Wald CI	Ratio	Wald CI	
Univariable						
Preexisting cancer diagnosis						
Yes	66	77.8	58.7 to 103.1	Reference		*N/A*
No	70	91.8	77.4 to 108.8	1.18	0.85 to 1.64	*0.325*
Affected Levels						
Cervical	8	124.3	48.9 to 316.0	Reference		*N/A*
Lumbar	22	93.0	71.7 to 120.7	0.65	0.25 to 1.67	*0.368*
Thoracic	106	80.4	67.8 to 95.3	0.75	0.28 to 1.97	*0.559*
Histology						
Gastro-intestinal	11	122.6	75.5 to 199.1	Reference		*N/A*
Lung	25	107.1	87.9 to 145.5	0.87	0.49 to 1.55	*0.644*
Other	9	84.6	53.1 to 134.7	0.69	0.35 to 1.35	*0.278*
Breast	20	79.6	59.6 to 106.2	0.65	0.37 to 1.14	*0.133*
Urogenital	35	79.8	53.7 to 118.5	0.65	0.35 to 1.22	*0.178*
Hematological	29	69.9	49.9 to 97.8	0.57	0.32 to 1.03	*0.062*
Multivariable						
Preexisting cancer diagnosis						
Yes	63	95.4	60.1 to 151.6	Reference		*N/A*
No	66	128.2	87.4 to 188.1	1.34	0.97 to 1.86	*0.077*
Affected Levels						
Cervical	7	161.1	49.7 to 521.8	Reference		*N/A*
Lumbar	21	101.3	76.1 to 134.7	0.63	0.18 to 2.19	*0.466*
Thoracic	101	83.0	69.7 to 98.7	0.52	0.16 to 1.70	*0.276*
Histology						
Gastro-intestinal	11	164.6	87.7 to 309.1	Reference		*N/A*
Lung	25	127.0	80.0 to 201.5	0.77	0.41 to 1.46	*0.424*
Other	9	108.7	60.3 to 196.0	0.66	0.34 to 1.30	*0.227*
Breast	20	105.2	68.0 to 162.7	0.64	0.35 to 1.18	*0.150*
Urogenital	35	93.6	51.9 to 168.5	0.57	0.32 to 1.02	*0.059*
Hematological	29	81.8	51.7 to 129.3	0.50	0.26 to 0.94	***0.032***

Of the 141 patients who developed neurological deficits, 28 patients developed neurological deficits during patient delay, 60 during diagnostic delay, 53 during referral delay and none during treatment delay. In total, 247 patients had no neurological deficits at the time of surgical intervention (**Figure 2**).

FIGURE 2. Delay intervals (in median days) stratified for when neurological deficits occurred during the referral pattern.



A) Neurological deficits occurred prior to any medical involvement.
B) Neurological deficits occurred during diagnostic investigation.
C) Neurological deficits occurred after diagnosis, but prior to referral to a spine surgeon.
D) Patients were neurologically intact at surgery.

DISCUSSION

In the current study, the time between onset of symptoms related to spinal metastases and occurrence of neurological deficits was analysed. Our results show that the time to neurological deficits after the first symptoms of spinal metastasis may be longer than was previously described [3,14]. Multivariable analysis showed large numerical variation in the time to neurological symptoms between different primary tumours, affected spinal levels and metachronous vs synchronous metastases. Furthermore, the current results show that 80% of neurological deficits occurred after patients had already sought medical attention for symptoms related to their spinal metastases. Moreover, 38% of neurological deficits occurred after the diagnosis of metastatic spinal disease but prior to initiation of treatment, suggesting a lack of awareness and/or sense of urgency of metastatic spinal disease amongst oncological care providers.

A previous study by Gilbert et al. showed a median duration of 49 days (7 weeks) of preceding pain prior to developing neurological symptoms related to metastatic spinal disease [14]. In a later study by Bach et al., a slightly longer mean duration from the first symptoms until the diagnosis of MESCC of 58 days (approximately 8 weeks) was found. The median time to neurological deficits in the current study was 64 days (9 weeks). The upward trend in time to neurological deficits may be the result of improvements in primary cancer care over the past decades [4]. Nonetheless, despite this increase, a considerable proportion of patients still develops symptomatic MESCC, emphasizing the need for more efficient identification of patients at risk of developing MESCC.

In previous studies, MESCC was the first manifestation of malignant disease (synchronous presentation) in 20-25% of the patients [15,16]. In the current study, a pre-existing cancer diagnosis was absent in 40.6% of all patients and showed a trend to a longer time to neurological deficits (IRR of 1.34). Potentially, metachronous spinal metastases behave more aggressively, which is supported by previous studies showing worse survival rates in metastatic spinal disease patients with a pre-existing cancer diagnosis [17]. Speculatively, most patients with MESCC and pre-existing cancer may have received some form of anti-cancer treatment, and their newly developed spinal metastases thus represent a treatment-resistant component of their malignancy. The current study also showed that primary tumours associated with unfavourable median survival rates, such as gastro-intestinal and lung tumours, showed a non-significant trend towards longer time to neurological deficits. In contrast, tumours associated with favourable median survival rates, such as haematological tumours, were associated with a significantly more rapid onset of neurological deficits. It is important for oncological health-care providers to be aware of these differences, especially since patients with relatively favourable

oncological prognoses may benefit most from preventing or reversing neurological deterioration. Finally, neurological deficits were primarily observed in patients suffering from spinal metastases at the thoracic level, confirming previous findings [18]. It has been suggested that MESCC is most commonly observed in the thoracic spine due to the narrowness of the spinal canal in that region, resulting in less space for the spinal cord and therefore early manifestation of deficits upon direct compression from a spinal metastasis [6]. These anatomical differences may also explain why thoracic spinal metastases showed a trend towards a relatively short mean time to neurological deficits in the current study. The current findings suggest that timely identification and treatment of metastatic spinal disease is especially important when thoracic spinal metastases progress and grow into the spinal canal. Even though back pain is one of the most common complaints in the general population, this generally concerns lower back pain rather than pain located at the thoracic level, which is often perceived and located between the shoulders [19,20].

Metastatic spinal disease forms an increasing challenge in cancer patients [21]. Due to improvements in primary cancer care, cancer patients now live longer, which results in an increased prevalence of malignant disease as well as a growing percentage of cancer patients developing MESCC [3–5]. The development of MESCC negatively impacts quality of life and also has a direct negative impact on patient survival [22,23]. In previous studies, it was shown that attempting to improve patient care paths may be beneficial to patient outcome [24]. For example, adopting a multidisciplinary treatment system has been shown to decrease the occurrence of MESCC within the oncological population [25].

Another important aspect of timely identification and treatment may be proper patient education. Since 75% of neurological deficits have been described to occur while patients are not in the hospital, cancer patients need to be aware of the symptoms associated with MESCC and the urgency of medical consultation once these symptoms occur [26]. For this reason, the Dutch national guideline on spinal metastatic disease contains a patient folder aimed at educating cancer patients on alarming symptoms [27]. In previous studies, 20% of all diagnosed neurological deficits were found on routine medical examinations, suggesting that patients at risk of MESCC are not aware of the (importance of) symptoms indicative of MESCC [26]. Furthermore, it is important for HCP's involved in the care for oncological patients to realize that (symptomatic) metastatic spinal disease is a (pending) medical emergency and requires urgent specialized consultation. At the time of diagnosis, approximately 90% of MESCC patients have concomitant back pain, frequently present as a prodromal symptom for several weeks prior to the onset of any neurological symptoms [20,28]. HCPs should familiarize themselves with factors related to a shorter time to neurological deficits to aid in the prevention of MESCC. Rapid neurological deterioration has been associated with inferior postoperative neurological recovery, lower rates of local tumour control and survival, further emphasizing the importance of awareness of the time to neurological deficits [29–33].

The current study has several limitations. First, the study failed to identify factors significantly associated with a more rapid onset of neurological deficits, even though trends of an association between primary histology, spinal segments and the absence or presence of a pre-existing cancer diagnosis with the time to neurological deficits were visible. Because there is large variation in the time to neurological deficits, the current study may have lacked the statistical power to show these correlations. In the future, larger studies should be able to more accurately assess if patient- and disease-related factors contribute to the time to neurological deficits. Second, when calculating the time to neurological deficits, only patients who experienced a neurological deterioration can be included into the analyses. Some patients will have received surgical treatment (with or without subsequent radiation or systemic therapy) before MESCC could occur, thereby obscuring the time to neurological deficits. Hence, (surgical) treatment may be considered a 'competing risk' for the onset of MESCC and the true mean time to neurological deficits may have been longer or shorter. Unfortunately, it is virtually impossible to study the natural course of advanced cancer in order to avoid such bias [34]. Third, inclusion in our cohort was based on an eventual surgical intervention. This will have introduced selection bias, since we did not include patients with MESCC-related neurological deficits who underwent primary radiotherapy. It is unclear whether such patients have a comparable timeframe, and whether determinants of timing of neurological deficits overlap with those in our surgical cohort. Finally, the retrospective nature of this study may have led to information bias. This also led to using the Frankel score for defining neurological deficits – as the necessary information for this score was available consistently – rather than a more detailed neurological evaluation. Nonetheless, multiple different electronic data records were consulted, including those of the GP containing written summaries of all the medical consultations by the patients. Therefore, the results from the current study are suggested to yield a valid representation of the time from any symptoms related to spinal metastases until the onset of neurological deficits.

CONCLUSION

In conclusion, the median time from any symptoms related to spinal metastases until the onset of neurological deficits was 64 days varied based on different patient and disease related factors. A considerable number of patients develops neurological deficits while under active medical surveillance, suggesting a lack of awareness/urgency upon the diagnosis and treatment of metastatic spinal disease. In general, the results from this study should serve to increase awareness amongst (oncological) health-care providers of the limited time available for the identification and treatment of metastatic spinal disease.

CONFLICTS OF INTEREST

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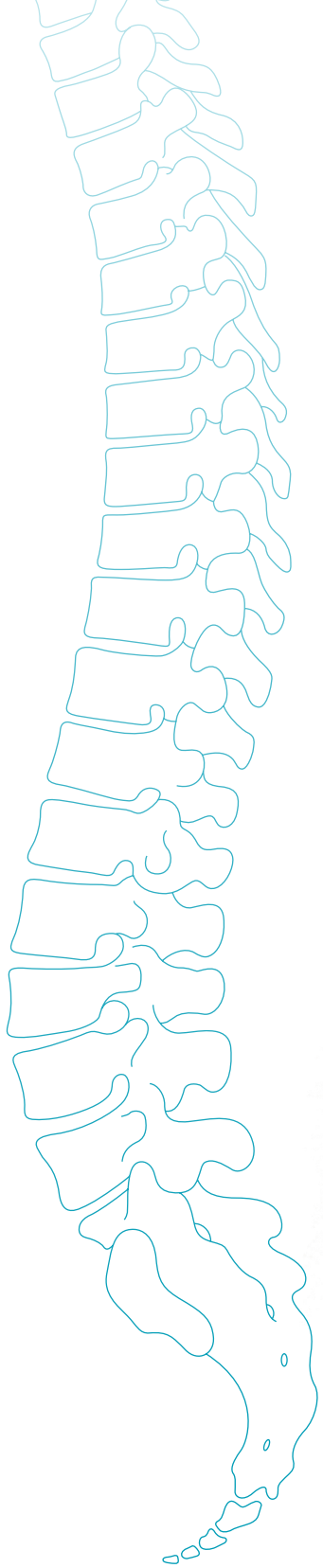

CHAPTER 7

The Use of Red Flags during the Referral Chain of Patients Surgically Treated for Symptomatic Spinal Metastases

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ABSTRACT

BACKGROUND

The use of so-called 'red flags' may be beneficial in identifying patients with metastatic spinal disease. This study examined the utility and efficacy of these red flags in the referral chain of patients surgically treated for spinal metastases.

METHODS

The referral chains from the onset of symptoms until surgical treatment for all patients receiving surgery for spinal metastases between March 2009 and December 2020 were reconstructed. The documentation of red flags, as defined by the Dutch National Guideline on Metastatic Spinal Disease, was assessed for each healthcare provider involved.

RESULTS

A total of 389 patients were included in the study. On average, 33.3% of red flags were documented as present, 3.6% were documented as absent and 63.1% were undocumented. A higher rate of red flags documented as present was associated with a longer time to diagnosis, but a shorter time to definitive treatment by a spine surgeon. Moreover, red flags were documented as present more often in patients who developed neurological symptoms at any point during the referral chain than those who remained neurologically intact.

CONCLUSIONS

The association of red flags with developing neurological deficits highlights their significance in clinical assessment. However, the presence of red flags was not found to decrease delays prior to referral to a spine surgeon, indicating that their relevance is currently not sufficiently recognized by healthcare providers. Raising awareness of symptoms indicative of spinal metastases may expedite timely (surgical) treatment and thus improve treatment outcome.

Keywords: Spinal metastases, metastatic spinal disease, surgery, delay, red flags

INTRODUCTION

As metastatic spinal disease progresses, patients may experience mechanical pain, radiculopathy or neurological deficits due to epidural spinal cord compression [1]. Early diagnosis and treatment are critical in avoiding irreversible neurological damage and achieving the best clinical outcome [2–4].

Patients presenting with back pain as a symptom of advanced cancer often experience a delay of several weeks before being diagnosed with spinal metastases [5]. This delay in diagnosis and treatment may be caused by patients not seeking medical attention in a timely manner and/or health-care providers not recognising the symptoms [6]. Additionally, the high prevalence of non-specific back pain in the general population makes it difficult for healthcare providers to distinguish between a serious underlying pathology (i.e., advanced cancer) and/or a common benign condition.

