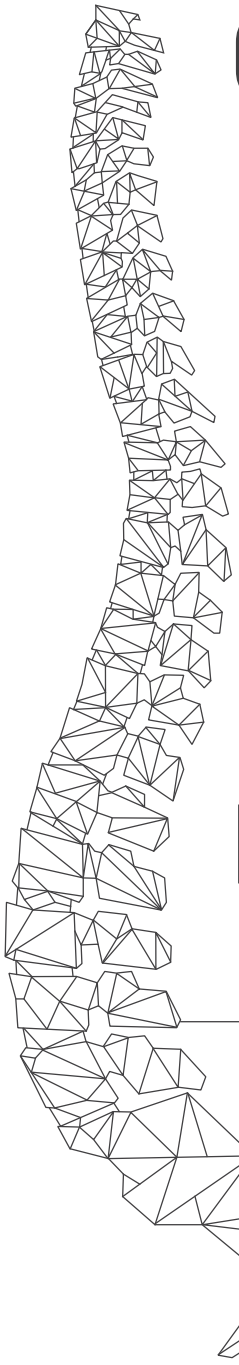

OPTIMIZING CARE FOR PATIENTS WITH SPINAL METASTASES

Anne Versteeg

Optimizing care for patients with spinal metastases
PhD dissertation, Utrecht University, The Netherlands

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OPTIMIZING CARE FOR PATIENTS WITH SPINAL METASTASES

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(met een samenvatting in het Nederlands)

Proefschrift

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VOOR MIJN OUDERS

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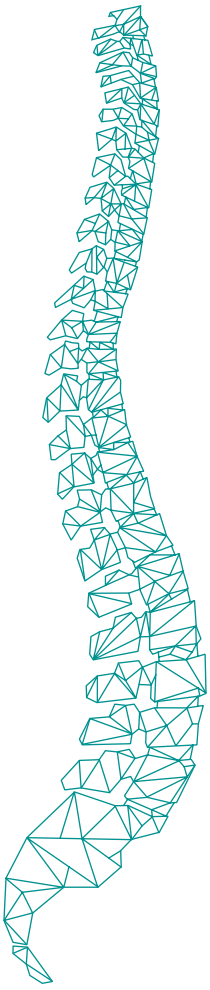
PART III - ADVANCES IN TREATMENT STRATEGY

ADDENDA



CHAPTER 1

General introduction and thesis outline

INTRODUCTION

Cancer is the second most common cause of death in Europe and the United States (US) *[1, 2]* and is a significant public health concern with a predicted increase of 20% in new cancer diagnoses in the US by 2020 *[3]*. However, with advances in systemic treatments and early detection methods, the 5-year survival rate of patients diagnosed with cancer has increased with 20% between 1975 and 2011 in the US, and with 15% between 1989 and 2012 in the Netherlands *[1, 4]*.

In patients with advanced cancer, bone is the third most common site of metastases, after lung and liver *[5]*. Bone metastases occur most frequently in patients with breast, lung or prostate cancer, with up to 70% of patients having evidence of bony metastatic disease at autopsy *[5]*. While the exact prevalence of bone metastases is unknown, it was estimated that in 2008, approximately 280 000 people in the US were diagnosed with bone metastases *[6]*. The spine is the most common location for bone metastases. With the increasing incidence of cancer, combined with improving survival rates, the number of patients with spine metastases will continue to increase. It has been estimated that annually, approximately 25 000 cancer patients will be diagnosed with spinal metastases in the Netherlands *[7]*.

Bone metastases often cause severe pain and increase the risk of pathological fractures, with devastating impact on activities of daily living and quality of life *[8]*. The mechanism of bone cancer pain is not completely understood. Generally, two types of bone pain from metastases are discriminated; pain from local tumor activity and pain caused by compromised mechanical integrity *[5, 9]*. Local tumor activity may consist of direct invasion of tumor cells into bone, periosteal stretching, or the release of inflammatory mediators *[5, 10, 11]*. At the same time, disruption of the homeostasis between osteoclasts and osteoblasts can cause loss of bone strength and subsequently compromise mechanical integrity leading to painful (micro-) motion within the bone *[5]*. In all likelihood, both generators of pain (local tumor-related and/or related to mechanical failure) are present simultaneously in bone metastases although their relative contribution to pain may vary.

Spinal metastases have a unique clinical position compared to bone metastases at other sites, as they can cause neurological impairment through metastatic epidural spinal cord compression (MESCC), nerve root compression and/or destabilization of the spinal column. Patients with spinal metastases can therefore have debilitating back pain with (impending) neurological deficits, which can further compromise their performance status and quality of life.

SPINAL INSTABILITY

The concept of spinal instability is critical in the management and evaluation of patients with spinal metastases *[12]*. Spinal metastases affect bone quality and subsequent bone healing capacity *[12]*. Moreover, the bony and ligamentous involvement in metastatic disease differs from traumatic injuries, differentiating neoplastic related spinal instability from traumatic spinal instability *[12]*. Neoplastic spinal instability has previously been defined as '…loss of spinal integrity as a result of a neo-plastic process that is associated with movement-related pain, symptomatic or progressive deformity and/or neural compromise under physiological loads' *[12]*.

The Spinal Instability Neoplastic Score (SINS) was developed in response to the absence of guidelines to assess neoplastic related spinal instability *[12]*. The SINS is a tool, which guides referrals to a spine surgeon and improves communication between physicians involved in the care of patients with spinal metastases *[12]*. The SINS consists of six parameters; five radiographic and one clinical parameter including location of the lesion, bone lesion quality, degree of vertebral collapse, spinal alignment, involvement of the posterolateral elements and quality of the perceived pain **(Table 1)** *[12]*. The total score, ranging between 0 and 18, is based on the sum of these six parameters *[12]*. The total score is subsequently grouped into three categories of spinal stability defined as stable (0 to 6 points), indeterminate unstable (7 to 12 points), and unstable (13 to 18 points) *[12]*. Consultation of a spine surgeon is recommended for patients with a SINS score of ≥ 7 *[12]*. The SINS is the first instrument available, based on expert consensus, to objectively quantify the degree of spinal instability. As such, consistent use of the SINS may not only optimize routine clinical practice for patients with spinal metastases, but it may also aid in the evaluation of the prognostic value of spinal (in)stability for treatment outcome. The impact of SINS on clinical practice and its prognostic value for radiotherapy response is investigated in Part I of this thesis.

TREATMENT OF SPINAL METASTASES

The main treatment goal for patients with spinal metastases is to maintain or improve quality of life by the alleviation of pain, and preservation or restoration of spinal stability and neurological function. The decision between management with surgery, radiotherapy or a combination of these treatment modalities is based on the evaluation of the four pillars of the NOMS framework *[13]*. NOMS is an acronym, representing the four pillars: Neurology, Oncology, Mechanical stability and Systemic disease *[13]*. The neurology and oncology pillars are evaluated together, with the clinical and radiological assessment of the degree of epidural spinal cord compression and the susceptibility of the tumor for ionizing radiation (radiosensitivity) *[13]*. The mechanical pillar addresses the assessment of spinal

TABLE 1. THE SINS CLASSIFICATION ACCORDING TO FISHER ET AL. [12]

	Score
Location	
Junctional (occiput-C2, C7-T2, T11-L1, L5-S1)	3
Mobile spine (C3-C6, L2-L4)	2
Semi rigid (T3-T10)	1
Rigid (S2-S5)	1
Pain *	
Yes	3
Occasional pain but not mechanical	1
Pain-free lesion	0
Bone lesion	
Lytic	2
Mixed (lytic/blastic)	1
Blastic	0
Radiographic spinal alignment	
Subluxation/translation present	4
De novo deformity (kyphosis/scoliosis)	2
Normal alignment	0
Vertebral body collapse	
> 50% collapse	3
< 50% collapse	2
No collapse with > 50% body involved	1
None of the above	0
Posterolateral involvement of spinal elements†	
Bilateral	3
Unilateral	1
None of the above	0

* Pain improvement with recumbency and/or pain with movement/loading of spine
† Facet, pedicle, or costovertebral joint fracture or replacement with tumor

stability *[13]*. Lastly, the systemic disease pillar addresses the overall clinical picture of the patient including performance status, systemic disease status and life expectancy *[13]*.