To reduce delay in the diagnosis and treatment of spinal metastases, it is essential that both patients at risk and healthcare providers are cognizant of potential early warning signs. To this end, the Netherlands Comprehensive Cancer Organisation (IKNL) has identified five 'red flags' that are indicative of metastatic spinal disease and included them in the Dutch national guideline on metastatic spinal disease [7]. These red flags include new onset of back pain, progressive back pain, nocturnal back pain, pain on palpation and poor general health (e.g. weight loss) [8]. Previous research has demonstrated that the presence of these red flags may increase the likelihood of metastatic spinal disease, with multiple red flags showing the highest predictive value [9,10]. However, no studies have examined the use of red flags in clinical decision making.

The primary aim of this study was to evaluate the documentation of red flags by Dutch healthcare providers for patients with and without a pre-existing malignancy across primary, secondary, and tertiary healthcare. As a secondary aim, we sought to better comprehend how the presence of red flags influences the referral chain by analysing the association between red flags and delays in the referral chain. We hypothesized that the presence of red flags leads to expedited diagnosis, referral, and treatment. Additionally, we aimed to assess the clinical significance of red flags by correlating their presence to the development of neurological symptoms. We hypothesized that the presence of red flags is associated with faster neurological decline.

MATERIALS AND METHODS

PATIENT POPULATION AND STUDY DESIGN

The institutional review board approved a waiver for informed consent for this single-centre retrospective cohort study (protocol no. 17-695/C). This study included patients aged 18 years and older who underwent primary surgery for symptomatic spinal metastases between March 2009 and December 2020 at the University Medical Centre Utrecht in the Netherlands. Additionally, patients with spinal localisations of haematological tumours, including multiple myeloma or malignant lymphoma, were included due to similarities in clinical presentation and surgical treatment compared with spinal metastases originating from solid tumours. Patients with sacral metastases or primary tumours of the spine and patients who received revision surgery were excluded from the study.

DATA-COLLECTION

Data on patient age, sex, tumour histology, history of cancer, neurological status, healthcare providers involved in the referral chain, levels of care (i.e., primary, secondary, or tertiary care hospital) and documentation of the five (IKNL) red flags were extracted from patients' electronic medical records. Neurological deficits were defined as grades A-D on the American Spinal Injury Association (ASIA) scale. Referral chains from the first symptoms related to metastatic spinal disease until surgery were reconstructed using data from the hospital's medical records as well as the patients' records kept by their general practitioners.

The interval between the onset of symptoms caused by the spinal metastasis/metastases and the start of definitive treatment was defined as the total delay, which could be divided into four sub-intervals: patient delay (period between the onset of symptoms and patient's first contact with a healthcare provider), diagnostic delay (time interval between the first medical consultation and confirmed diagnosis of spinal metastases), referral delay (time interval between the diagnosis date and referral to the spine surgeon), and treatment delay (time interval between referral to the spine surgeon and surgical treatment). The combined diagnostic, referral and treatment intervals were referred to as doctor delay.

OUTCOMES

The medical records of each healthcare provider involved in the referral chain were examined to report the presence or absence of all 5 red flags (new onset of back pain, progressive back pain, nocturnal back pain, pain on palpation, and poor general health). The average number of red flags documented as present or absent, as well as the number of undocumented red flags were calculated for each patient across all healthcare providers.

STATISTICAL ANALYSIS

Continuous variables were reported as means with standard deviations or medians and interquartile ranges, depending on their distribution. Categorical variables were reported as frequencies and percentages.

To compare the documentation of red flags between patients with and without previous malignancy and to compare the presence of red flags between patients who had developed neurological symptoms upon final consultation versus patients who had not, Mann-Whitney U tests were used (for non-normally distributed data). Sub-analyses using Mann-Whitney U tests were conducted to compare the percentage of documented red flags of each of the individual red flags between patients with pre-existing malignancy and patients without. To assess the relationship between the presence of red flags and different delay intervals, the percentage of red flags documented as present was stratified into five 20% intervals (for interpretability) and delay intervals between these strata were compared using Kruskal-Wallis analyses. Analyses were held to a significant threshold of $p \leq .05$. All analyses were conducted using IBM SPSS Statistics, version 24 (IBM Corp).

RESULTS

A total of 400 patients who underwent surgery for symptomatic spinal metastases within the study period met the inclusion criteria. In 11 patients, no data could be retrieved from their general practitioner (n = 11), leaving a total of 389 patients to be included in the current study (**Figure 1**).

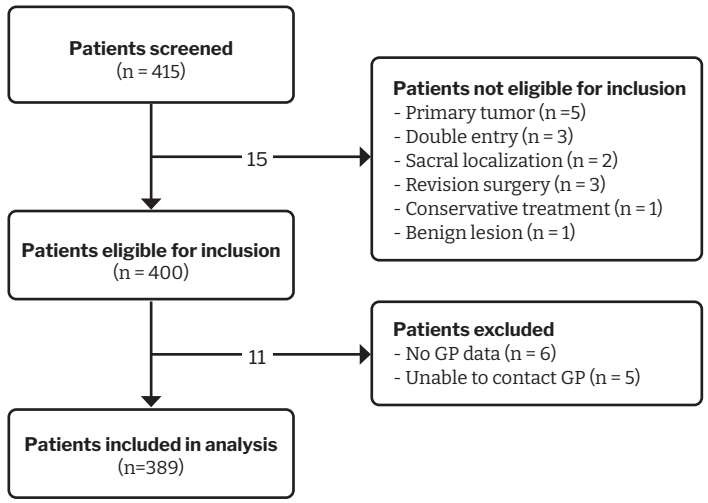

FIGURE 1. Flowchart of patient inclusion.

Table 1 provides the characteristics of all 389 patients, which comprised 231 patients with a pre-existing malignancy and 158 patients without. Overall, 218 (56.0%) of patients were male. The mean age at time of surgery was 62.3 years (SD ± 11.5 years). The most common primary tumours were urogenital (21.9%), haematological (19.8%) and breast cancer (18.8%). A median of 2 (IQR: 2-3) healthcare providers were involved in the referral chain before referral to the spine surgeon. Of all patients, 147 (37.8%) had developed neurological symptoms before definitive treatment, while the remaining 242 (62.2%) were neurologically intact at the final consultation.

TABLE 1. BASELINE CHARACTERISTICS

Characteristic	All patients n = 389
Age at surgery (years), mean (SD)	62.3 (11.5)
Sex, male, n (%)	218 (56.0%)
Tumour histology, n (%)	
Urogenital	85 (21.9%)
Haematological	77 (19.8%)
Breast	73 (18.8%)
Lung	58 (14.9%)
Gastrointestinal	25 (6.4%)
Gynaecologic	6 (1.5%)
Other	56 (14.4%)
Unknown	9 (2.3%)
Number of HCPs involved before treatment, n (%)	
One	78 (20.1%)
Two	149 (38.8%)
Three	115 (29.6%)
Four	34 (8.7%)
Five or more	13 (3.3%)
Type of first HCP involved, n (%)	
General practitioner	253 (65.0%)
Emergency unit	30 (7.7%)
Oncological caregiver	81 (20.8%)
Radiation oncologist	6 (1.5%)
Orthopaedic surgeon	4 (1.0%)
Neurologist	9 (2.3%)
Other	6 (1.5%)
Level of care on entry, n (%)	
Primary	253 (65.0%)
Secondary	91 (23.4%)
Tertiary	45 (11.6%)

SD: standard deviation, HCP: healthcare provider

DOCUMENTATION OF RED FLAGS

On average, 36.9% of the potential 5 red flags per healthcare provider were documented prior to the diagnosis of spinal metastases, with 90.3% documented as present. A statistically significant difference (p=0.028) was found in the documentation of red flags between patients without a history of cancer (median 40%; IQR 32-45%) and those with a pre-existing malignant diagnosis (median 35%; IQR 28-40%). Additionally, documentation of red flags was lowest in primary care (32.2%) compared with secondary (35.6%) and tertiary care (40.4%), these data are summarized in **Table 2**.

TABLE 2. MEAN PERCENTAGE OF DOCUMENTED RED FLAGS STRATIFIED FOR PATIENTS WITH AND WITHOUT A PRE-EXISTING MALIGNANCY AND THE TYPE OF CARE

Type of care	Total n = 389	Pre-existing malignancy n = 231	No pre-existing malignancy n = 158
% red flags documented			
Primary care	32.2%	30.2%	33.8%
Secondary care	35.6%	32.8%	38.8%
Tertiary care	40.4%	39.8%	41.2%

Of the red flags, new onset of back pain was the most frequently documented (in 97.8% of healthcare providers at any time point), whereas nocturnal back pain and poor general health were documented the least (8.5% and 9.2%, respectively), as summarized in **Table 3**.

TABLE 3. MEAN PERCENTAGE OF INDIVIDUAL DOCUMENTED RED FLAGS (AS EITHER PRESENT OR ABSENT)

	Documented
Red flag	
Nocturnal back pain	8.5%
New back pain	97.8%
Progressive back pain	50.2%
Pain on palpation	18.7%
Poor general health	9.2%

GUIDANCE OF THE REFERRAL PROCESS THROUGH RED FLAGS

The presence of red flags was significantly correlated with longer diagnostic delay and shorter treatment delay, as demonstrated by **Table 4**. No significant association between the presence of red flags and any other delay intervals was identified.

TABLE 4. KRUSKAL-WALLIS TEST COMPARING THE MEDIAN (IQR) DELAY (IN DAYS) ACROSS FIVE DIFFERENT PATIENT CATEGORIES, based on the percentage of red flags documented as present out of all documented red flags

	% of red flags documented as present			
	0-60% n=15	61-80% n=47	81-100% n=314	*P-value*
Delay interval				
Total delay	59	130	97	*0.078*
Patient delay	14	15	19.5	*0.652*
Doctor delay	37	71	53	*0.120*
Diagnostic delay	3	47	22	***<0.001***
Referral delay	4	11	7	*0.290*
Treatment delay	16	8	6	***0.013***

RED FLAGS AS PREDICTORS FOR NEUROLOGICAL DEFICITS

In 260 patients (66.8%), all documented red flags were present. Of those who had developed neurological deficits at any point in the referral chain, all documented red flags were present in 109 patients (74.7%). Conversely, all documented red flags were present in 151 (62.7%) patients who remained neurologically intact. The presence of red flags at any point during the referral chain was significantly more prevalent among those who developed neurological deficits before definitive treatment compared with patients who remained neurologically intact (p = 0.006).

DISCUSSION

This study aimed to investigate the use and utility of a set of five red flags in patients with symptomatic spinal metastases who underwent surgical intervention. Despite the opportunity for all healthcare providers to document 5 red flags (regardless of whether any of the red flags were actually raised), only 36.9% were recorded. This suggests that clinicians may not be sufficiently aware of the symptoms indicating severe spinal pathology and as a result may not ask for (the presence of) red flags. Contrary to the initial hypothesis, a higher number of red flags documented as present did not lead to a faster diagnosis and referral. However, a higher percentage of red flags documented as present was associated with an increased risk of developing neurological deficits before definitive treatment, confirming the second research hypothesis. These findings emphasize the need for systematic use of red flags, as patient outcome is largely dependent upon neurological status before treatment [11].

Back pain is a frequent complaint among primary care patients, with up to 70% of people experiencing an episode of (non-specific) back pain in their lifetime [12]. While it is generally self-limiting, a small percentage of patients may have a serious underlying condition such as metastatic spinal disease. Studies have shown that the prevalence of spinal malignancy in patients with back pain ranges from 0% to 0.7%, while it increases to 7.0% in hospital settings [13,14]. The current study found that 36.9% of red flags were documented, a rate similar to that reported in a study by Ferguson et al. (33%) [15], but lower than that reported by Leerar et al. (63.7%) [16]. Both studies, however, did not focus solely on red flags indicative of spinal metastases, but also examined red flags indicative of fractures or infectious disease. Additionally, the studies by Leerar et al. and Ferguson et al. examined the documentation of red flags by physical therapists, while the current study looked at the percentage of documented red flags by general practitioners and hospital-based medical specialists. Ferguson and co-workers found that the documentation of red flags improved from 33% to 65% after an active intervention, consisting of the development and implementation of action plans, was conducted. The results from their study clearly underline the potential for education to help raise awareness and have doctors explicitly ask for the presence of red flags. It has previously been suggested that despite the inclusion of red flags in clinical guidelines, patients are not always evaluated in line with the recommendations from the guidelines [17]. This is also supported by a study of Amorin-Woods et al. who demonstrated that only 5% of medical practitioners followed the recommendations of clinical guidelines to identify red flags in patients with low back pain [18]

Healthcare providers documented fewer red flags in patients with a pre-existing malignancy compared with those without. Patients with a pre-existing malignancy may be more likely to visit their oncology professional, who may be less inclined to screen for red flags associated with spinal metastases as the combination of a pre-existing malignancy and back pain may already warrant further diagnostics. Additionally, these patients may have more other complaints or side effects of cancer treatments, which could reduce the focus on back pain and associated symptoms. Moreover, symptoms such as poor general health are not specific to spinal metastases and may not raise immediate new concerns or suspicions in oncological patients. In contrast, patients without a pre-existing malignancy will likely visit their general practitioner where an extensive medical history and physical examination focussing on the primary complaint, i.e., back pain, takes place.

The current investigation of the documentation of red flags revealed that healthcare providers documented specific red flags such as new onset of back pain (97.8%) more often than symptoms like nocturnal pain and poor general health (8.5% and 9.2%, respectively) regardless of whether they were documented as present or absent. This discrepancy in documentation could be due to the fact that new onset of back pain is frequently the primary reason for seeking medical aid, whereas poor general health is usually reported in later stages of malignant disease [19,20]. These results suggest that healthcare providers may not be screening for poor general health or nocturnal pain during the initial consultation, which could explain the low documentation rate observed in the current study.