Single fraction or multi-fraction external beam radiotherapy (EBRT) is the mainstay of treatment for most patients with symptomatic spinal metastases *[14, 15]*. EBRT has been shown to achieve some degree of pain relief in up to 70% of patients, but only one-third of these patients achieve complete pain relief *[16, 17]*. The remaining 30% of patients, however, do not experience any alleviation of pain *[16, 17]*. Why some patients respond to radiotherapy, while others do not, needs to be further unravelled in order to improve patient selection. We hypothesized that pain predominantly caused by mechanical instability has an inferior response to radiotherapy compared to pain predominantly caused by local tumor activity *[18]*. This hypothesis is supported by a retrospective study conducted by our research group, which demonstrated an independent association between an increasing SINS score, representing higher levels of spinal instability, and the risk of radiotherapy failure *[18]*. Spinal instability is, however, likely only one factor that influences the lack of response to EBRT; a dose response relation may be another explanation. Radiation dose delivery with EBRT is non-conformal. The radiation dose administered to the spinal metastasis is therefore limited by the radiation tolerance of the neighboring spinal cord *[19, 20]*. Advances in radiotherapy techniques have led to the increased application of stereotactic body radiotherapy (SBRT) for the treatment of spinal metastases *[21, 22]*. SBRT allows for the delivery of ablative radiation doses to the tumor while limiting the radiation dose to the spinal cord and other organs at risk due to highly conformal dose distributions *[23, 24, 25]*. The results of the first, mainly retrospective, studies evaluating SBRT for spinal metastases are promising with high rates of pain relief and local control independent of tumor histology *[22, 21, 29, 26, 28, 27]*. Yet, to date, no results of prospective trials comparing the effectiveness of SBRT to EBRT for the treatment of spinal metastases are available.

Surgery is considered for patients with intractable pain after previous radiotherapy, spinal instability and/or metastatic epidural spinal cord compression (MESCC). Preservation or restoration of spinal instability is important in the management of patients with spinal metastases because spinal instability can cause severe pain, impairment in physical function and increase the risk of neurological compromise [30, 31]. Loss of neurological function and ambulatory status due to spinal instability is often preventable if patients are closely monitored and timely treated. Early identification of patients with spinal instability and/or MESCC is imperative as pre-treatment loss of neurological function and ambulatory status are poor prognostic factors for post-treatment ambulatory status and survival *[32, 33, 34]*.

The primary goals of surgery in patients with spinal metastases are pain control, maintaining function and quality of life through stabilization of the biomechanically compromised spine and, if necessary, decompression of neurological elements. For the majority of patients, surgery is followed by post-operative radiotherapy for local tumor control and additional pain relief. A time interval of at least 1-2 weeks between surgery and radiotherapy is currently recommended to prevent disruption of the wound healing process by radiation *[35, 36]*. Several studies have demonstrated the positive impact of surgery with or without adjuvant radiotherapy on pain control and health related quality of life (HRQOL) *[13, 30, 37]*. However, surgical interventions inherently carry the risk of adverse events. The potential benefits should therefore be thoughtfully weighed against the risks of the surgical procedure, especially considering its palliative intent. Advances in surgical techniques have led to the increased use of less invasive techniques, including vertebroplasty, kyphoplasty and/or percutaneous pedicle screw fixation, in patients with spinal metastases potentially decreasing the risk of adverse events *[38, 39]*. The outcomes of surgical management of patients treated for (indeterminate) unstable spinal metastases and/or neurological deficits are evaluated in Part II of this thesis.

Historically, outcome reporting for the treatment of spinal metastases mainly consisted of physician reported outcomes and survival rather than patient reported outcomes on HRQOL. However, the importance of patient reported outcomes measures (PROMs) in treatment evaluation has increasingly been recognized over the last decades *[40, 41]*. PROMs are not only important from a research perspective but should also play a role in daily clinical practice *[42]*. PROMs often assess several aspects of the multidimensional construct of quality of life, including mental health and daily functioning, which may otherwise not be addressed *[42]*. Furthermore, systematic treatment evaluation with PROMs may serve to quantify the impact of treatment on HRQOL *[42]*. Lastly, systematic use of PROMs in clinical practice may improve communication between patient and physician regarding outcomes *[42]*. Improved patient-physician communication may facilitate realistic treatment expectations, which is important to enhance patient satisfaction with treatment outcomes *[42]*.

Many generic and disease-specific PROMs exist to evaluate HRQOL. A generic questionnaire can be used to evaluate HRQOL in different patient populations, independent of the condition, and also facilitates the comparison of HRQOL among different patient populations. The use of a disease-specific questionnaire, together with a generic tool, is recommended for a comprehensive assessment of HRQOL. A disease-specific questionnaire is important as this enhances the specificity and the sensitivity to detect changes in quality of life for patients with a specific condition *[43]*. The Spine Oncology Study Group Outcomes Questionnaire (SOSGOQ) is the first questionnaire

specifically designed for evaluating outcomes in the spine oncology patient population *[43]*. The validity and reliability of the SOSGOQ is evaluated in Part II of this thesis.

Decreasing treatment burden while simultaneously increasing positive treatment outcomes is desirable for patients with spinal metastases, particularly in light of the palliative intent of therapeutic interventions. With advances in radiotherapy and surgical techniques, it may be possible to shorten or even eliminate the time interval between treatments. As a result, the patient may experience the analgesic effect from irradiation earlier and both interventions can be planned and performed in a single, shorter hospital admission period. The safety and feasibility of combining SBRT and surgery is addressed in Part III of this thesis.

THESIS OUTLINE

The research presented in this thesis aimed to optimize care for patients with symptomatic spinal metastases, through improvements in patient screening and treatment strategies. To this end, the value of SINS as a referral and prognostic tool is investigated in Part I. Part II describes the evaluation and outcomes of treatment for patients with spinal metastases. Finally, a novel treatment strategy for patients with symptomatic unstable spinal metastases is evaluated in Part III.

The following research objectives were defined:

Part I – Patient selection

- Chapter 2: To evaluate the literature regarding the use of the Spinal Instability Neoplastic Score (SINS) in the management of patients with spinal metastases
- Chapter 3: To estimate the effect of SINS on routine clinical practice for patients with symptomatic spinal metastases.
- Chapter 4: To assess the association between mechanical instability and response to palliative radiotherapy for spinal metastases.

Part II – Treatment evaluation

- Chapter 5: To evaluate the validity and reliability of the Spine Oncology Study Group Outcome Questionnaire (SOSGOQ).
- Chapter 6: To measure the effect of surgery (+/- radiotherapy) and radiotherapy alone on HRQOL for the treatment of indeterminate spinal instability.

- Chapter 7: To determine the incidence of adverse events after conventional open surgical intervention for spinal metastases.
- Chapter 8: To determine the incidence of adverse events after percutaneous pedicle screw fixation for spinal metastases.

Part III – Advances in treatment strategy

- Chapter 9: To compare the radiation dose in the posterior surgical area between external beam radiotherapy (EBRT), stereotactic body radiotherapy (SBRT) and SBRT with active sparing of the posterior surgical area.
- Chapter 10: To evaluate the safety of SBRT followed by surgical stabilization within 24 hours for the treatment of unstable spinal metastases.

The results, implications of the results for clinical practice and future perspectives are summarized and discussed in chapter 11.

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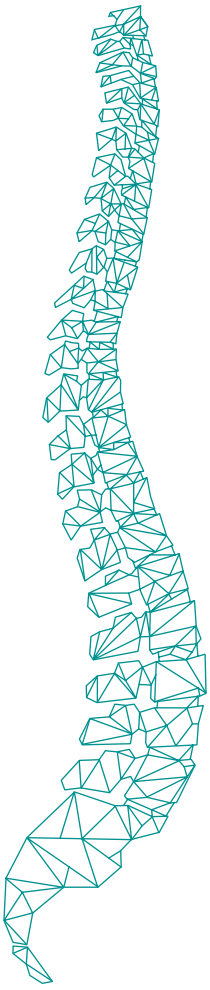
PART I

Patient selection



CHAPTER 2

The Spinal Instability Neoplastic Score: impact on oncologic decision-making.

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JJ Verlaan,
A. Sahgal,
E. Mendel,
N.A. Quraishi,
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Spine. 2016 Oct 15;41 Suppl 20:S231-S237.

ABSTRACT

Study design
Systematic literature review

Objective
To address the following questions in a systematic literature review:
1. How is spinal neoplastic instability defined or classified in the literature before and after the introduction of the Spinal Instability Neoplastic Score (SINS)?
2. How has SINS affected daily clinical practice?
3. Can SINS be used as a prognostic tool?

Summary of background data
Spinal neoplastic-related instability was defined in 2010 and simultaneously SINS was introduced as a novel tool with criteria agreed upon by expert consensus to assess the degree of spinal stability.

Methods
Pubmed, Embase, and clinical trial databases were searched with the key words "spinal neoplasm", "spinal instability", "spinal instability neoplastic score", and synonyms. Studies describing spinal neoplastic-related instability were eligible for inclusion. Primary outcomes included studies describing and/or defining neoplastic-related instability, SINS, and studies using SINS as a prognostic factor.

Results
The search identified 1414 articles, of which 51 met the inclusion criteria. No precise definition or validated assessment tool was used specific to spinal neoplastic-related instability prior to the introduction of SINS. Since the publication of SINS in 2010, the vast majority of the literature regarding spinal instability has used SINS to assess or describe instability. Twelve studies specifically investigated the prognostic value of SINS in patients who underwent radiotherapy or surgery.

Conclusion
No consensus could be determined regarding the definition, assessment, or reporting of neoplastic-related instability before introduction of SINS. Defining spinal neoplastic-related instability and the introduction of SINS have led to improved uniform reporting within the spinal neoplastic literature. Currently, the prognostic value of SINS is controversial.