In the current study, it was found that treatment delay (i.e., the interval between referral to the spine surgeon and surgical treatment) was significantly reduced as the number of red flags documented as present increased. Interestingly, an increased presence of red flags was associated with a longer diagnostic delay (i.e., the interval between the first medical consultation and confirmed diagnosis of spinal metastases), indicating a potential issue in how red flags are currently being used to aid healthcare providers in their clinical decision making. In the presence of red flags, patients would preferably be referred and/or diagnosed in an accelerated manner. It was also found that presence of red flags was not significantly associated with a reduction in patient delay. A possible explanation for this finding may include patients who have a known pre-existing malignancy not properly being informed about the existence and importance of red flags or not reporting on them. Furthermore, while for oncological patients, education about red flags as warning signs for spinal metastases could potentially reduce patient delay, this is not feasible for those unaware of an underlying malignancy. Another potential explanation is that red flags are simply less frequently present in the early stages of the referral chain.

Since this study only included patients with confirmed metastatic spinal disease, no conclusions can be drawn on the specificity or sensitivity of the described red flags. However, in the current study, the presence of red flags was associated with neurological deterioration prior to definitive treatment. This finding suggests that the presence of (multiple) red flags may be indicative of a more advanced stage of metastatic spinal disease, emphasizing the importance of red flags for a timely diagnosis, referral and treatment.

This study has limitations that need to be taken into account when interpreting the results. Firstly, the current study was retrospective with its inherent risks of bias. Only red flags that were documented in the electronic patient records could be considered, potentially leading to an underestimation of red flags that were present. Healthcare providers may not have documented the red flags that were absent in their patient, causing a potential discrepancy between red flags that were documented and the red flags that were discussed but not recorded during medical consultation. Nevertheless, it is likely that the underreporting of red flags was consistent across all patients included and thus would not have influenced the conclusions. Moreover, a prospective study on red flags for metastatic spinal disease would be difficult to conduct due to the low incidence of metastatic spinal disease in the general population, which adds to the value of the current study. Secondly, only patients who received surgical treatment were included in this study; those who underwent radiotherapy or systemic treatment were not included. Healthcare providers may have been more likely to screen for red flags in surgical patients, as they are generally more severely affected. This may have resulted in a higher proportion of red flags documented as present in these patients. Lastly, this was a single centre study, thus the results may not be applicable to other locations. Nonetheless, data was collected from referral chains throughout the entire region, suggesting that the results are representative for the Netherlands.

In conclusion, the current study provides insight into the use of red flags in the referral process of patients undergoing surgical treatment for symptomatic spinal metastases. Documentation of red flags among healthcare providers was limited, and the presence of red flags was not associated with shorter delays prior to referral to the definitive caregiver. However, a greater proportion of red flags documented as present was associated with poorer neurological outcomes. This finding supports the notion red flags are important in clinical decision making and suggests that promoting the appropriate use of red flags may help reduce delays and clinical outcomes for patients with metastatic spinal disease.

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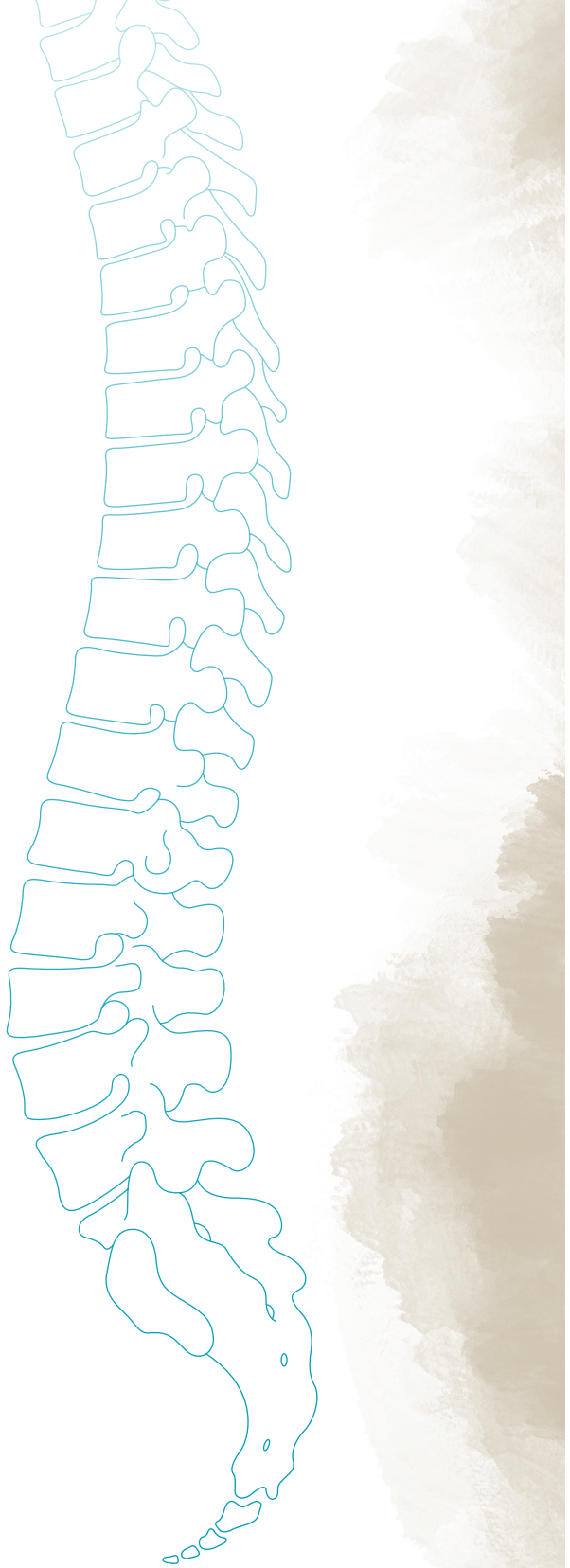

CHAPTER 8

Summarizing Discussion

Advances in cancer care have led to increased life expectancy for cancer patients, but also a rise in cases of metastatic spinal disease [1,2]. In the early stages of metastatic spinal disease, non-surgical treatments such as systemic anti-cancer therapy or palliative radiotherapy may be sufficiently effective [3]. However, if left untreated, spinal metastases can lead to intractable mechanical pain, compromise bone integrity, or induce neurological deficits, which may require invasive surgical intervention [4]. Given the longer survival period of these patients, it is crucial to promote the preservation and restoration of their quality of life during the palliative phase of malignant disease.

The management of spinal metastases is often intricate and requires a multidisciplinary approach. Early diagnosis can be challenging due to the similarity of symptoms to non-cancer-related back or neck pain, which may lead to delayed diagnostic procedures and referrals [5]. To develop future strategies aimed at identifying and addressing delays in the diagnosis and treatment of patients with metastatic spinal disease, a systematic and more uniform approach is necessary [6]

The research presented in this thesis highlights the significance of prompt diagnosis, referral, and treatment of patients with metastatic spinal disease for favourable clinical outcomes and cost-effective care. Additionally, this thesis establishes the groundwork for forthcoming strategies aimed at mitigating various forms of delay. The principal findings, clinical practice implications, ongoing difficulties and future perspectives will be deliberated in the ensuing sections.

THE IMPORTANCE OF TIMELY TREATMENT

The importance of timely diagnosis, referral, and treatment of patients with metastatic spinal disease is widely acknowledged and is believed to have a substantial influence on patient outcome [7–10]. However, the detrimental effects of delayed diagnosis, referral, and treatment were previously not completely understood. Due to its progressive nature, untreated spinal metastases pose a considerable risk of irreversible complications such as pathologic fractures and neurological deficits, occurring in 25%-50% of all patients with spinal metastases [11–13]. To fully comprehend the consequence of delayed treatment, this thesis examined a cohort of over 300 patients who received surgical treatment for their metastatic spinal disease at a single tertiary care centre. The urgency of delivered surgical treatment for each patient as determined by the treating physician was classified into one of three categories: Emergency (<24 hours), urgent (1-3 days) and scheduled (>3 days). Following criteria established by the Global Spine Tumour Study Group (GSTSG), patients were divided into two groups based on the three-day cut-off: [14] (1) patients who could undergo elective and scheduled surgery after presenting at the spine surgery department in the absence of alarming symptoms, and (2) patients who had to undergo emergency surgery within three days after presenting at the spine surgery department due to alarming symptoms (e.g., neurological deficits, signs of gross mechanical instability). The first group of patients represented 'timely treatment', while the second group represented 'delayed treatment'. By comparing the outcomes of these two groups, the impact of delayed treatment on various outcome measures was thoroughly evaluated.

In palliative oncology care, the primary focus is typically on preserving or restoring quality of life. Therefore, when comparing various treatments or interventions, the impact on quality of life is usually a crucial consideration. Previous research has linked emergency surgery with lower survival rates in patients with metastatic spinal disease [10]. Thus, comparing timely and delayed treatment at the mid- or long-term may lead to a biased view due to a higher mortality rate following delayed treatment. As a result, short-term outcomes must also be considered when assessing the differences between timely and delayed treatment. In **Chapter 2**, surgical and direct postoperative parameters were compared between patients who received timely or delayed treatment. Among the surgical parameters, the largest difference was observed in the surgical approach utilized. Timely intervention allowed for less invasive techniques in 53% of cases, whereas delayed treatment permitted this in only 13% of cases [15]Delayed treatment, required by 80% of patients with neurological deficits, necessitated more invasive surgeries, leading to longer operating times, over twice the blood loss, and increased transfusion needs, which negatively affect survival rates in these patients [16–19]. Furthermore, delayed treatment doubled the complications rate (48% vs. 26%) and worsened neurological and am-

bulatory status. Hospital stay was almost twice as long (13 vs 5 days), and fewer patients could return home post-surgery (41% vs 83%). This is important, as returning home is vital for quality of life, especially in patients with a limited life-expectancy.

Chapter 3 examined mid- and long-term quality of life, functional status, and survival in the same two patient cohorts receiving timely or delayed treatment. Timely treatment was associated with a Karnofsky Performance Status (KPS) score of 70, versus 60 with delayed treatment [20]. Both treatments showed a 10-point KPS increase, maintained up to 6 months [20]. This 10-point difference is crucial, as it marks the transition from independence to requiring assistance [21]. Previous research also reported a 10-point KPS increase, regardless of baseline scores [22]. This suggests that KPS score declines are largely irreversible, underscoring the importance of timely intervention. Quality of life, measured by EQ-5D scores, showed preoperative differences between timely (0.57) and delayed treatment (0.24). Both treatments increased EQ-5D scores at 3 and 6 months, with delayed treatment showing a greater increase, equalizing scores at 6 months. This might be due to patients adapting to their neurological condition, a 'response shift' [23]. Delayed treatment reduced survival substantially, yielding a one-year survival rate of 51% compared to 70% for timely treatment. Neurological status could drive this survival difference, as it greatly impacts overall survival [24].

To ensure prompt diagnosis, referral, and treatment, it is important to optimize referral pathways for oncological patients. This will likely require improvements in the coordination and communication between healthcare providers, leading to more efficient patient management. However, more extensive diagnostics and referrals may result in increased costs, potentially deterring healthcare systems from investing in such improvements. Nevertheless, any improvement in treatment outcome due to timely treatment may subsequently reduce the clinical and aftercare costs of patients considerably, potentially even outweighing the upfront costs of enhanced and more effective referral pathways. In **Chapter 4**, pre-surgical, in-hospital, and aftercare costs were compared for timely and delayed treatments up to three months post-treatment. Timely treatment costs were approximately €20,000, while delayed treatment costs reached €34,000 [25]. Aftercare costs contributed the most to this difference, averaging €4,000 for timely treatment and €14,000 for delayed treatment. Considering the costs per quality-adjusted life year (QALY), timely treatment displayed a more favourable cost-utility ratio. Thus, investing in optimized referral patterns may lead to better clinical outcomes at lower overall costs.

When comparing timely treatment to delayed treatment, it is essential to consider the factors driving the differences in treatment outcomes. A critical factor in the difference in treatment outcomes is baseline neurological status. The relationship between neurological deficits and unfavourable treatment outcomes has been well-established over the past few decades. Various studies have demonstrated the negative impact of neurological deficits on functional status, quality of life, and survival, both directly and indirectly [4,10,18,26–31]. However, in both **Chapters 2 and 3**, the association between delayed treatment and inferior outcomes persisted even after adjusting for the preoperative neurological status of patients. This suggests that other aspects of delayed treatment also warrant consideration. Firstly, it has been demonstrated that surgery during after-hours results in higher morbidity and mortality rates [31,32]. Similarly, admission during weekends has been linked to increased delays in treatment [33,34]. It is possible that the surgeon on call, as well as the supporting staff, may not be as experienced in the treatment of metastatic spinal disease as a specialized oncological spine surgeon. Secondly, the presence of neurological deficits necessitates prompt surgical intervention. In the case of neurological deterioration, emergency surgery is commonly preferred within 24-48 hours to maximize the chances of neurological recovery or prevent further neurological decline [35–37]. However, the limited time available for a proper patient work-up may compromise the optimal treatment strategy [38].

Besides differences in their neurological status, the two treatment cohorts analysed in **Chapters 2, 3 & 4** were almost indistinguishable in terms of age, sex, comorbidities, primary tumour-associated median survival, prior systemic and/or radiotherapeutic treatments, number of affected levels, and the presence of other metastases. The primary difference between these two cohorts was that one progressed to the development of neurological deficits while the other was diagnosed, referred, and treated before any neurological compromise had occurred. The vast and favourable differences in treatment outcomes between the two groups underscore the importance of timely treatment as one of the most crucial factors in achieving a satisfactory outcome in metastatic spinal disease.

PATIENT JOURNEYS IN METASTATIC SPINAL DISEASE

To mitigate the detrimental effects of delayed treatment, improving timely diagnosis, referral and treatment is paramount. However, there is unlikely to be a one-size-fits-all solution for expediting treatment in patients with metastatic spinal disease. To inform future strategies aimed at timely treatment, it is important to understand the various stages that comprise the patient journey from the onset of symptoms to definitive treatment. For the current thesis, an established framework identifying and analysing factors contributing to delays in diagnosis, treatment, and referral processes for primary cancer was tailored towards metastatic spinal disease. This adapted model identifies several critical milestones in the referral pathway that define the cut-offs between different phases in the patient journey. The first of these is the detection of bodily changes (i.e., symptoms) by the patient, which marks the start of patient delay. During patient delay, the patient must first appraise the symptoms, decide to seek medical help, and then schedule an appointment. The next milestone is the initial consultation with a healthcare provider, which signals the end of patient delay and the start of diagnostic phase. During this phase, the healthcare provider(s) involved must also appraise the symptoms, potentially refer the patient, and/or perform diagnostic tests. Once a definitive diagnosis of spinal metastases is established, the diagnosis delay phase is concluded. Of particular interest to the complex, multidisciplinary scenario of metastatic spinal disease is the subsequent referral delay. During this phase, the healthcare provider who made the diagnosis must categorize definitive treatment into broad categories, such as systemic, radiotherapeutic, or surgical treatment. Once the patient has been referred to their definitive caregiver, the final phase, treatment delay, begins. Treatment delay is complete upon definitive treatment, regardless of the treatment modality.

Chapter 5 analysed patient journeys of a cohort with symptomatic spinal metastases, focusing on delay intervals. The median total delay was 99 days, comprising patient delay (19 days), diagnostic delay (21.5 days), referral delay (7 days), and treatment delay (8 days) [39]. These findings are in line with previous studies reporting total delays between 73.5 and 90 days, underlining the delicate balance between timely and delayed treatment and the need for strategies to reduce these delays [35,40,41]. When analysed separately for patients with known (metachronous) and unknown (synchronous) cancer history, median total delay was identical, despite differences in separate delay intervals. Synchronous metastasis was linked with longer patient (25 vs 14 days) and diagnostic delays (34 vs 15 days), but shorter referral (4 vs 9.5 days) and treatment delays (5 vs 11 days), balancing the total delay across both groups [39]. This suggests different strategies may be needed to optimize timely diagnosis, referral, and treatment for patients with synchronous versus metachronous metastases.

Chapter 6 explores the time until irreversible neurological symptoms occur in patients with metastatic spinal disease, a crucial factor given only 20-40% of patients with MSCC achieve complete resolution of neurological symptoms post-treatment [35,36,42]. Earlier research reported 7-8 weeks between initial symptoms and onset of neurological deficits [43–45]. Our study, encompassing 141 patients who developed neurological deficits before surgery, found a median time of 64 days [46]. We further analysed the influence of patient- and disease-related factors on this interval, comparing synchronous and metachronous metastases, spinal metastasis localisation, and various primary tumours. This is key, as rapid neurological deterioration correlates with inferior postoperative neurological recovery, lower local tumour control, and reduced survival rates [8,47–50]. Our findings showed that metachronous metastases associated with a faster neurological decline than synchronous metastases, potentially due to treatment-resistant malignancy components. Thoracic spinal metastases trended towards shorter time to neurological deficits compared to lumbar and cervical lesions, likely due to the narrower thoracic spinal canal and reduced spinal cord blood flow [51,52]. Thoracic symptoms, even in patients with non-specific back pain, should therefore prompt immediate concern [5,53]. Notably, patients with haematological tumours exhibited the shortest time to neurological deficits, underscoring the need for vigilance especially since their generally more favourable survival prognosis.

Chapter 6's secondary objective analysed the occurrence of neurological deficits in relation to delay intervals. It found that 20% of neurological deficits occurred during patient delay, 43% during diagnostic delay, and 38% during referral delay. This highlights inefficiencies in referral pathways, as nearly half of all neurological deficits occurred in patients already diagnosed with metastatic spinal disease awaiting referral. Interestingly, neurological deficits' development didn't correlate with longer referral delays. Patients neurologically intact at the time of definitive treatment experienced the longest total delays, possibly due to neurological deficits' emergent nature expediting the referral process once they occur [34,40]. However, in patients who developed neurological deficits, even the preceding delay intervals were not significantly longer than those in neurologically intact patients. It is possible that two opposing mechanisms are at play, effectively neutralizing each other. One mechanism involves treatment delays potentially leading to the development of neurological deficits. Conversely, patients who have received comprehensive evaluations and are considered low risk for neurological deficits may be justifiably managed with decreased urgency. This phenomenon has previously been described as the waiting time paradox, referring to the counterintuitive observation that longer waiting times for cancer treatment can sometimes be associated with better outcomes [54,55]. In some patients, longer delay intervals may reflect a more careful and thorough diagnostic

and work-up process and subsequent risk assessment, resulting in a longer time to treatment.

Chapter 7 investigated the documentation of five 'red flags' indicative of metastatic spinal disease, as defined by the Netherlands Comprehensive Cancer Organisation (IKNL) [56]. These red flags include new onset back pain, progressive back pain, nocturnal back pain, pain on palpation, and poor general health (e.g., weight loss) [57]. The study found that 33.3% of red flags were documented as present, 3.6% were documented as absent, and 63.1% were undocumented [58]. Despite potential disparities due to the study's retrospective nature, these findings align with previous report rates of 33-64% [59,60]. Prior studies indicate that multiple red flags may increase the likelihood of metastatic spinal disease [61,62]. Therefore, a systematic screening for all red flags in patients experiencing (low) back pain is crucial.

REDUCING DELAY

The results of this thesis affirm that accelerating the diagnosis, referral, and treatment of metastatic spinal disease cannot be achieved by a single intervention. Instead, it necessitates numerous small endeavours across all aspects of the patient journey. Depending on the distribution of delays throughout the referral chain, several potentially effective strategies can be contemplated for each of the four delay intervals. In the subsequent sections, various recommendations are provided based on different delay intervals, oncological history, and types of care. These recommendations aim to address specific issues related to each situation and ensure proper management of patients with spinal metastases. **Table 1** offers a concise summary of these recommendations.

The second largest contributor to the total delay experienced was patient delay. Strategies aimed at reducing patient delay will undoubtedly involve extensive patient education and empowerment. In a study by Guzik et al., patients who noticed a decline in their neurological status still exhibited a mean patient delay of four days from the onset of neurological deterioration [63]. Moreover, in the same study, 20% of all diagnosed neurological deficits were detected during routine medical examinations, indicating that patients are often unaware of critical symptoms requiring urgent medical consultation. As 75% of neurological deficits occur outside of the hospital, adequately informing patients about when to seek medical attention is crucial [63]. When targeting patients for educational purposes, it is essential to differentiate between those with a previously established malignancy and those without. In the case of oncological patients, new onset back pain should lead to immediate medical consultation. In a study conducted by Caraceni et al., it was found that for oncological patients, 92.5% of experienced pain was related to the tumour, while only 2.3% of the pain was not connected to the

tumour or its treatment [64]. To assist with oncological patient education, the Dutch national guideline on spinal metastatic disease includes a patient brochure aimed at informing cancer patients about alarming symptoms [65]. Targeting patients who are unfamiliar with malignant disease is one of the more challenging aspects, as lower back pain is one of the most common complaints in the general population [5,53]. In approximately 25-50% of patients with MSCC, this was the initial manifestation of malignant disease, making it practically impossible to prevent [66,67]. However, a previous study on patients treated with radiotherapy for their spinal metastases demonstrated the relevance of attempting to do so for the other 75-50%, where the median delay from the onset of MSCC until radiotherapeutic treatment was 5.5 days for patients who suspected a relationship between the symptoms and their oncological history and 17 days for those who did not [68]. Therefore, general patient education tools (e.g., the broadly informative website thuisarts.nl) should include clear instructions on alarming symptoms that require immediate medical consultation. Nevertheless, patient delay will always face generic challenges such as limited health literacy, cultural beliefs and practices, fear and anxiety, access to care or a lack of symptoms or symptom specificity. If patient education does not adequately address these factors, it is improbable that any educational program will genuinely have a serious impact on patient delay.

Unsurprisingly, the biggest contributor to total delay is diagnostic delay. In a previous study by Bach et al., even after presenting with symptoms indicative of MSCC, patients still experienced a mean diagnostic delay of 23 days, which is consistent with our findings [43]. As with patient delay, it is crucial to differentiate between patients with and without a prior oncological diagnosis when developing strategies aimed at reducing diagnostic delay. In the case of patients without a prior diagnosis, timely identification remains challenging as 70% of individuals experience an episode of back pain in their lifetime71,72 The incidence of malignant spinal disease in all patients with lower back pain is approximately 0.7% [69]. Nevertheless, the prevalence increases almost tenfold to 5-7% in the hospital setting [70–72]. The systematic utilization and reporting of red flags may prove advantageous in reducing delays. In a previous study, documentation of red flags increased from 33% to 65% after an active intervention consisting of action plan development and implementation [59]. The actual potential of red flags in reducing delays has yet to be confirmed [58]. In the case of patients with a history of cancer, new onset back pain should be regarded as spinal metastases until proven otherwise. A previous study analysing oncological patients with new onset back pain found that 60% of patients without abnormalities on neurological examination still exhibited radiologic evidence of spinal metastases [73]. In patients diagnosed with MSCC, 90% have concomitant back pain, which is often present as a prodromal symptom for several weeks before the onset of any neurological

symptoms [53,74]. In patients with a history of cancer and new onset back pain, diagnostic imaging using MRI should be performed within a few days to confirm or refute the diagnosis, even if the healthcare provider is not equipped to provide definitive care [67]. However, there may be instances where an MRI is not immediately accessible, or a patient may not be suitable for MRI. In such situations, a Computerized Tomography (CT) scan serves as the second most sensitive alternative for identifying large, symptomatic lesions. CT scans can provide a detailed image of the bony structures of the spine and can detect lytic or sclerotic changes related to metastatic disease. While a CT scan may not be as effective as an MRI in detecting early marrow involvement or spinal cord compression, it can confirm or rule out significant bony metastases, which often cause pain and can lead to spinal instability. Unpublished data from the patient cohort examined in this thesis indicates that in primary care, the median time to referral was 8 days for patients without conventional radiographs, compared to 47 days for patients with conventional radiographs that displayed no abnormalities. This observation suggests that primary healthcare providers may be falsely reassured by the absence of abnormalities on conventional radiographs, potentially leading to delays in appropriate care for patients with spinal metastases. Conventional radiographs are less sensitive for detecting early spinal metastasis, typically requiring 30-50% vertebral destruction before spinal metastases become visible [75]. In a study by Mattes et al., which describes an educational campaign aimed at expediting and enhancing multidisciplinary care for MSCC, the use of whole-spine MRIs increased from 44% to 64% in the first year after this Quality Improvement (QI) initiative [76]. Additionally, data from the same cohort showed that the number of referrals between the initial presentation to any healthcare provider and the final diagnosis has an almost exponential correlation with the duration of diagnostic delay. Specifically, patients with 1, 2, 3, and 4 referrals before diagnosis experienced median diagnostic delays of 0, 35, 38, and 85.5 days, respectively. This finding emphasizes the importance of promptly initiating diagnostic evaluations upon suspicion of metastatic spinal disease, even if healthcare providers are not able to provide definitive care themselves, in order to minimize delays in diagnosis and treatment. Educational programs similar to the one by Mattes et al., educating healthcare providers involved throughout the patient journey of metastatic spinal disease on the urgency of proper diagnostics, will undoubtedly play a crucial role in reducing diagnostic delay.

Facilitating appropriate and timely referrals following the diagnosis of spinal metastases, thereby decreasing referral delay, is another critical step to ensure that patients receive timely and appropriate care. For non-specialized healthcare providers, spinal metastatic disease is a relatively uncommon pathology. As a result, not all healthcare providers are aware of the urgency of treatment, as shown in a study by Galasko et al., which revealed that only 22% of patients with painful skeletal metastases were referred in a group of women diagnosed with and treated for breast cancer [77]. Even if the necessity of treatment is recognized, the appropriate treatment modality is not always chosen. Unpublished data from the patient cohort studied in this thesis revealed that patients were referred to the appropriate caregiver after diagnosis in only 43% of cases when the diagnosis was made in local hospitals, compared to 84% when the diagnosis was established at a different department within the tertiary care center. Furthermore, the associated median referral delay was 4 days when patients were directly referred to the appropriate caregiver, 11 days when there was one inappropriate referral, and 24 days when there were two or more inappropriate referrals before reaching the definitive caregiver. This is highlighted further by a survey by Vulto et al., which found that 80% of general practitioners believe radiotherapy is an effective treatment for MSCC, despite a 2005 landmark study by Patchell et al. showing far superior outcomes for a combination of direct surgical decompression followed by radiotherapy [78]. Educating healthcare providers on the use of referral tools such as the Spinal Instability Neoplastic Score (SINS) is one strategy to ensure appropriate referrals after confirmation of spinal metastases [79]. Nevertheless, due to the multidisciplinary nature of metastatic spinal disease treatment, it is likely more effective to involve spine surgeons, radiation oncologists, radiologists and potentially medical oncologists or neurologists in a multidisciplinary setting as soon as the diagnosis has been established. In the previously mentioned study on the Quality Improvement (QI) initiative by Mattes et al., it was shown that the time to radiation oncology consultation decreased from 3 to 1 day after confirmation of MSCC on MRI following the introduction of a multidisciplinary clinical pathway [76]. Another study showed that, after the introduction of a multidisciplinary system, the incidence of neurological deficits decreased from 13.2% to 3.4%, and the improvement of neurological deficits after intervention increased from 5.3% to 28.6%, likely due to more urgent surgical intervention [80]. At the core of this multidisciplinary system were radiologists who assessed the diagnostic imaging for signs of MSCC and/or vertebral destruction and subsequently recommended referral to a spine surgery department or radiation therapy. However, such systems may be challenging to implement across multiple centres in a catchment area. In regional specialized cancer centres, including tertiary care centres for the treatment of spinal metastases, up to 70% of patients are referred from regional hospitals [51]. It has been shown that patients with MSCC experience significantly more total delay when referred from a regional hospital, as opposed to being admitted directly to the regional cancer center [81]. One potential solution to reduce the chance of inappropriate referrals, regardless of their origin, is to establish a multidisciplinary outpatient clinic where spine surgeons and radiation oncologists see patients together and determine appropriate treatment. Such initiatives rely heavily on strong communication channels and referral systems between regional and specialised care-centres. In an interventional study

by Lee et al., the introduction of such a multidisciplinary project team, consisting of a radiation oncologist, diagnostic radiologist, medical oncologist, and orthopaedic surgeon, reduced the response time to steroid therapy and radiotherapy by 60-70% and the length of stay and subsequent costs of treatment by 35-40% [82]. Additionally, healthcare providers less familiar with the treatment of spinal metastases are supported in their treatment decision-making, reducing the risk of inappropriate referrals, and further expediting definitive treatment.