INTRODUCTION

Cancer incidence rates are expected to increase; however, cancer-related deaths are expected to decrease due to improved systemic therapy *[1]*. As a result, the incidence of patients with spinal metastases will increase as will the complexity of management. Spinal metastases can be devastating with the development of spinal instability, which can cause neurological injury and severe pain. Therefore, early recognition of spinal instability is increasingly important and a concept that has previously been under-recognized within oncology. The diagnosis of instability is challenging and both clinical signs and symptoms, and radiological findings must be considered.

Criteria used to define and diagnose neoplastic-related spinal instability should be unambiguous and easily assessable for physicians taking care of this patient population to prevent interobserver variability. A previous systematic review by Weber et al. demonstrated the controversy about the definition, diagnosis, and assessment of spinal neoplastic-related instability *[2]*. In response, the spinal oncology study group (SOSG) defined spinal neoplastic-related instability as "loss of spinal integrity as a result of a neoplastic process that is associated with movement-related pain, symptomatic or progressive deformity, and/or neural compromise under physiologic loads" *[3]*. Subsequently, the Spinal Instability Neoplastic Score (SINS) was developed to assess the degree of spinal (in)stability in a standardized way *[3]*. The aims of SINS were to improve communication and referrals amongst medical specialists involved in the treatment of spinal metastases*[3]*. Furthermore, SINS could enhance the uniform reporting of spinal neoplastic-related instability in scientific studies *[3]*. Therefore, the objective of this study was to determine the impact of SINS, since its introduction by publication in 2010, on clinical decision-making and outcome reporting in patients with spinal metastases.
The following questions were addressed in this systematic literature review:

1. How is spinal neoplastic instability defined or classified in the literature before and after introduction of SINS?
2. How has SINS affected daily clinical practice?
3. Can SINS be used as a prognostic tool?

METHODS

Search strategy

This systematic literature review is conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines *[4]*. An electronic search was conducted in December 2015 using the Pubmed, Embase, Clinicaltrials.gov, National Institutes of Health, and controlled clinical trials databases. The search strategy was adopted to fit the specific database. The following search terms, synonyms, and related

key words, were combined using boolean operators: "spinal neoplasms"[Mesh], "Neoplasm metastasis"[Mesh], "spine"[Mesh], "vertebral column"[Title/Abstract], "unstable"[Title/Abstract], "spinal instability" [Title/Abstract], and "spinal instability neoplastic score" [Title/Abstract]. The search strategy was designed to secure a broad range of articles concerning neoplastic-related spinal instability. Inclusion of articles was limited to English publications. Duplicates were removed.

Study selection

Studies concerning the definition or classification of spinal neoplastic-related instability were eligible for inclusion. Titles and abstracts were screened for relevance using pre-specified inclusion and exclusion criteria. Full-text papers were screened and assessed for eligibility according to the selection criteria described in Table 1. Studies without a radiographic or clinical description, definition, or classification of spinal instability were excluded. References of included articles were hand-searched to identify additional articles.

Data extraction

Data extraction was performed by one reviewer (AV) using a pre-specified form relevant to the related question. The primary outcomes for the study questions were;

1. Any definition and/or radiographic criteria and/or classification of spinal (in) stability in vertebrae with metastases.
2. Any study describing the use of SINS.
3. SINS as prognostic factor.

Quality assessment

Considering the descriptive nature of this review and the wide range of study designs, quality of evidence was only assessed for studies related to the third research question and was assessed by a single reviewer (AV) using pre-specified criteria, including the description of the research question, methodology, study population, data collection, and reporting of results. Quality of evidence was rated as high, moderate, low or very low according to the GRADE system *[5]*.

RESULTS

Figure 1 outlines the literature search and selection process. The electronic search yielded 1414 unique articles after removal of 619 duplicates. Most articles were excluded during title and abstract screening because of failure to describe patients with neoplastic-related instability. A total of 51 articles and 18 (ongoing) trials met the inclusion criteria.

Radiographic and clinical definitions of stability

The majority of papers describing spinal instability due to spinal metastases used a clinical definition or report-specific radiographic criteria. A total of 11 papers used the presence of mechanical back pain, defined as pain aggravated by movement and relieved by recumbency, as the critical symptom for the presence of spinal instability *[6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16]*.

In addition to mechanical back pain, several authors described radiographic signs for spinal neoplastic-related instability. Radiographic signs that may be considered as evidence of spinal instability include; >40% tumor involvement of the vertebral body *[10]*, presence of 50% or more vertebral body collapse *[10, 16]*, presence of kyphotic deformity *[17]*, progressive deformity *[15]*, subluxation *[15, 17]*, translation *[15]*, or a retro-pulsed bone fragment in the spinal canal *[17]*.

TABLE 1. ELIGIBILITY CRITERIA

Inclusion criteria

Full-text article:

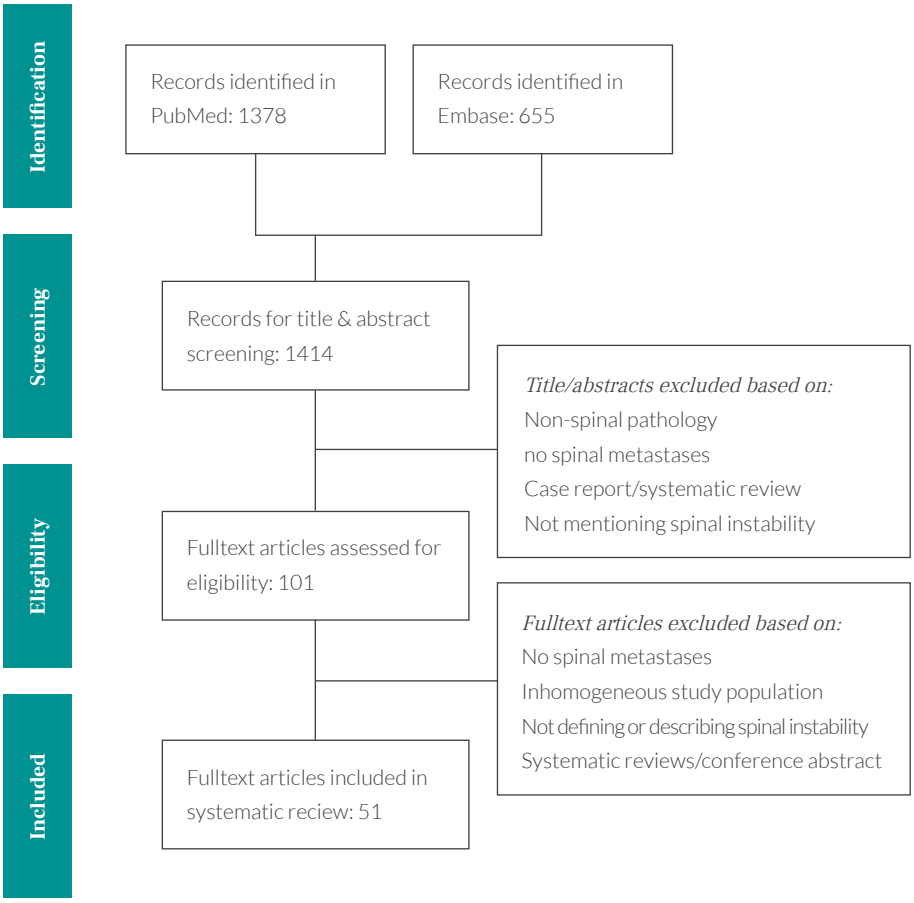
1) Study population consisting of patients with spinal metastases or model simulating spinal metastatic disease
2) Describing the radiographic signs and/or classification and/or (clinical) definition of neoplastic related spinal instability*
3) Using the SINS as study variable*

Exclusion criteria

1) Non-homogenous study population (>25% of the patients with a diagnosis other than spinal metastatic disease)
2) Sample size <10 cases.
3) Not describing, defining or classifying spinal instability
4) Systematic reviews, meta-analysis, case reports and conference abstracts

* Either adherence to criteria 2 or 3

FIGURE 1.



(In)stability classifications before development of SINS

Historically, biomechanical criteria developed for traumatic fractures were applied to assess spinal instability in patients with spinal metastases *[18]*. In an attempt to develop specific criteria for spinal neoplastic-related instability, Kostuik and Errico modified the three-column system of Denis et al. *[19]* into a six-column system by dividing the columns in the sagittal plane *[18, 20, 21]*. Involvement of three or four columns is deemed as "impending unstable" and involvement of five or six columns as "unstable" *[21]*.

The retrospective study by Asdourian et al. reported the pathogenesis of spinal deformity due to vertebral metastases in a cohort using radiographic imaging *[22]*. A consistent pattern of vertebral failure was observed and a classification system was developed to describe the different stages of vertebral failure *[22]*.

Siegal et al. proposed the following criteria for spinal instability in patients with spinal metastases; 1) anterior and middle column involvement or >50% collapse of vertebral body height, 2) Middle and posterior column involvement or shearing deformity, 3) three column involvement, 4) involvement of the same column in two or more adjacent vertebrae or 5) iatrogenic instability: laminectomy, resection of >50% of the surface of the vertebral body *[23, 24]*.