The final stage of the patient journey is treatment delay. As patients have been referred to the appropriate definitive caregiver, the necessary expertise for a proper risk assessment on the timing of definitive treatment is typically available. **Chapter 6** provides further support to this claim, as none of the neurological deficits occurred during this final interval [46]. Nonetheless, a uniform method of treatment selection for metastatic spinal disease can further synchronise clinical decision making and communication between care providers. A widely used tool to improve decision-making is the NOMS (Neurologic, Oncologic, Mechanic, and Systemic) algorithm, which assesses four pillars [83]. However, to improve its application, there should be a uniform approach to assessing each pillar. For example, the neurologic pillar should include clinical examination as well as reliable and reproducible radiological assessment using the Bilsky grading system to evaluate the degree of epidural involvement [84]. Additionally, a consensus on the most appropriate tool to assess eligibility for surgical treatment for the systemic pillar should be established [85].

INTERVAL	ONCOLOGICAL HISTORY	TYPE OF CARE	RECOMMENDATION
PATIENT DELAY	Unknown malignancy	N/A	Provide accessible, national-level patient education tools focusing on non-specific lower back pain. Promote early recognition of symptoms related to spinal metastases and other conditions requiring medical attention.
	Pre-existing malignancy	N/A	Advise high-risk oncological patients to seek immediate medical attention for new or worsening back pain, nerve-related symptoms, or bowel and bladder dysfunction.
DIAGNOSTIC DELAY	Unknown malignancy	Primary/secondary	Use and document red flags when evaluating patients with non-specific back pain.
	Pre-existing malignancy	Primary/secondary	Treat new or progressive back pain in oncological patients as spinal metastasis until proven otherwise. Immediate further diagnostic evaluation is warranted.
	Both	Primary/secondary	Use MRI for diagnosing metastatic spinal disease when clinically suspected. Conventional radiographs may not rule out metastatic spinal disease.
	Both	Primary/secondary	Initiate diagnostic evaluations instead of referring patients, even if unable to provide definitive care.
REFERRAL DELAY	N/A	Primary/secondary	Use referral tools like SINS for appropriate caregiver referral when no designated point of contact for definitive care exists.
	N/A	Primary/secondary	If healthcare providers are unfamiliar or uncomfortable with such referral tools, consult with a specialized provider before referral to ensure proper care.
	N/A	Tertiary	Designate a single specialty in tertiary care centers to receive referrals from other departments or local hospitals, organizing appropriate care for patients with confirmed metastatic spinal disease.
TREATMENT DELAY	N/A	Tertiary	Utilize up-to-date and uniform treatment algorithms, such as the NOMS algorithm, to ensure consistent and evidence-based definitive care.

FUTURE PERSPECTIVES

Both the incidence of cancer and the life expectancy of oncological patients are on the rise. Specifically, patients with spinal metastases typically have a limited life expectancy, which further emphasizes the importance of preventing harmful complications such as pathologic fractures or neurological deficits that can negatively impact their quality of life. Nonetheless, several studies report an alarming increase in the incidence of spinal cord injury and a corresponding rise in the number of patients requiring emergency surgery due to metastatic spinal disease [86,87]

Although the importance of timely and proactive treatment of metastatic spinal disease for favourable treatment outcome is widely acknowledged, there is a lack of specific methods to achieve this goal [88–90]. Because of the multidisciplinary nature of metastatic spinal disease, it requires the involvement of various healthcare providers throughout the patient journey, who are in unique and impactful positions to improve outcomes [91]. This thesis establishes a foundation for specific interventions targeting various types of delay. By analysing how different aspects of the patient journey contribute to timely or delayed treatment, interventions can be designed to promote timely treatment.

Ideally, a comprehensive, coordinated care model for managing metastatic spinal disease would involve the integration of oncology, radiology, radiotherapy, and surgery teams to promote interdisciplinary collaboration and streamline patient care. This model should incorporate centralized care coordination by establishing a designated care coordination team responsible for overseeing and managing the patient's treatment journey. This team could be entrusted to one of the medical specialties involved in the care of these patients. Alternatively, it could consist of dedicated case managers, nurse navigators, or even medical students, to ensure effective communication between the various specialists involved in the patient's care. Moreover, a combined outpatient clinic or regular multidisciplinary tumour board meetings attended by oncologists, radiologists, spine surgeons, and other relevant specialists would facilitate a multidisciplinary approach and enable discussions of complex cases, leading to the development of comprehensive, personalized treatment plans. Ideally, implementing a unified electronic health record (EHR) system, accessible to all specialists involved in the patient's care across the entire catchment area would improve communication and information flow among care providers, reducing the potential for errors and delays in treatment. Since these types of systems often introduce risks pertaining to data breaches, a viable alternative is to develop a standardized referral procedure, which would facilitate faster and more efficient transfer of patients between specialists. This process could include digital referral platforms and predefined referral criteria. Lastly, continuous quality improvement (CQI) through monitoring and evaluating the coordinated care model's performance would help identify areas for improvement and drive continuous enhancement of patient outcomes. This could involve tracking key performance indicators, conducting patient satisfaction surveys, and implementing targeted quality improvement initiatives. Since the milestones representing the cut-off points for each delay interval are relatively easy to obtain retrospectively, incorporating a monitoring tool to continuously measure these intervals' duration would be beneficial. This monitoring tool can then be used to identify any decline in the referral chain's efficiency or to monitor any interventions aimed at improving it.

Interventions designed to improve the management of metastatic spinal disease are only effective if they are adopted by healthcare providers. Studies have shown that adherence to clinical practice guidelines is not always optimal, with only 52% of medical practitioners fully adhering to these guidelines [92]. A study conducted three years after the initial publication of the Spinal Instability Neoplastic Score (SINS) found that only 21.4% of patients with SINS 13-18, indicating instability, were referred to a spine surgeon prior to receiving radiation therapy [93]. Likewise, the authors of a landmark paper on referral patterns in metastatic spinal disease, "Always on a Friday?" from 2001, published a follow-up paper in 2013 showing an identical distribution of referrals throughout the week between 1998 and 2009, despite their efforts to change this [94,95]. There are, however, also examples of successful efforts to alter the fate of patients with spinal metastases. A study by Fahed et al. assessed the percentage of patients operated as an emergency and found a slow but steady decline after the implementation of a multidisciplinary staff meeting [96]. These findings highlight the importance of developing effective educational materials and expertise on how to engage healthcare providers to promote timely and appropriate management of metastatic spinal disease.

CONCLUSION

In conclusion, timely treatment plays a crucial role in achieving positive outcomes for patients with metastatic spinal disease. Delayed treatment has a negative impact on surgical and clinical outcomes, physical functioning, quality of life, survival, and treatment costs. To promote timely treatment, a comprehensive approach is necessary that involves numerous minor improvements throughout the entire patient journey, instead of looking for a single solution. Continuous monitoring of various delay intervals can help evaluate the effectiveness of interventions aimed at reducing delays. Additionally, educational programs should be developed in collaboration with educational experts to ensure their adoption by healthcare providers.

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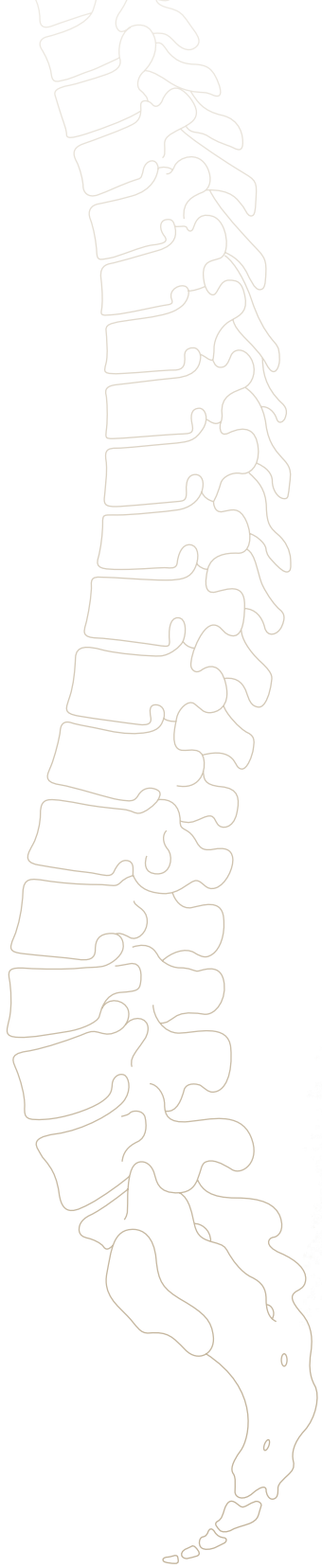
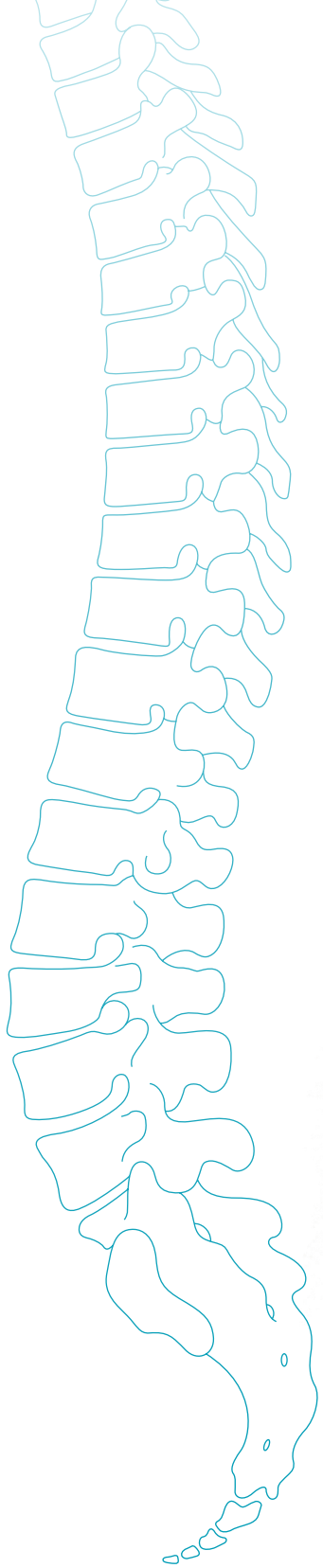
Appendices





ANSWER TO THE LETTER TO THE EDITOR

Of K. Huang concerning

"The Importance of Timely Treatment

for Quality of Life and Survival in Patients

with Symptomatic Spinal Metastases"

By van Tol Fr, Et Al.

F.R. van Tol
J.J. Verlaan

We thank the authors of this letter for their interest in our work and appreciate the remarks that were raised.

The first comment addresses the use of a three-day cut-off for dichotomization of treatment into 'emergency' and 'elective' surgery. This cut-off is a reduced form of a classification proposed by the Global Spine Tumour Study Group (GSTSG), a worldwide consortium of clinical experts on metastatic spinal disease, originally defining scheduled surgery (>3 days), urgent surgery (1-3 days) and emergency surgery (<24 hours) [1]. As stated in our methods section, we did not consider the actual timing of surgical treatment after presentation to the spine surgeon for patient group allocation, but rather the preferred timing of surgical treatment as assessed by the treating physician. In this way, the authors are confident that the groups that were used in the current study appropriately reflect the urgency of the required surgical interventions.

By extension, we fully agree with the statement that the patient's course of disease must be taken into account to determine (non-)timely treatment. The natural course of metastatic spinal disease, most importantly the rate of progression, is extremely heterogeneous by nature and the associated timeline is therefore unique for every patient. Because of this, the authors have opted for outcome-based stratification of 'timely' versus 'delayed' treatment, rather than absolute numerals. In one of the examples provided by the authors of the letter, a patient without preexisting symptoms presents with Metastatic Spinal Cord Compression (MSCC), requiring emergency surgical decompression. Even though such a case would be extremely difficult (if not impossible) to subject to earlier treatment prior to the occurrence of MSCC, the authors would still argue that preferably treatment would have commenced at an earlier stage, thus rendering his/her treatment as non-timely, or rather 'delayed'.

The authors of the letter would probably agree that sudden lower limb paralysis without any preceding warning symptoms would represent an exceedingly unfortunate and rare case as most often there are early symptoms including new back pain, progressive back pain, nocturnal back pain, pain on palpation, and poor general health (representing the classic 'red flags' suggestive of metastatic spinal disease) long before the development of neurological deficits. Ignoring these red flags (representing patient delay) or failure to identify/act upon red flags (doctor delay) may both substantially contribute to the cases defined in the original work as having undergone 'delayed treatment'. As shown in several of our publications, delayed treatment instigates a (largely irreversible) chain of events leading to inferior surgical/clinical outcome, quality of life and survival at a higher cost [2].

Once again, we would like to thank the authors of the letter for their interest in our work and for appropriately addressing the importance of the individual patient's course of disease for the timing of surgical treatment. We hope that it will be beneficial to both clinicians and patients.

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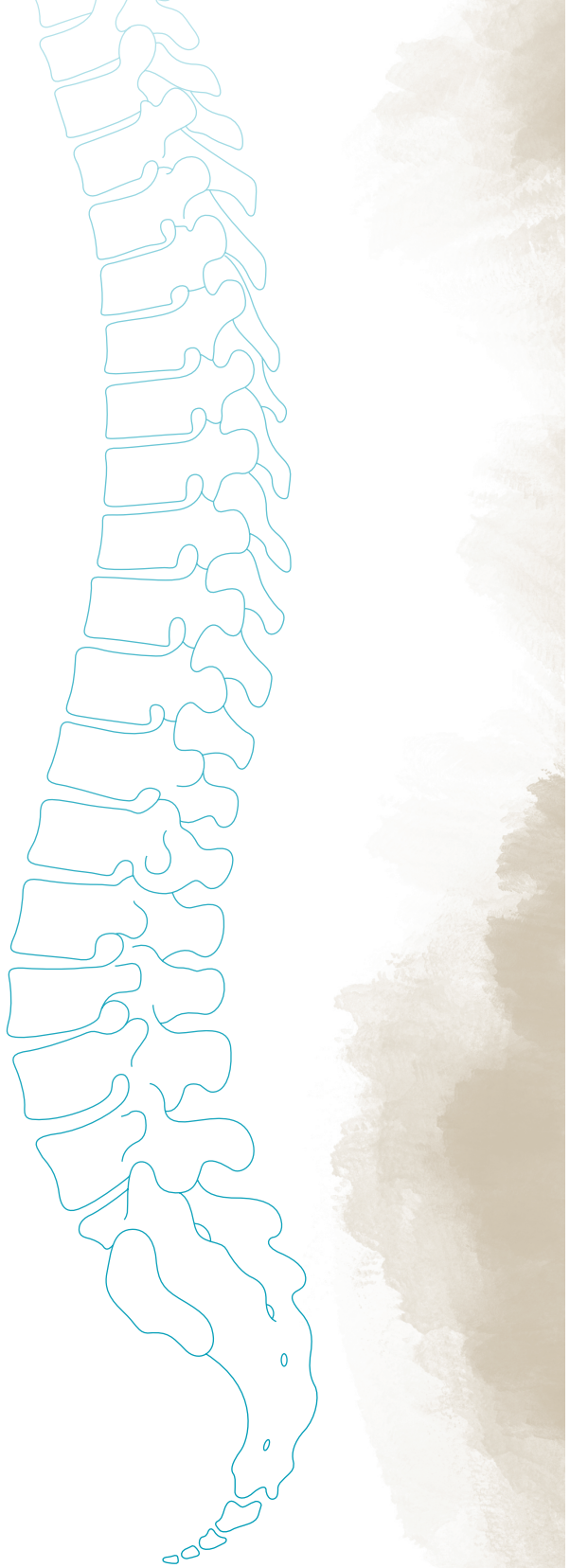


SUMMARY IN DUTCH

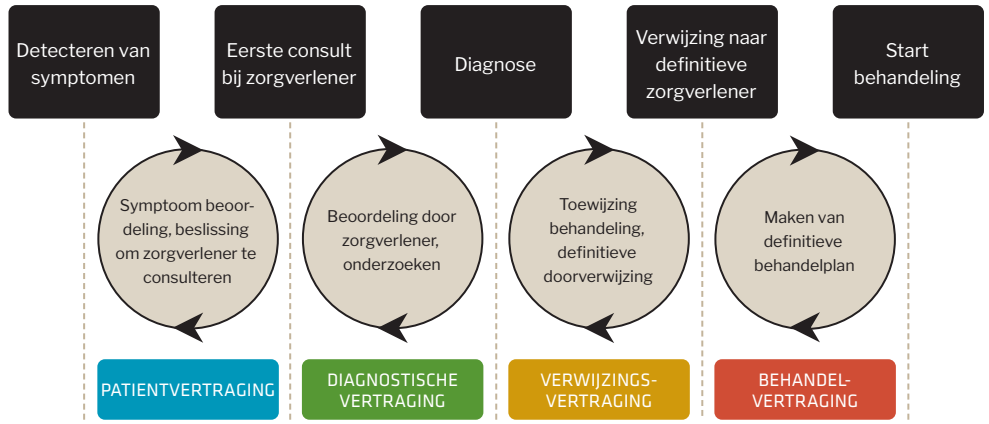
Nederlandse Samenvatting

ACHTERGROND

Kanker is een van de voornaamste oorzaken van sterfte wereldwijd, met ongeveer 10 miljoen sterfgevallen in 2020. De wereldwijde incidentie van kanker neemt toe door factoren zoals vergrijzing, blootstelling aan milieuvervuiling en verbeterde diagnostische opties. In Nederland is het aantal kankerdiagnoses in de afgelopen 30 jaar verdrievoudigd. Tegelijkertijd hebben nieuwe therapieën zoals immunotherapie en gentherapie de overlevingskans van sommige tumortypen sterk verbeterd. Door de combinatie van deze twee ontwikkelingen neemt het aantal patiënten met uitgezaaide kanker toe. Vroeger betekende de aanwezigheid van metastasen (uitzaaiingen) vaak een terminale diagnose met weinig behandelopties, maar nieuwe behandelingen hebben de overlevingsduur verlengd.

Het skelet is een veelvoorkomende plek voor metastasen, waarbij ongeveer 60% van de overleden kankerpatiënten botmetastasen heeft bij autopsie. Vooral patiënten met metastasen van nier-, long-, borst- en prostaatkanker lopen risico. De wervelkolom is de meest voorkomende locatie voor botmetastasen. Botmetastasen veroorzaken vaak hevige pijn, die de kwaliteit van leven sterk kan beïnvloeden. Ook kunnen metastasen de mechanische stabiliteit van de wervelkolom in gevaar brengen en neurologische uitval veroorzaken, zoals spierzwakte en gevoelloosheid, door het beknellen van zenuwstructuren. De behandeling van uitgezaaide kanker is voornamelijk gericht op het verbeteren van de kwaliteit van leven door het verlichten van symptomen. Dit kan via systemische behandelingen, radiotherapie of operatieve behandeling. Bij het kiezen van een behandeling is het belangrijk dat gekeken wordt naar zowel neurologische, oncologische, mechanische en systemische aspecten van de ziekte. Hiermee kunnen zorgverleners en patiënten samen geïnformeerde beslissingen nemen over de beste behandeling voor de individuele situatie van de patiënt.

In de vroege stadia zijn symptomen vaak mild of afwezig, waardoor de ziekte niet altijd op tijd wordt herkend en behandeld. Het tijdig diagnosticeren, doorverwijzen en behandelen van patiënten met wervelmetastasen is echter van groot belang en heeft een aanzienlijke invloed op de uitkomst van de behandeling. Door hun progressieve karakter, kunnen onbehandelde wervelmetastasen leiden tot onomkeerbare complicaties, zoals pathologische fracturen en neurologische uitval. Ondanks het belang van tijdige behandeling van wervelmetastasen, ontwikkelt 25-50% van de patiënten toch dergelijke complicaties. Uitdagingen in het tijdig stellen van de diagnose en initiëren van de behandeling zijn onder meer het feit dat symptomen vaak lijken op 'normale' rug- of nekpijn, en het feit dat er veel specialismen betrokken (kunnen) zijn bij de behandeling. Er is ook een gebrek aan kennis onder zorgverleners over effectieve behandelingsmethoden, en patiënten moeten vaak worden doorverwezen naar gespecialiseerde centra, wat extra tijd kost. Om deze vertragingen te bestrijden, is het nodig om het verwijstraject van de patiënt, van het ontstaan van het de eerste symptomen tot aan de uiteindelijke behandeling, volledig te begrijpen. Voor dit proefschrift hebben we voor dit doel een bestaand model om vertragingen in oncologische diagnostiek in kaart te brengen (het Andersen model) aangepast en geschikt gemaakt voor wervelmetastasen, zie hiervoor **Figuur 1**.



FIGUUR 1. Andersen Model, aangepast voor het onderzoeken van verwijstrajecten binnen wervelmetastasen

A

Deel I – De invloed van vertraagde behandeling op de behandeluitkomsten

In **het eerste deel** van dit proefschrift hebben we de invloed van tijdige versus vertraagde behandeling van wervelmetastasen onderzocht. Een cohort van circa 300 patiënten die chirurgische behandeld zijn voor wervelmetastasen, werd ingedeeld in twee groepen en met elkaar vergeleken:

1. Tijdige behandeling: Dit betreft patiënten die geen acute symptomen vertoonden en gepland konden worden voor een operatie.
2. Vertraagde behandeling: Deze groep bestaat uit patiënten die vanwege de ernst van hun symptomen binnen drie dagen een spoedoperatie moesten ondergaan.

In **hoofdstuk 2** werden chirurgische en direct postoperatieve parameters vergeleken tussen tijdige en vertraagde behandeling. Het grootste verschil in chirurgische parameters was te zien in de gebruikte chirurgische benadering. Bij tijdige interventie werden in 53% van de gevallen minimaal invasieve technieken gebruikt, tegenover slechts 13% bij vertraagde behandeling. De ingrijpendere operaties in de vertraagde groep gingen gepaard met een langere operatieduur met meer dan twee keer zoveel bloedverlies. Bovendien verdubbelde vertraagde behandeling het aantal complicaties (48% vs 26%) en verslechterde de neurologische status en het vermogen om zelfstandig te mobiliseren. De opname in het ziekenhuis duurde bijna twee keer zo lang (13 vs 5 dagen) en minder patiënten konden na de operatie terugkeren naar hun eigen huis (41% vs 83%).

Hoofdstuk 3 onderzocht de kwaliteit van leven, functionele status en overleving op middellange en lange termijn bij dezelfde twee patiëntgroepen. Tijdige behandeling was geassocieerd met een preoperatieve Karnofsky Performance Status (KPS) score van 70, vergeleken met 60 bij vertraagde behandeling. Beide behandelingen lieten een stijging zien van 10 KPS-punten, die tot 6 maanden bleef gehandhaafd. De kwaliteit van leven, gemeten met EQ-5D scores, toonde preoperatieve verschillen tussen tijdige (0,57) en vertraagde behandeling (0,24). Beide behandelingen verhoogden de EQ-5D scores op 3 en 6 maanden, met een grotere stijging bij vertraagde behandeling, waardoor de scores na 6 maanden gelijk werden. Dit kan deels verklaard worden doordat patiënten zich aanpassen aan hun neurologische toestand, een zogenaamde 'respons shift'. Vertraagde behandeling verminderde de overleving aanzienlijk, met een overlevingspercentage 1 jaar na behandeling van 51% vergeleken met 70% voor tijdige behandeling. Het verschil in overleving kan deels worden beïnvloed door het verschil in neurologische status, aangezien neurologische uitval geassocieerd is met slechtere overleving.

Voor snellere diagnostiek, verwijzingen en behandeling is het belangrijk om de verwijstrajecten voor oncologische patiënten te optimaliseren. Dit zal waarschijnlijk verbeteringen vereisen in de coördinatie en communicatie tussen zorgverleners. Echter, het uitbreiden van diagnostiek en verwijzingen kan leiden tot hogere initiële kosten, wat zorginstellingen kan ontmoedigen te investeren in dergelijke verbeteringen. Mogelijk wegen eventuele kostenbesparingen van het tijdig behandelen van patiënten met wervelmetastasen hiertegen op. In **hoofdstuk 4** werden de kosten in de aanloop naar de operatie, in het ziekenhuis en van de nazorg vergeleken tussen tijdige en vertraagde behandelingen tot drie maanden na de operatie. De kosten van tijdige behandeling bedroegen ongeveer €20.000, terwijl de kosten van vertraagde behandeling opliepen tot €34.000. Kosten van nazorg droegen het meest bij aan dit verschil, gemiddeld €4.000 voor tijdige behandeling en €14.000 voor vertraagde behandeling.

Bij het vergelijken van tijdige behandeling met vertraagde behandeling is het essentieel om de factoren die de verschillen in behandelingsresultaten beïnvloeden te overwegen. Een cruciale factor in het verschil in behandelingsresultaten is de neurologische status bij aanvang. De relatie tussen neurologische uitval en ongunstige behandelresultaten is al lange tijd bekend. Echter, het eerste deel van dit proefschrift bleef het verband tussen vertraagde behandeling en ongunstige uitkomsten bestaan, zelfs na correctie voor de preoperatieve neurologische status van patiënten. Dit suggereert dat andere aspecten van vertraagde behandeling eveneens een negatieve invloed hebben op de uitkomsten. Voorbeelden hiervan zijn operaties tijdens de dienst, opnames in het weekend en beperkte tijd om de patiënt volledig in kaart te brengen.