Following these reports, Taneichi et al. investigated the association between the occurrence of vertebral body collapse and the size and location of a lytic lesion to determine a critical defect size *[25]*. A score for the lumbar and thoracic vertebrae was developed to determine the risk of vertebral body collapse *[25]*. However, none of these classification systems have been validated.

SINS

In response to the controversy about the definition and assessment of spinal neoplastic-related instability, the SOSG defined spinal neoplastic-related instability and simultaneously developed the SINS score as tool to assess spinal instability. SINS consists of five radiographic and one clinical parameters [Table 2] *[3]*. The sum of these parameters results in a total score between zero and 18. Zero to six points denotes spinal stability, seven to 12 denotes impending spinal instability, and a score above 12 denotes spinal instability *[3]*. Consultation of a spine surgeon is recommended for scores of seven and above *[3]*. Of note, SINS was not developed as a treatment guide, but merely as a classification tool to assess spinal (in)stability and to improve communication and referrals between medical specialists *[3]*.

Reliability and predictive validity was first tested among the members of the SOSG, including thirty international spine oncology experts primarily from neurosurgical and orthopaedic specialties *[26]*. Validity of SINS was tested comparing the consensus opinion regarding stability (gold standard) to a binary SINS score of stability (stable vs. (impending) unstable) *[26]*. A sensitivity and specificity for the binary SINS score of 95.7% and 79.5%, respectively was demonstrated. Near-perfect intra- and inter-observer reliability could be determined for the total SINS score *[26]*.

TABLE 2. SINS SCORE ACCORDING TO FISHER ET AL. [3]

	Score
Location	
Junctional (occiput-C2, C7-T2, T11-L1, L5- S1)	3
Mobile spine (C3-C6, L2-L4)	2
Semi rigid (T3-T10)	1
Rigid (S2-S5)	0
Pain *	
Mechanical pain	3
Occasional pain but not mechanical	1
Pain-free lesion	0
Bone lesion	
Lytic	2
Mixed (lytic/blastic)	1
Blastic	0
Radiographic spinal alignment	
Subluxation/translation present	4
De novo deformity (kyphosis/scoliosis)	2
Normal alignment	0
Vertebral body collapse	
> 50% collapse	3
< 50% collapse	2
No collapse with > 50% body involved	1
None of the above	0
Posterolateral involvement of spinal elements†	
Bilateral	3
Unilateral	1
None of the above	0

* Pain improvement with recumbency and/or pain with movement/loading of spine
† Facet, pedicle, or costovertebral joint fracture or replacement with tumor

In view of the multidisciplinary aspect of care of patients with spinal metastases, the AOSpine Knowledge Forum Tumor (AOSKFT) also tested the reliability of SINS among an international panel of radiation oncologists and radiologists. Substantial inter-observer and excellent intra-observer reproducibility to distinguish between stable and (impending) unstable lesions was demonstrated *[27, 28]*.

Besides the reliability studies of the AOSKFT, reliability of SINS was also tested in three independently conducted studies *[29, 30, 31]*. The studies of Teixeira et al. and Campos et al. demonstrated fair to excellent inter-observer reliability for the total SINS score *[29, 30]*. Clinical experience with spinal metastases demonstrated to increase reliability *[30]*. The observers in these studies mainly consisted of spinal surgeons. Arana et al. used 83 medical specialists, including neurosurgeons, medical oncologists, radiation oncologists, radiologists, and orthopaedic surgeons to rate SINS on 90 cases *[31]*. Excellent intra-observer and moderate inter-observer reliability was found for the total SINS score *[31]*.

SINS in clinical practice

After publication of the SINS classification, numerous studies used SINS to classify the degree of spinal (in)stability in patients that underwent surgery or radiotherapy for spinal metastases *[32, 33, 34, 35, 36, 37, 38, 39]*. However, Rief et al. used the Taneichi classification to assess spinal instability *[40, 41]*. Moreover, the definition of spinal instability and the SINS score have been adopted in several clinical practice guidelines and decision frameworks for patients with spinal metastases. The NOMS criteria are a clinical decision framework for patients with spinal metastases; including four critical assessments: Neurologic (N), Oncologic (O), Mechanical stability (M), and Systemic disease (S) *[14]*. Assessment of the mechanical component consisted of the presence or absence of mechanical pain before the development of SINS *[12, 13, 42]*. After publication, SINS was incorporated in the NOMS criteria as classification to assess mechanical instability *[14]*. Ivanishvili et al. advocated their own decision framework called LMNOP *[43]*. The LMNOP framework considers; Location of the disease (L), Mechanical instability as assessed by SINS (M), Neurologic status (N), Oncological history (O), and the Physical status of the patient (P) *[43]*. Furthermore, the American College of Radiology (ACR) has incorporated SINS in their practice guideline for metastatic spinal cord compression and recurrent metastatic disease *[44]*. The American Academy of Orthopedic Surgeons (AAOS) incorporated SINS as classification for spinal instability in an instructional lecture on the management of patients with bone metastases for general practitioners *[45]*. With SINS increasingly being implemented in clinical guidelines, Versteeg et al. sought to determine the influence of implementing SINS in clinical practice *[46]*. A decrease in SINS scores was found in both a surgical and radiotherapy cohort after introduction of SINS. This effect was explained by increased awareness of spinal (in)stability in patients with spinal metastases and subsequent earlier referral to a spinal surgeon *[46]*.

Prognostic value of SINS

A total of 12 studies investigated the prognostic value of SINS, quality of evidence of the articles was rated as low to very low. Huisman et al. investigated the relationship between the degree of spinal instability, as reflected by the SINS score, and the need for re-irradiation *[47]*. The risk on the need for retreatment increased with an increasing SINS score (HR1.3, 95%CI 1.1-1.5) *[47]*. Lam et al. studied the relationship between the SINS score and occurrence of Spinal Adverse Events (SAE) after palliative radiotherapy *[48]*. Multivariate analysis revealed an increased risk on SAE with a SINS score of 11 or above (HR2.5, 95%CI1.3-4.9) *[48]*. Three studies investigated the prognostic value of SINS for survival after surgical treatment. All three studies demonstrated no prognostic value of SINS for postoperative survival *[34, 35, 49]*.

The majority of studies investigated the predictive value of SINS and/or components of SINS for the occurrence of vertebral compression fracture (VCF) after stereotactic body radiotherapy (SBRT) *[50, 51, 52, 53, 54, 55, 56]*. Factors that were independently associated with post-SBRT occurrence of VCF included: the presence of vertebral body collapse at baseline, the presence of a lytic lesion, malalignment of the spine, higher overall SINS score, and non-SINS related factors including a higher dose per fraction and single fraction SBRT *[50, 51, 52, 53, 54]* (Table 3). In contrast, two other studies demonstrated no relationship between SINS or SINS components and the occurrence of VCF post-SBRT *[55, 56]*.

Spinal stability in (ongoing) trials

A total of 18 registered clinical trials were retrieved that included spinal stability in their research protocol, either as in- or exclusion criteria, or as an outcome parameter *[57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74]*. Four of these trials incorporated SINS as a parameter for stability *[58, 60, 62, 72]*.

DISCUSSION

The SINS classification was published in 2010 in response to the controversy that existed regarding the definition and assessment of spinal neoplastic-related instability *[3]*. Originally, SINS was developed as a classification to assess the degree of spinal instability and to improve communication among the different medical specialists involved with the care of patients with spinal metastases *[3]*. More than five years later we sought to investigate the effect of the introduction of SINS on the literature concerning spinal neoplastic-related instability. A lack of consensus existed regarding the definition, assessment, and reporting about spinal neoplastic-related instability before publication of SINS. After the introduction of SINS, almost all published studies concerning spinal instability used SINS to classify the degree

TABLE 3. HAZARD RATIOS AND 95%CI FOR VCF RISK.

Authors	Sample size	Study design	Risk factors	[HR, 95%CI]
Cunha et al. *[49]*	90	R	Spinal alignment	[0.09, 0.024-0.33]
			Lytic Lesion	[0.082, 0.017-0.386]
Sahgal et al. *[50]*	252	R	Spinal alignment	[2.99, 1.57-5.70]
			Baseline VCF	
			<50% collapse	[8.98, 4.48-18.0]
			No VCF but >50% involved	[4.46, 2.08-9.57]
			Lesion type	[3.53, 1.58-7.93]
			Dose per fraction	
			>24Gy	[5.25, 2.29-12.01]
			20-23Gy	[4.91, 1.96-12.28]
Thibault et al. *[52]*	37	R	Baseline VCF	[9.25, 1.64-52.31]
			Single fraction SBRT	[5.03, 1.19-21.28]
Finnigan et al. *[51]*	34	R	Overall SINS score*	
Lee et al. *[53]*	79	R	SINS score (>7) age	[5.63, 2.41-13.13] [2.15, 1.07-4.32]

* no hazard ratios reported
R= retrospective study

of spinal neoplastic-related instability *[32, 33, 34, 35, 36, 37, 38, 39]*. Furthermore, several studies sought to investigate if spinal instability, as reflected by SINS, has a prognostic value for patients who undergo surgical or radiotherapy treatment *[34, 35, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56]*. It should be noted that the SINS score is the sum of individual components of which some quantify the risk of spinal instability (e.g. location, lesion quality) while other factors express the current degree of spinal instability (e.g. the presence of mechanical pain, deformity). SINS may, therefore, not be the optimal tool to assess the prognostic value of spinal neoplastic-related instability. Furthermore, mechanical stability is only one component that influences clinical decision-making and treatment outcome. Future studies

should, therefore, focus on the impact of the individual components of SINS on treatment outcome, as was demonstrated in earlier published studies *[51]*, combined with other known prognostic factors such as performance status *[75]*.