Deel II – Verwijstrajecten van patiënten met wervelmetastasen

In **het tweede deel** van dit proefschrift worden de verschillende stadia die een patiënt doorloopt vanaf het ontstaan van symptomen tot definitieve behandeling in kaart gebracht. Om toekomstige strategieën voor tijdige behandeling vorm te geven, moeten we de verschillende stadia begrijpen die de patiënt doorloopt van de eerste symptomen tot definitieve behandeling. Voor deze scriptie is een methode aangepast welke ontwikkeld is om factoren te identificeren die bijdragen aan vertragingen in diagnose en behandeling. Dit model identificeert eerst kritieke momenten in het verwijzingstraject. De eerste is wanneer de patiënt veranderingen (symptomen) opmerkt, wat het begin van de patiëntvertraging markeert. Na de eerste consultatie met een zorgverlener begint de diagnostische fase. Zodra diagnose wervelmetastasen definitief is vastgesteld, eindigt de diagnostische vertraging. Vooral van belang is de daaropvolgende verwijzingsvertraging. Voor een adequate verwijzing is kennis nodig over de juiste behandeling, bijvoorbeeld systemisch, radiotherapeutisch of chirurgisch. Na de verwijzing naar

de definitieve behandelaar begint de laatste fase, de behandelvertraging. Die eindigt met de definitieve behandeling van de wervelmetastase.

Hoofdstuk 5 analyseerde de verwijstrajecten van patiënten met symptomatische wervelmetastasen, waarbij de nadruk lag op vertragingstijden. De mediane totale vertraging was 99 dagen, bestaande uit patiëntvertraging (19 dagen), diagnostische vertraging (21,5 dagen), verwijzingsvertraging (7 dagen) en behandelvertraging (8 dagen). Wanneer afzonderlijk geanalyseerd voor patiënten die al bekend waren met een maligniteit (metachrone metastasering) en patiënten met een blanco oncologische voorgeschiedenis (synchrone metastasering), was de mediane totale vertraging identiek. Synchrone metastasering werd geassocieerd met langere patiëntvertraging (25 vs 14 dagen) en diagnostische vertraging (34 vs 15 dagen), maar kortere verwijzingsvertraging (4 vs 9,5 dagen) en behandelvertraging (5 vs 11 dagen). Dit suggereert dat er uiteenlopende strategieën nodig kunnen zijn om tijdige diagnose, verwijzing en behandeling te optimaliseren voor patiënten met synchrone versus metachrone wervelmetastasen.

Hoofdstuk 6 onderzocht de tijd tot het optreden van neurologische uitval bij patiënten met wervelmetastasen. Dit is belangrijk aangezien slechts 20-40% van de patiënten met neurologische uitval weer volledig neurologisch herstelt na behandeling. In onze studie werden de verwijstrajecten van 141 patiënten die neurologische uitval ontwikkelden voordat ze behandeld konden worden onderzocht. De mediane tijd tussen de eerste symptomen van de wervelmetastasen en het ontwikkelen van neurologische uitval was 64 dagen. Onze bevindingen toonden aan dat metachrone metastasen en een thoracale lokalisatie van wervelmetastasen geassocieerd leken met een snellere neurologische achteruitgang dan synchrone metastasen en lumbale en cervicale laesies. Patiënten met hematologische maligniteiten vertoonden de kortste tijd tot het ontwikkelen van neurologische uitval, wat het belang benadrukt van tijdige verwijzing en behandeling, vooral gezien de over het algemeen gunstigere overlevingsprognose van dergelijke maligniteiten.

Hoofdstuk 7 onderzocht de documentatie van vijf alarmsymptomen die wijzen op wervelmetastasen, zoals gedefinieerd door het Integraal Kankercentrum Nederland (IKNL). Deze rode vlaggen zijn: nieuw ontstane rugpijn, progressieve rugpijn, nachtelijke rugpijn, pijn bij palpatie en een matige algehele conditie (bijv. gewichtsverlies). Uit het onderzoek bleek dat 33,3% van de rode vlaggen gedocumenteerd werd als aanwezig, 3,6% werd gedocumenteerd als afwezig en 63,1% was niet gedocumenteerd. Eerdere onderzoeken tonen aan dat de aanwezigheid van (meerdere) alarmsymptomen de kans op wervelmetastasen vergroten. Daarom is systematische screening op alle alarmsymptomen bij patiënten met (lage) rugpijn van essentieel belang.

VERTRAGING REDUCEREN

De resultaten van dit proefschrift tonen aan dat het bespoedigen van de diagnose, verwijzing en behandeling van wervelmetastasen niet bereikt kan worden met één enkele interventie. Het vereist eerder talrijke kleine inspanningen over alle aspecten van het patiënttraject. Voor elk van de vier soorten vertraging kunnen verschillende potentieel effectieve strategieën worden bedacht. In dit proefschrift worden diverse aanbevelingen gegeven op basis van verschillende vertragingstermijnen, de oncologische voorgeschiedenis van de patiënt en het type zorgverlener (eerste-, tweede- of derdelijns). Een samenvatting hiervan is te vinden in tabel 1.

PATIËNTENVERTRAGING

De op één na grootste bijdrage aan de totale vertraging was patiëntvertraging. Strategieën gericht op het verminderen van patiëntvertraging zullen per definitie moeten bestaan uit uitvoerige patiëntenvoorlichting. In een eerdere studie hadden patiënten die een achteruitgang in hun neurologische status opmerkten, nog steeds een gemiddelde patiëntvertraging van vier dagen vanaf het begin van de neurologische verslechtering. Bovendien werd in dezelfde studie 20% van alle neurologische uitval ontdekt tijdens routinematige medische onderzoeken, wat aangeeft dat patiënten zich vaak niet bewust zijn van kritieke symptomen die dringend medische aandacht vereisen. Aangezien in totaal 75% van de neurologische uitval buiten het ziekenhuis optreedt, is het essentieel patiënten adequaat te informeren over wanneer zij medische hulp moeten zoeken. Bij het inrichten van educatieve programma's is het essentieel onderscheid te maken tussen patiënten die reeds bekend zijn met een maligniteit, en patiënten met een blanco oncologische voorgeschiedenis. Voor oncologische patiënten moet nieuw ontstane rugpijn leiden tot snelle diagnostiek. Uit een eerdere studie bleek dat bij oncologische patiënten 92,5% van de ervaren pijn verband hield met de tumor, terwijl slechts 2,3% van de pijn niet verbonden was met de tumor of de behandeling ervan. De Nederlandse landelijke richtlijn over wervelmetastasen bevat een patiënten brochure om kankerpatiënten te informeren over alarmsymptomen. Patiënten die voorheen onbekend waren met een maligniteit blijven een uitdagende categorie, aangezien lage rugpijn een van de meest voorkomende klachten is in de algemene bevolking. Sterker nog, bij ongeveer 25-50% van de patiënten met neurologische uitval ten gevolge van een wervelmetastase was dit de eerste uiting van hun ziekte. Voor beide groepen geldt dat generieke patiënten informatie (bijv. de website thuisarts.nl) duidelijke instructies moet bevatten over alarmerende symptomen die onmiddellijke medische aandacht vereisen. Desalniettemin zal patiëntvertraging altijd uitdagend blijven door zaken zoals beperkt ziekte-inzicht, culturele aspecten, angst en gebrekkige toegang tot zorg. Als patiënten educatie geen rekening houdt met deze factoren, is het onwaarschijnlijk dat enig educatief programma daadwerkelijk een serieuze impact zal hebben op dit type vertraging.

DIAGNOSTISCHE VERTRAGING

De grootste bijdrage aan de totale vertraging is diagnostische vertraging. In een eerdere studie van Bach et al. ondervonden patiënten, zelfs na het presenteren van met neurologische symptomen, nog steeds een gemiddelde diagnostische vertraging van 23 dagen, wat overeenkomt met onze bevindingen. Het is wederom essentieel om onderscheid te maken tussen patiënten met en zonder een eerdere oncologische diagnose bij het ontwikkelen van strategieën gericht op het verminderen van diagnostische vertraging. Vergelijkbaar met patiëntvertraging, is het voor patiënten zonder voorafgaande oncologische diagnose uitdagend omdat 70% van de mensen ooit rugpijn ervaart. De prevalentie van maligne spinale aandoeningen bij alle patienten met lage rugpijn is ongeveer 0,7%. Bij patiënten die eenmaal zijn doorverwezen naar het ziekenhuis stijgt dit naar 5-7%. Het stimuleren van systematisch gebruik en rapportage van alarmsymptomen kan vertragingen helpen verminderen. Een eerdere studie toonde aan dat de documentatie van alarmsymptomen steeg van 33% naar 65% na een actieve interventie. Voor patiënten met een maligniteit in de voorgeschiedenis moet nieuwe rugpijn worden beschouwd als wervelmetastase tot het tegendeel is bewezen. Bij deze patiënten moet binnen enkele dagen een MRI worden uitgevoerd. Als een MRI niet mogelijk is, kan een CT-scan worden gebruikt. In een eerdere studie steeg middels 'quality improvement' methodieken het gebruik van MRI's van 44% naar 64% bij een verdenking op wervelmetastasen. Dergelijke educatieve programma's die zorgverleners informeren over het belang van snelle en adequate diagnostiek zijn cruciaal bij het verminderen van diagnostische vertraging.

VERWIJZINGSVERTRAGING

Het faciliteren van correcte en tijdige doorverwijzingen na de diagnose van spinale metastasen, om zo verwijzingsvertraging te verminderen, is een belangrijke stap om ervoor te zorgen dat patiënten tijdige en adequate zorg ontvangen. Voor de meeste oncologisch hulpverleners zijn wervelmetastasen een relatief zeldzame aandoening. Ongepubliceerde data uit dit proefschrift toonden aan dat patiënten in slechts 43% van de gevallen naar de juiste zorgverlener werden doorverwezen als de diagnose in perifere ziekenhuizen werd gesteld, vergeleken met 84% in een academisch ziekenhuis. De gemiddelde verwijzingsvertraging varieerde hierbij sterk, afhankelijk van het aantal doorverwijzingen, voordat de patiënt uiteindelijk bij de juiste zorgverlener terecht kwam. Het onderwijzen van zorgverleners over verwijzingstools zoals de Spinal Instability Neoplastic Score (SINS) kan helpen bij het waarborgen van passende verwijzingen. Door het multidisciplinaire karakter van in het ideale scenario verschillende specialisten betrokken na het stellen van de diagnose. In een eerdere studie nam de tijd tot consultatie van een radiotherapeut af van 3 naar 1 dag na de introductie van een multidisciplinair klinisch traject. Een ander onderzoek met een vergelijkbare interventie toonde aan dat de incidentie van neurologische uitval afnam en de verbetering ervan toenam door snellere chirurgische interventie.

BEHANDELVERTRAGING

De laatste fase van het verwijstraject is de behandelvertraging. Nadat patiënten zijn doorverwezen naar hun definitieve zorgverlener, is de benodigde expertise voor een juiste risicobeoordeling meestal aanwezig. De data uit hoofdstuk 6 ondersteunen dit, aangezien er tijdens dit laatste interval bij geen van de patiënten nog neurologische uitval optrad. Desondanks kan een uniforme methode voor het selecteren van de juiste behandeling voor wervelmetastasen de klinische besluitvorming en communicatie tussen zorgverleners verder optimaliseren. Een veelgebruikt instrument om de besluitvorming te verbeteren is het NOMS (Neurologisch, Oncologisch, Mechanisch en Systemisch) algoritme, dat vier pijlers beoordeelt. Om de inzet hiervan nog verder te verbeteren, zou er een uniforme benadering moeten zijn voor het beoordelen van elke pijler.

INTERVAL	ONCOLOGISCHE VOOR-GESCHIEDENIS	TYPE ZORG-VERLENING	AANBEVELING
PATIËNTEN VERTRAGING	Onbekend met een maligniteit	N/A	Verschaf toegankelijke, landelijke patiënten-educatietools gericht op aspecifieke lage rugpijn. Bevorder vroege herkenning van symptomen gerelateerd aan wervelmetastasen en andere aandoeningen die dringende medische aandacht vereisen.
	Bekend met een maligniteit	N/A	Adviseer oncologisch patiënten om direct medische hulp te zoeken bij nieuwe of verergerende rugpijn, zenuwuitval , of darm- en blaasdisfunctie.
DIAGNOSTICHE VERTRAGING	Onbekend met een maligniteit	Eerste-/ Tweedelijns	Gebruik en documenteer rode vlaggen bij de evaluatie van patiënten met aspecifieke lage rugpijn.
	Bekend met een maligniteit	Eerste-/ Tweedelijns	Behandel nieuwe of progressieve rugpijn bij actieve of recente oncologische patiënten als wervelmetastasen totdat het tegendeel is bewezen. Onmiddellijke verdere diagnostische evaluatie is vereist.
	Beiden	Eerste-/ Tweedelijns	Gebruik MRI voor het diagnosticeren van wervelmetastasen bij een klinische verdenking. Conventionele röntgenfoto's kunnen spinale metastasen niet uitsluiten.
	Beiden	Eerste-/ Tweedelijns	Zet diagnostiek in, in plaats van patiënten door te verwijzen, zelfs als u niet in staat bent om definitieve zorg te bieden.
VERWIJZINGS-VERTRAGING	N/A	Eerste-/ Tweedelijns	Gebruik doorverwijzingstools zoals SINS voor adequate doorverwijzing naar zorgverlener wanneer er geen centraal loket voor definitieve zorg bestaat.
	N/A	Eerste-/ Tweedelijns	Als zorgverleners onbekend zijn met dergelijke doorverwijzingstools, raadpleeg dan een gespecialiseerde zorgverlener vóór de door-verwijzing om de juiste zorg te garanderen.
	N/A	Derdelijns	Stel een enkele specialiteit in tertiaire zorg-centra aan om doorverwijzingen van andere afdelingen of lokale ziekenhuizen te ontvangen, en organiseer passende zorg voor patiënten met bevestigde wervelmetastasen.
BEHANDELINGS-VERTRAGING	N/A	Derdelijns	Gebruik actuele en uniforme behandelalgo-ritmen, zoals het NOMS-algoritme, om consis-tente en evidence based zorg te garanderen.