The total SINS score or individual components of SINS demonstrated to have a prognostic value for radiotherapy failure and the occurrence of VCF post-SBRT. However, these studies were limited by a lack of unstable cases (SINS >12) and a non-normal distribution of the SINS score. The prognostic value of SINS was investigated mainly in studies concerning patients who were treated with radiotherapy. The lack of unstable cases can be explained by the use of the SINS score in clinical practice as demonstrated by the study by Versteeg et al., which showed a decrease in SINS scores in both the radiotherapy and surgical cohort after introduction of SINS *[46]*. This phenomenon is thought to occur due to increased awareness of spinal instability when using SINS and subsequent earlier referral to a spinal surgeon, as spinal instability is a (relative) indication for surgical intervention *[46]*. These results support the use of SINS as a valuable tool in daily clinical practice to facilitate timely referral. It should, however, be noted that SINS is not (prospectively) validated due to the lack of a gold standard and moreover as a wait-and-see policy to assess progression of instability is unethical. The prognostic value of SINS for progression of instability is therefore unknown. Consultation of a spine surgeon is recommended for SINS scores above 7, reflecting impending spinal instability (7 – 12) or spinal instability (>12) *[3]*. However, due to the construction of the SINS score, including components that quantify both the degree of instability and the risk of instability, a score of 9 may identify a patient with impending instability, but could also reflect an unstable situation. In its current form, the total SINS score is calculated by the sum of each category. This approach ignores the fact that some combinations of components are more unstable than others which might be overcome by multiplication of certain categories if they coexist instead of the sum of the individual components.

The increasing incidence of spinal metastases has led to an increased need for surgical and radiotherapy interventions to maintain or improve patient-related quality of life. In order to develop evidence-based treatment strategies for spinal neoplastic-related instability it is important to use uniform definitions and outcome parameters. Consistent use of SINS and/or the components of SINS to study spinal instability will facilitate uniform reporting of results and could ultimately enhance the quality of the research and patient outcomes. Several investigators have used finite element modeling to investigate risk factors for pathologic vertebral fracture and to develop a CT-scan based model to assess the present risk *[2]*. However, none of these studies has led to the development of an instrument for clinical practice. Snyder et al. used CTRA as a non-invasive method to predict vertebral fracture in breast cancer patients with spinal metastases *[76]*. However,

clinical implementation is limited due to the requirement of advanced operator input to create bone models for evaluation *[76]*. In addition, the time required for analysis is lengthy *[76]*. Furthermore, the CTRA's application in the spine is questionable given that not all vertebral fractures are symptomatic or suggest instability. In contrast, spinal (in)stability as classified by SINS is based on six common radiographic and clinical parameters and does not need sophisticated analyzing methods. Moreover, the results of Versteeg et al. seem to support the clinical usefulness as a referral tool *[46]*. It should, however, be noted that the final judgment of current or prospective (in)stability still depends on the experience of the spinal surgeon. Future studies working towards a practical and reliable simulation model based on individualized CT-data could, therefore, still be beneficial for daily clinical practice.

CONCLUSION

SINS was originally developed as a classification tool to assess spinal (in)stability in response to the existing controversy surrounding spinal neoplastic-related instability. Aims of the SINS were to improve communication and referrals among different medical specialists. The SINS consists of components quantifying the risk and the current degree of spinal instability and therefore, may not be appropriate to use as a prognostic tool. However, the SINS components: vertebral body collapse, lytic lesion, and malalignment of the spine demonstrated to be associated with post-SBRT VCF *[50, 51, 52, 53, 54]*. Following its introduction, SINS has been widely used to classify the degree of spinal instability. Moreover, SINS has been incorporated in multiple treatment guidelines, resulting in more uniform reporting and defining of spinal neoplastic-related instability, and earlier referral of patients with (impending) unstable spinal metastases to a spinal surgeon. This new practice may lead to a more standardized approach of treating unstable spinal metastases, to improved patient care, and ultimately, to improved clinical outcomes.

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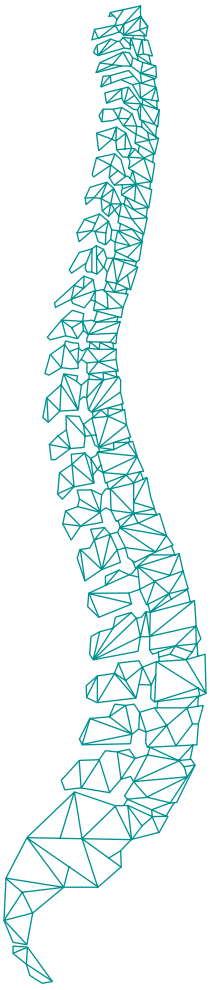

CHAPTER 3

The effect of introducing the Spinal Instability Neoplastic Score in routine clinical practice for patients with spinal metastases.

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ABSTRACT

Background

Stable spinal metastases are effectively treated with radiotherapy, whereas unstable spinal metastases often need surgical fixation followed by radiotherapy for local control. The Spinal Instability Neoplastic Score (SINS) was developed as a tool to assess spinal neoplastic related instability with the goal of helping to guide referrals among oncology specialists. We compare the average degree of spinal instability between patients with spinal metastases referred for surgery or for radiotherapy, and evaluate whether this difference changed after introduction of the SINS score in clinical practice.

Methods

All patients with spinal metastases treated with palliative surgery or radiotherapy in the period 2009-2013 were identified in two spine centers. For all patients the SINS was scored on pre-treatment imaging. The SINS scores before and after introduction of the SINS in 2011 were compared within the surgical and radiotherapy group. Furthermore, the overall SINS score was compared between the two groups.

Results

The overall SINS score was significantly higher in the surgical group with a mean SINS score of 10.7 (median 11) versus 7.2 (median 8) for the radiotherapy group. The mean SINS score decreased significantly for both groups after introduction of the SINS in clinical practice from 11.2 to 10.3 in the surgical group and from 8.4 to 7.2 in the radiotherapy group.

Conclusions

SINS scores differed significantly between patients treated with surgery or radiotherapy. The introduction of SINS led to a decrease in SINS scores for both groups, suggesting that using SINS in metastatic spinal disease increases awareness for instability and may subsequently result in earlier referrals for surgical intervention.

INTRODUCTION

The skeleton is the most common site of metastases in advanced cancer, with the spine being the most frequent location *[1]*. The median survival time of patients with bone metastases has substantially improved over the last decades, mostly because of advances in oncological treatment options *[2]*. Bone metastases greatly increase the risk of skeletal related events, which have a substantial negative impact on quality of life and daily functioning *[3, 4]*. Because the presence of spinal metastases represents advanced cancer, the goal of treatment shifts from long-term survival to preservation of quality of life for the remaining lifetime by retaining function and relieving symptoms *[2]*.

External beam radiotherapy has been the cornerstone of palliative treatment for painful spinal metastases, and has been reported to be effective in 50%-80% of patients *[5]*. For more complex cases, such as patients with spinal cord compression, neurological deficits and/or spinal mechanical instability, medical oncologists, radiation oncologists and spinal surgeons need to collaborate to provide the best supportive care possible *[6]*. Neurological deficits and spinal cord compression are relatively easy to assess with physical/neurological examination and appropriate imaging. In contrast, evaluating spinal instability is more demanding especially for nonspine surgeons, yet it is important because spinal instability increases the risk for neurological compromise and persisting disabling pain *[7]*. Considering the potential prognostic implications, spinal instability should be suspected in every patient with a proven malignancy and spinal complaints. To help direct referrals to a radiation oncologist or spine surgeon the Spine Oncology Study Group (SOSG) developed the Spinal Instability Neoplastic Score (SINS) in 2010 to assess the degree of spinal (in)stability caused by metastatic disease *[7]*. The score consists of the sum of five radiographical and one clinical parameter, resulting in a total (summed) score between 0 and 18 points **(Table 1)** *[7]*. The total score is divided in three categories of spinal stability: stable (0-6 points), impending/potentially unstable (7-12 points) and unstable (13-18 points) *[7]*. The SINS score does not provide a treatment recommendation but consultation of a spinal surgeon is currently advised for SINS scores equal to or greater than 7 points *[7]*. The SINS has undergone extensive reliability testing among different oncology specialists and radiologists, reflecting the multidisciplinary aspect of care for cancer patients [*8*, *9*, *10]*. Excellent agreement was found between radiation oncologists, radiologists and spinal surgeons for the differentiation between stable and (impending) unstable cases *[9, 10]*. With the repeatability of the SINS confirmed to assess spinal instability the next step would be to determine the influence of implementing the SINS in routine clinical practice for patients with spinal metastases. After introduction and application of the SINS in clinical practice a change in referral pattern should be expected, with a decrease in inappropriate and/or late referrals. Therefore the aim of this study was to compare the average degree of spinal instability in patients with spinal metastases referred for surgery or radiotherapy before and after introduction of the SINS in clinical practice.

TABLE 1. SINS SCORE ACCORDING TO FISHER ET AL. [7]

	Score
Location	
Junctional (occiput-C2, C7-T2, T11-L1, L5- S1)	3
Mobile spine (C3-C6, L2-L4)	2
Semi rigid (T3-T10)	1
Rigid (S2-S5)	0
Pain *	
Mechanical pain	3
Occasional pain but not mechanical	1
Pain-free lesion	0
Bone lesion	
Lytic	2
Mixed (lytic/blastic)	1
Blastic	0
Radiographic spinal alignment	
Subluxation/translation present	4
De novo deformity (kyphosis/scoliosis)	2
Normal alignment	0
Vertebral body collapse	
> 50% collapse	3
< 50% collapse	2
No collapse with > 50% body involved	1
None of the above	0
Posterolateral involvement of spinal elements†	
Bilateral	3
Unilateral	1
None of the above	0

* Pain improvement with recumbency and/or pain with movement/loading of spine
† Facet, pedicle, or costovertebral joint fracture or replacement with tumor

METHODS

An international retrospective review was performed of patients who underwent stabilizing surgery or radiotherapy for spinal metastases in two tertiary academic centers between January 2009 and December 2013. Both spine centers are tertiary referral centers specialized in spinal oncology. The time frame was chosen because the SINS was introduced in 2011 in our institutions, resulting in an equal distribution of time before and after introduction of the SINS. The SINS score was introduced among the oncologists and radiation oncologists through an instructional lecture and/or by providing pocket-cards with SINS methodology for clinical use. Surgical referral was recommended for patients with a SINS score of 7 or above. Indications for treatment of patients with spinal metastases were comparable for both spine centers. The study was approved by the institutional review board of both participating centers.

Study Population

Patients were included if they were diagnosed with spinal metastases, were treated with radiotherapy or surgery, and were neurologically minimally impaired or intact. Neurological status was classified according to the American Spinal Injury Association (ASIA) classification *[11]*, with ASIA E representing normal neurological function and ASIA D without progressive neurological deficits being interpreted as minimally impaired neurological function. All surgical patients presented with symptoms warranting palliative surgical intervention including pathological fracture, intractable back pain, and impending deterioration of neurological status.

Surgical patients were included in both spine centers and compared to patients from a cohort of radiotherapy patients with spinal metastases who underwent palliative radiotherapy at the European center. Patients in the radiotherapy group that would never have been surgical candidates based on their limited prognosis (as reflected by their short follow-up time) were excluded. For this purpose, we required radiotherapy patients to have the same follow-up time as the surgical group or at least 12 months of follow-up. Because the number of patients treated with radiotherapy exceeded the number of surgically treated patients, a random sample of 160 patients was selected from the radiotherapy group to equal the number of surgically treated patients.

The exclusion criteria were the presence of a primary spinal tumor, intradural tumor, epidural metastasis without bony involvement, or progressive neurological impairment. Patients classified with progressive neurological impairment were excluded to eliminate neurological compromise as primary indication for treatment.

Outcomes

Demographic characteristics and clinical data were collected from medical charts. Governmental databases were accessed to retrieve information regarding vital statistics. The SINS score was calculated for each patient using pre-treatment computed tomography (CT) scans. Pre-treatment CT scans were obtained using 16 detector row CT scanners or superior (Philips Medical Systems, Eindhoven, The Netherlands), for adequate visualization of the spinal column. All CT scans were reviewed using the same window and level settings; window level +300 HU and window width +1,000 HU.

In case of multiple spinal metastases the SINS was calculated for each lesion in the treatment area and the lesion with the highest SINS score was used for analysis. Information regarding the pain component was retrieved from the medical chart and was scored with identical criteria for both groups, three points whenever pain was continuously present, and one point when pain was occasionally present or of non-mechanical origin *[6]*. The SINS was scored by one observer experienced in assessing spinal stability; in ambiguous cases a spine surgeon with a special focus on spinal oncology was consulted for consensus on the final SINS score. The observers were blinded for patient characteristics but not for treatment type.

Statistical Analysis

Patients treated with surgery or radiotherapy were compared for age, gender, primary tumor type, disease extent, pain symptoms, neurological status (ASIA score), total SINS score (continuous score) and categorical SINS (stable, potentially unstable, unstable). In addition, the SINS scores before and after introduction of the SINS in routine clinical practice were compared within the two cohorts. The chi-square and fisher exact test were used for categorical variables and the independent sample T-test for continuous variables. P <0.05 defined statistical significance. All statistical analyses were performed using SPSS 21.0 (IBM corp, Armonk, NY).

RESULTS

Patient characteristics

A total of 1509 patients were identified, 160 underwent stabilizing surgery and 1349 received radiotherapy. From the radiotherapy cohort, 160 patients were randomly selected for analysis. Of the surgically treated patients, 84 were treated in Europe and 76 in North America. Surgical patients were younger (P=0.002), had less often a primary breast, prostate or lung tumor (P<0.001), had a shorter time between diagnosis of spinal metastases and treatment (P=0.013), and were more often classified as ASIA D (P<0.001) compared to radiotherapy patients (Table 2).

TABLE 2. BASELINE CHARACTERISTICS

	Surgery (N=160)	Radiotherapy (N=160)
Age	60.5 (± 11.1)	64.5 (± 12.5)
Spinal metastases time*	5 (0-369)	12 (0-276)
Treatment time**	5 (0-401)	8 (0-449)
Gender N, %		63 (39)
Male	90 (56)	97 (61)
Female	70 (44)	63 (39)
Tumor category N, %		
Breast	25 (16)	47 (29)
Prostate	15 (9)	41 (26)
Lung	26 (16)	24 (15
Renal cell	25 (16)	9 (6)
Others	69(43)	39 (24)
Disease extent N, %		
Local + bone	69 (43)	76 (48)
Local/bone/lymph node	39 (24)	32 (20)
Local/bone/lymph node/organ	52 (33)	52 (32)
Presentation N, %		
No pain	5 (4)	14 (9)
Radicular pain	22 (16)	13 (8)
Back pain	87 (62)	106 (66)
Radicular and back pain	25 (18)	27 (17)
ASIA score N, %		
ASIA E	105 (66)	152 (95)
ASIA D	66 (34)	8 (5)

* time between primary tumor diagnosis and diagnosis of spinal metastases
** time between the diagnosis of spinal metastases and treatment.
abbreviation: ASIA, American Spinal Injury Association

No significant differences in demographic characteristics were found between the surgical cohorts from the two spine centers. Breast, renal cell, lung and prostate were

the most common primary tumor types. Median follow-up time was 10 months (range 0-67) in the surgical cohort, and 11 months (range 0-66) in the radiotherapy cohort. During follow-up, 210 (66%) of the patients died; 112 patients (70%) of the radiotherapy cohort and 98 patients (61%) of the surgical cohort.

SINS score

The majority of patients (73 %) were treated for a lesion in the junctional or semi-rigid spine and mechanical pain was present in 63% of the patients **(Table 3)**. The mean SINS score was significantly (P<0.001) higher for the surgical patients (10.7; median 11; range 3-17) compared to those receiving radiotherapy, (7.2; median 8; range 2-14). The mean SINS score in both groups decreased significantly after introduction of the SINS in routine clinical practice, from 11.2 to 10.3 in the surgical group and from 8.4 to 7.2 in the radiotherapy group **(Table 4)**.

Evaluation of the SINS scores by category of stability showed a significant (P<0.001) difference between the surgical and radiotherapy group, with more unstable lesions (28%) in the surgical group than in the radiotherapy group (3%). Additionally, 107 (67%) of the radiotherapy patients and 105 (66%) of the surgical patients fell in the category of impending instability (7-12 points) **(Figure 1A)**.

Twenty (23%) patients treated with radiotherapy had a SINS score below 7 before introduction of the SINS compared to 27 (39%) after introduction. Furthermore, 65 (73%) of the radiotherapy patients had a SINS score between 7 and 12 before introduction, and 42 (60%) patients had a SINS score between 7 and 12 after introduction of the SINS **(Figure 1B)**. In comparison, 31 (39%) of the surgically treated patients had a SINS score above 12 before introduction and 13 (17%) after introduction of the SINS. Forty-one (52%) of the surgically treated patients were within the category of impending instability before introduction and 57 (77%) after introduction of the SINS **(Figure 1C)**.