TOEKOMSTPERSPECTIEVEN

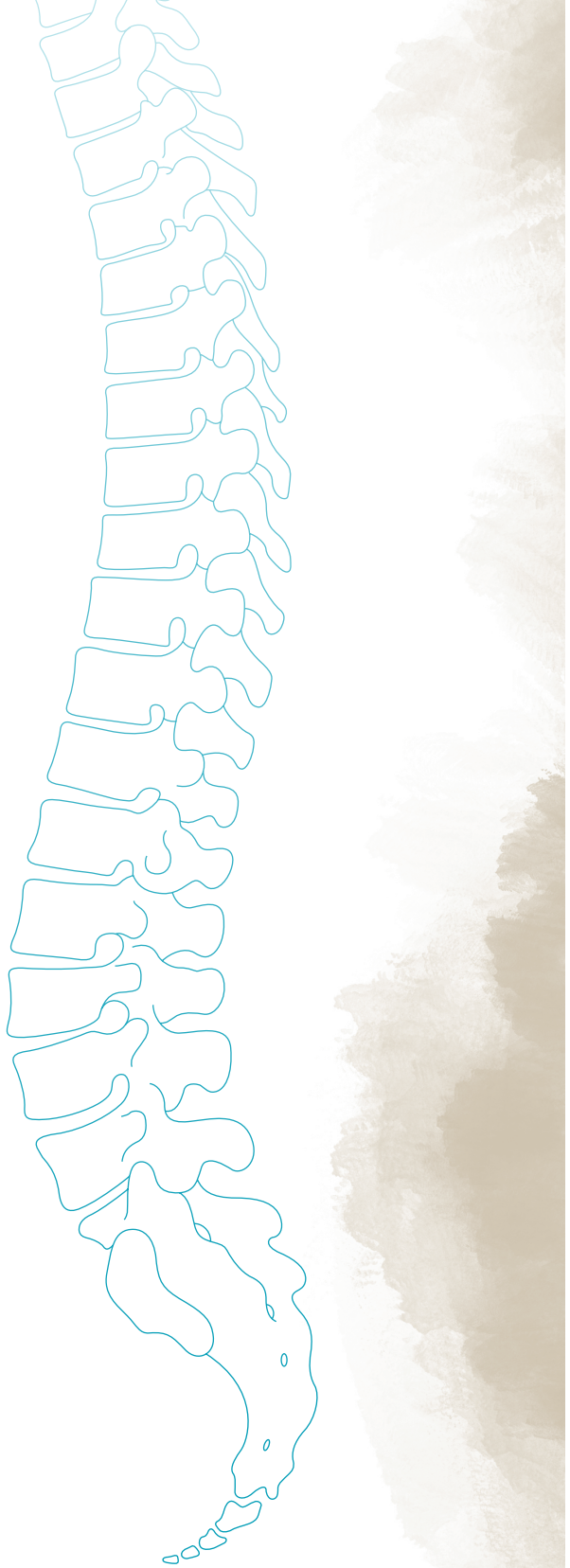
Zowel de incidentie van kanker als de levensverwachting van patiënten met kanker nemen toe. Patiënten met wervelmetastasen hebben meestal een beperkte levensverwachting, wat het belang van het voorkomen van schadelijke complicaties verder onderstreept. Desondanks melden diverse studies een zorgwekkende toename van het aantal gevallen van neurologische uitval en spoedoperaties wegens wervelmetastasen.

Hoewel het belang van tijdige en proactieve behandeling breed wordt erkend, ontbreekt het vaak aan specifieke methoden om dit te stimuleren. Dit proefschrift legt een basis voor specifieke interventies gericht op verschillende soorten vertraging. Door te analyseren hoe verschillende stadia binnen het verwijstraject bijdragen aan de duur tot aan definitieve behandeling, kunnen interventies worden ontworpen om tijdige behandeling te bevorderen.

Idealiter zou een uitgebreid, gecoördineerd zorgmodel de integratie van oncologie, radiologie, radiotherapie en chirurgie omvatten. Een dergelijk model zou centrale zorgcoördinatie moeten hebben, mogelijk uitgevoerd door gespecialiseerde casemanagers of zelfs medische studenten. Een multidisciplinair spreekuur of multidisciplinaire besprekingen zouden de kans op foutieve verwijzingen verminderen. Het implementeren van een landelijk of regionaal elektronisch patiëntendossier (EPD) zou de communicatie verder kunnen verbeteren, evenals het gebruik van gestandaardiseerde verwijzingsprocedures met eventueel digitale verwijsplatformen. Tevens is het belangrijk om continue verwijstrajecten te monitoren en bij te sturen waar nodig. Tot slot, zijn interventies alleen effectief als ze daadwerkelijk worden overgenomen door zorgverleners. Eerdere studies hebben aangetoond dat de naleving van klinische richtlijnen niet altijd optimaal is. Onderwijsprogramma's moeten daarom in samenwerking met onderwijsexperts worden ontwikkeld om de adoptie door zorgverleners te waarborgen.

CONCLUSIE

Tijdige behandeling speelt een cruciale rol bij het bereiken van goede uitkomsten voor patiënten met wervelmetastasen. Vertragingen in de behandeling hebben een negatieve impact op chirurgische en klinische uitkomsten, fysiek functioneren, kwaliteit van leven, overleving en de kosten van de behandeling. Om tijdige behandeling te bevorderen, is een alomvattende aanpak nodig die tal van kleine verbeteringen door het hele verwijstraject omvat. Voortdurende monitoring van verschillende vertragingsintervallen kan helpen bij het evalueren van de effectiviteit van interventies. Bovendien moeten educatieve programma's worden ontwikkeld om zorgverleners optimaal te kunnen bereiken.



LIST OF PUBLICATIONS

This thesis is based on the following publications and manuscripts:

van Tol FR, Versteeg AL, Snijders TJ, Suijkerbuijk KPM, Öner FC, Verkooijen HM, Verlaan JJ. Time between early symptoms caused by metastatic spinal disease and the potential onset of neurological deficits. In preparation.

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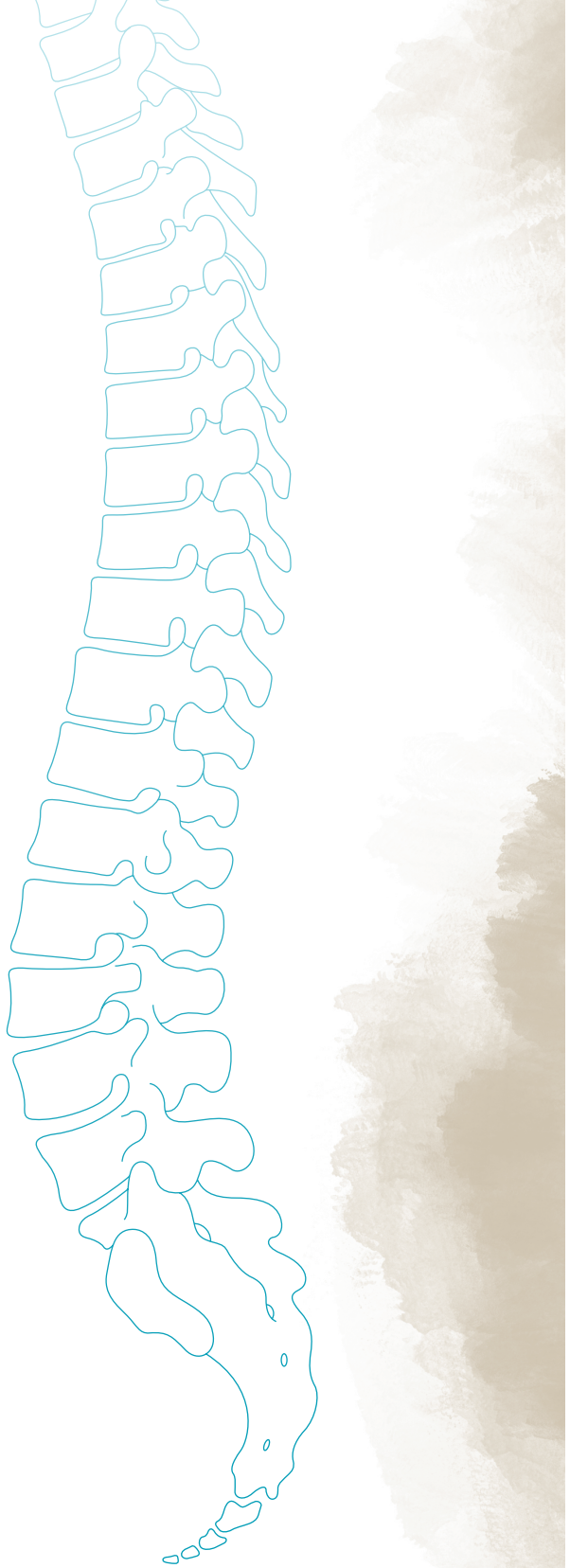

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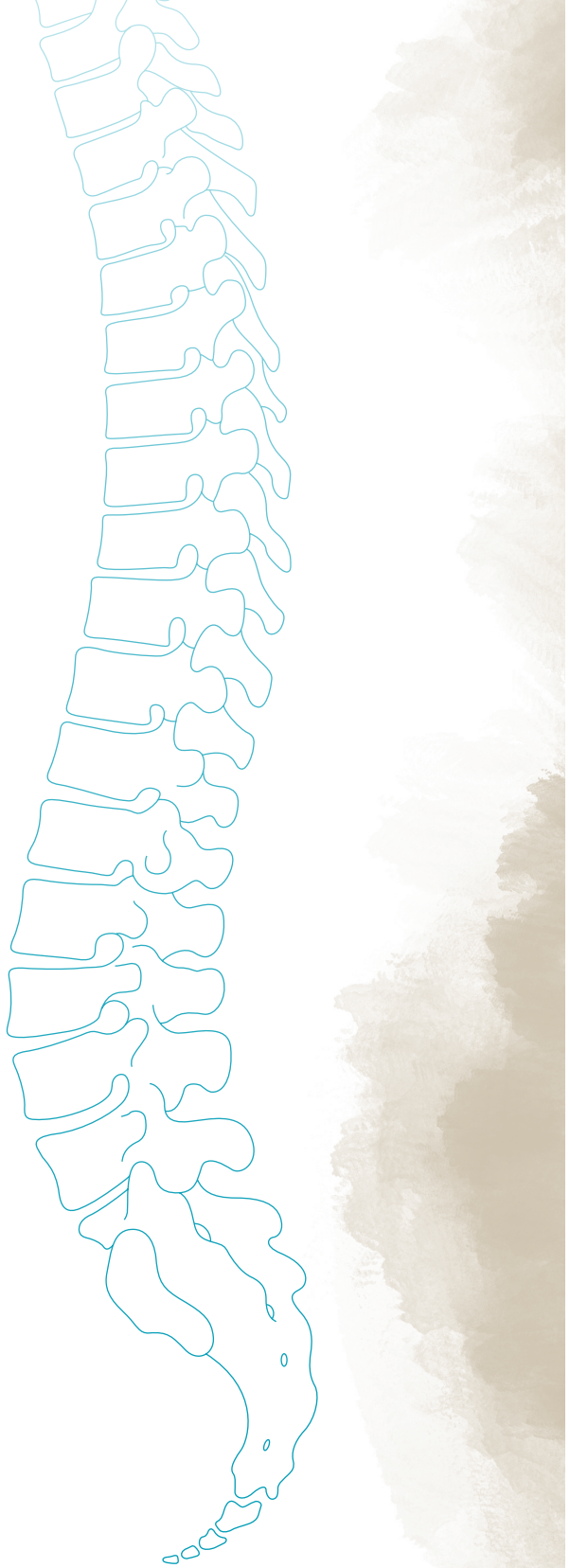

CURRICULUM VITAE

Floris Rudolf van Tol was born in Den Haag, the Netherlands on the 25th of July 1991, where he grew up in the loving company of his parents and younger sisters. In 2008 he graduated from high school (Gymnasium, Maerlant-Lyceum, Den Haag) and started his medicine study at the University of Leiden. After following an elective course on orthopaedic implants in his third year, Floris became a student researcher at the Leiden University Medical Center, where he conducted research on clinical outcome after hip or knee replacement surgery and staged anterior cruciate ligament revision. After graduating in 2016, Floris started worked as a non-training orthopedic resident at the University Medical Center Utrecht.

In 2017, Floris started working as a full-time researcher and PhD-candidate at the department of orthopaedic surgery at the University Medical Center Utrecht, initially under the guidance of prof. F.C. Öner, later of prof. J.J. Verlaan. During his PhD, Floris worked in close collaboration with the international Global Spine Tumour Study Group and the AOSpine network. These collaborations enabled him to present and discuss his scientific work at numerous leading international conferences and meetings. Based on some of the work presented in this thesis, Floris was awarded a Dutch Spine Society research grant in 2017.

In 2019, while continuing his PhD research part-time, Floris started working as a medical scientist at SentryX, a company developing a non-opioid implantable anesthetic for pain treatment after spine surgery. After the completion of his PhD thesis in 2023, Floris remains dedicated to developing superior pain treatments after musculoskeletal surgery.