Eleven (7%) of the surgically treated patients were in the stable category comprising one patient with a SINS score of 3, one patient with a SINS score of 4 and nine patients with a SINS score of 6. The two patients with a SINS score of 3 and 4 points were operated to avoid further neurological compromise but were without progressive neurological deficits at the time of consultation. The nine patients with a SINS score of 6 consisted of six patients with minimal neurological impairment (ASIA D) but no signs of progressive neurological deficits; five patients had lesions in the thoracolumbar or lumbosacral junction, combined with the presence of mechanical pain; or occasional pain and a lytic lesion. The remaining four patients had a lesion in the semi-rigid region, occasional pain, vertebral body collapse and unilateral involvement of the posterior elements.

TABLE 3. BASELINE SINS CHARACTERISTICS

	Surgery N (%)		Radiotherapy N (%)
SINS Components	*Europe*	*North-America*	
Location			
Junctional (occiput-C2, C7-T2, T11-L1, L5-S1)	33 (39)	28 (37)	62 (39)
Mobile spine (C3-C6, L2-L4)	18 (22)	17 (22)	50 (31)
Semi rigid (T3-T10)	33 (39)	30 (39)	46 (29)
Rigid (S2-S5)	0 (0)	1 (3)	1 (1)
Pain			
Mechanical pain	45 (54)	54 (71)	101 (63)
Occasional pain but not mechanical	33 (39)	14 (18)	41 (26)
Pain-free lesion	6 (7)	8 (11)	17 (11)
Bone lesion			
Lytic	61 (73)	44 (58)	73 (46)
Mixed (lytic/blastic)	13 (15)	30 (39)	54 (34)
Blastic	10 (12)	2 (3)	33 (20)
Radiographic spinal alignment			
Subluxation/translation present	5 (6)	10 (13)	0 (0)
De novo deformity (kyphosis/scoliosis)	22 (27)	24 (32)	12 (7)
Normal alignment	57 (68)	42 (55)	147 (93)
Vertebral body collapse			
> 50% collapse	30 (36)	19 (25)	14 (9)
< 50% collapse	32 (38)	26 (34)	40 (25)
No collapse with > 50% body involved	18 (22)	20 (26)	48 (30)
None of the above	4 (4)	11 (15)	57 (36)
Posterolateral involvement of spinal elements			
Bilateral	45 (54)	49 (64)	30 (19)
Unilateral	38 (45)	21 (28)	88 (55)
None of the above	1 (1)	6 (8)	41 (26)

TABLE 4. MEAN SINS SCORES BEFORE AND AFTER INTRODUCTION OF THE SINS IN CLINICAL CARE

	Before SINS (N=168)	After SINS (N=145)	P value
Radiotherapy	8.4	7.2	0.046
Surgery	11.2	10.3	0.002
Europe	10.8	10.3	
North-America	11.4	10.1	

FIGURE 1A. DISTRIBUTION OF SINS CATEGORIES

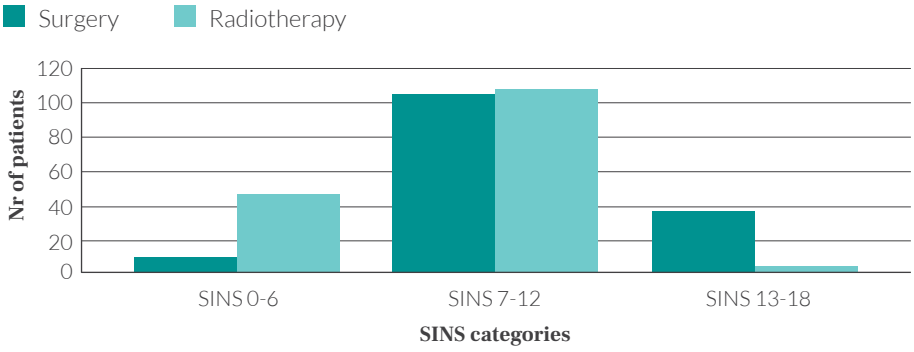


FIGURE 1B. DISTRIBUTION OF SINS IN RADIOTHERAPY COHORT

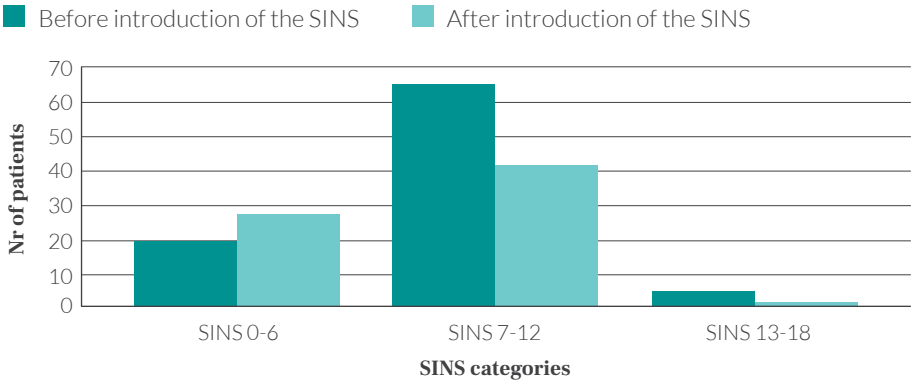
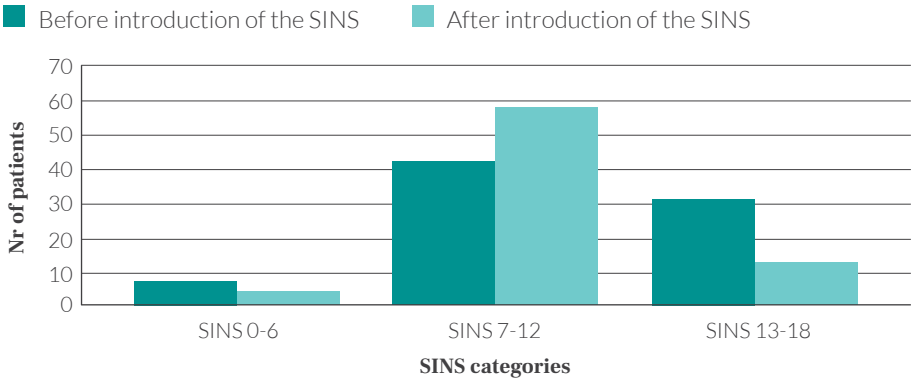


FIGURE 1C. DISTRIBUTION OF SINS IN SURGICAL COHORT



DISCUSSION

This study demonstrated a significant decrease in mean and median SINS score in both the surgical and radiotherapy groups after introduction of the SINS in routine clinical practice. In addition, a significant difference in overall mean, median and categorical SINS between the surgical and radiotherapy cohort was found. The decrease in SINS score may be explained by increased awareness of neoplastic related spinal instability, and earlier and more appropriate referral to the spine surgeon after introduction of the SINS in clinical practice. The SINS classification system was developed to classify spinal instability caused by metastatic disease and to provide a tool to guide referrals among the different specialists involved in the care of cancer patients. Evaluation of the SINS score has until now been limited to reliability and validity testing on selected case series *[8, 12, 13]*. This study is the first study to determine the influence of the SINS in a clinical setting with a substantial number of patients.

At baseline, significant differences were found between the surgical and radiotherapy cohort for age at time of treatment, primary tumor type, time between the diagnosis of spinal metastases and treatment, and neurological status. Although breast, prostate, lung and renal cell carcinoma represented more than 50% of the primary tumors in both the surgical and radiotherapy cohort, the surgical cohort contained significantly more (46%) 'other' primary tumor types compared with the radiotherapy cohort. This

may be explained by aggressiveness of other tumor types warranting earlier surgical intervention in patients still fit for surgery. In addition, the neurological status differed significantly between the two cohorts, with the surgical cohort containing more patients classified as ASIA D. This may be explained by the choice for a more aggressive (surgical) approach, in case a patient presents with the combination of (impending) spinal instability and minimal non-progressive neurological deficits. Furthermore, radiation oncologists refer patients with neurological deficits in an earlier stage for surgical evaluation, because neurological compromise is one of the key indications for surgical intervention *[14]*.

The decrease in mean SINS scores in both groups after introduction of the SINS score may be explained by the reverse of the "Will-Rogers phenomenon" *[15]*, an apparent epidemiological paradox named after comedian Will Rogers based on his following quotation "When the Oakies left Oklahoma and moved to California, they raised the average intelligence level in both states." This term has been used to describe stage migration in cancer patients, a change in diagnostic criteria or the improved sensitivity of diagnostic techniques to stage cancer results in the migration of patients with a better prognosis into a stage of patients with a worse prognosis resulting in improved survival rates for both groups *[15]*. Similarly, in our study patients with the highest SINS scores in the radiotherapy cohort, yet still in the lower range of spinal instability, shifted from the radiotherapy group to the surgical group resulting in decreased mean SINS scores in both cohorts. More patients with a score of impending spinal instability and an indication for surgical stabilization were operated.Minimally invasive procedures can effectively be used to treat impending instability whereas gross spinal instability requires extensive open surgery, which is less desirable in this fragile patient category. Increased awareness of (impending) spinal instability, earlier and more appropriate referral by different oncology specialists after the introduction of the SINS in clinical practice may account for these changes.

Considering the three different categories of spinal stability, it is known that most stable spinal metastases can effectively be treated with radiation therapy and that gross spinal instability is best treated with surgical stabilization provided the patient is fit for surgery *[5, 8]*. However, it is unknown what the optimal treatment is for patients with impending spinal instability. This is reflected by the large number of patients with impending instability in both the radiotherapy (66%) and surgical cohort (67%). Although radiotherapy is effective in 50% to 80% of the patients, a substantial number of patients do not gain any pain relief *[16, 17]*. It is not completely understood why some patients respond to radiotherapy and others do not. The current authors hypothesize that "metastatic bone pain caused predominantly by mechanical instability of the spine responds less well to radiotherapy than metastatic bone pain caused by local tumor activity" *[18]*. This was confirmed by a study from Huisman et al *[18]* demonstrating a relationship between the risk

on radiotherapy failure and a higher SINS score, every point increase in SINS risk increased the risk of radiotherapy failure with 30%. Patients with a high SINS should therefore not be subjected to radiotherapy before consultation of a spine surgeon to reduce the risk of radiotherapy failure and having to perform surgery after irradiation with its inherent risks around wound healing. However, this was a retrospective study with radiotherapy failure defined as the need for retreatment on the index site rather than using international consensus guidelines for radiotherapy response.

The SOSG recommends consultation of a spine surgeon for all patients with a SINS score of 7 or greater. In view of the increased burden of extra hospital visits for cancer patients to consult a spine surgeon, and more than 60% of the patients in the radiotherapy cohort having a SINS score above 7, increasing the threshold of the SINS score may be considered before recommending surgical consultation. Furthermore, considering the limited resources and increasing costs of health care *[19, 20]* it may be useful to increase the threshold of the SINS score to limit the number of inappropriate referrals. To find the optimal cut-off value a step wedge study design using different cut-off values in different centers should be performed.

Although this study demonstrated a significant difference in spinal stability between the surgical and radiotherapy groups and within the individual groups before and after introduction of the SINS, some study limitations can be identified. First, because of the retrospective nature of the study, scoring of the pain component is less reliable. According to the SOSG spinal instability is strongly related with the presence of mechanical pain as defined by presence of movement related pain improving with recumbency *[7]*. Scoring of the pain component was done with identical criteria in the radiotherapy and surgery cohort, in order to score the pain component uniformly. Any over- or underestimation would therefore be equal in both groups. However, this may have influenced the overall SINS scores for both groups to some extend. Second, the observer was not blinded for the treatment strategy of the patients, which could have biased scoring of the SINS. Furthermore, the SINS was scored by one rater. However, previous testing of the reliability of the SINS has demonstrated excellent inter- and intra-observer reliability to distinguish between the three different categories of spinal instability *[8]* and the judgment of one observer experienced with the SINS methodology was therefore deemed sufficient. Moreover, a spine surgeon was consulted in ambiguous cases to reach consensus.

CONCLUSION

This is the first study to evaluate the effect of the introduction of the SINS in clinical practice. The SINS was developed to evaluate the degree of spinal instability, improve communication and facilitate appropriate referrals among spine oncology specialists. Treatment of patients with spinal metastases is multidisciplinary and evaluation of spinal instability is only one of several factors that are taken into account. Our study demonstrated a significant decrease in mean SINS score after the introduction of the SINS in clinical practice. This may be explained by increased awareness of spinal neoplastic related instability, and earlier and more appropriate referral of patients to a spinal surgeon after introduction of the SINS. Future studies are needed to determine the optimal threshold to recommend surgical consultation in order to balance under- and over referral considering that most of the surgical and radiotherapy patients have a score of impending instability.

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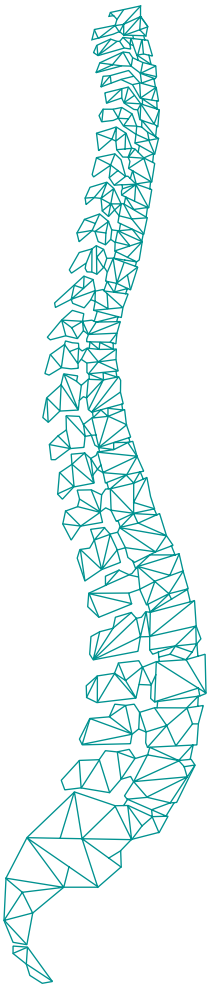

CHAPTER 4

Prospective evaluation of the relationship between mechanical stability and response to palliative radiotherapy for symptomatic spinal metastases.

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ABSTRACT

Purpose

A substantial number of patients with spinal metastases experience no treatment effect from palliative radiotherapy. Mechanical spinal instability, due to metastatic disease, could be associated with failed pain control following radiotherapy. This study investigates the relationship between the degree of spinal instability, as defined by the Spinal Instability Neoplastic Score (SINS), and response to radiotherapy in patients with symptomatic spinal metastases in a multi-institutional cohort.

Methods and Materials

The SINS of 155 patients with painful thoracic, lumbar or lumbosacral metastases from two tertiary hospitals was calculated using images from radiotherapy planning CT scans. Patient-reported pain response, available for 124 patients, was prospectively assessed. Pain response was categorized, according to international guidelines, as complete, partial, indeterminate, or progression of pain. The association between SINS and pain response was estimated by multivariable logistic regression analysis, correcting for predetermined clinical variables.

Results

Of the 124 patients, 16 patients experienced a complete response and 65 patients experienced a partial response. SINS was associated with a complete pain response (adjusted odds-radio [ORadj] 0.78; 95% confidence interval [CI] 0.62 – 0.98), but not with an overall pain response (ORadj 0.94; 95% CI 0.81–1.10).

Conclusions

A lower SINS, indicating spinal stability, is associated with a complete pain response to radiotherapy. This supports the hypothesis that pain resulting from mechanical spinal instability responds less well to radiotherapy compared to pain from local tumor activity. No association could be determined between SINS and an overall pain response, which might indicate that this referral tool is not yet optimal for prediction of treatment outcome.

INTRODUCTION

The incidence of patients with spinal metastases is increasing due to the increasing cancer incidence and the improved life expectancy of cancer patients *[1–3]*. Spinal metastases may cause debilitating pain and neurological deficits, impairing quality of life *[4, 5]*. Radiotherapy has been the standard of care for the treatment of uncomplicated painful spinal metastases. However, up to 70% of the patients treated with radiotherapy are resistant to treatment or experience only a partial response *[6]*. Surgery is offered to patients with mechanical spinal instability and patients with persisting or progressive neurological deficits.

To ensure fast and effective symptom relief, optimal treatment selection is crucial considering the limited life expectancy of these patients. Previous studies have tried to identify predictive factors for response to palliative radiotherapy, but have shown inconsistent results *[7–13]*. Therefore, to optimize treatment and/or patient selection we need to identify new factors to predict treatment outcome. Pain from spinal metastases can result from local tumor activity, pressure on neurological structures, and/or impaired mechanical integrity *[14]*. The Spine Oncology Study Group developed the Spinal Instability Neoplastic Score (SINS) to assess the degree of spinal instability in order to guide patient referral *[15]*. In two retrospective studies, it was shown that a higher SINS, reflecting a higher degree of spinal instability, was associated with radiotherapy failure *[16, 17]*. This suggests that discriminating mechanical pain from tumor pain could help in identifying patients at increased risk of radiation treatment failure. In order to confirm the retrospective data, a prospective cohort study was conducted to investigate the relationship between the degree of spinal (in)stability and response to radiotherapy.

METHODS AND MATERIALS

Study design

An observational cohort study including patients with spinal metastases treated with palliative radiotherapy was conducted between July 2013 and January 2015 in two tertiary referral centers in North America and Europe. Institutional review board approval was obtained for both institutions. Patients were prospectively enrolled and followed longitudinally for up to 6 weeks (time window -2 / +2 weeks) after treatment and all patients provided written informed consent to participate in this study. All patients from the department of radiation oncology with painful (i.e., a pain score of at least 2, on a scale of 0–10) thoracic, lumbar or lumbosacral metastases without invalidating neurological deficits (ASIA (American Spinal Injury Association [18]) E or D without progression) were eligible for inclusion. Patients with multiple myeloma, lymphoma, or a history of surgery to the same anatomic level were excluded. Patient characteristics were collected from medical

records at baseline and governmental databases were accessed to retrieve vital statistics. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for reporting of observational cohort studies was used *[19]*.

Measurements

A single senior spine surgeon, specialized in spine oncology, calculated the SINS score using images from routine treatment planning computed tomography (CT) scans, while blinded for radiotherapy outcome. The CT scans were obtained by a 16-detector row CT scanner (Brilliance, Philips Medical Systems, Eindhoven, The Netherlands) or GE LightSpeed RT16 (GE Healthcare, Mississauga, Canada) and were reviewed in standardized settings (window level at 300 Hounsfield Units (HU) and window width at 1,000 HU). The SINS was calculated by the sum of five radiological and one clinical component: spine location, pain, bone lesion quality, spinal alignment, vertebral body collapse, and posterolateral involvement of spinal elements **(Table 1)** *[15]*. In case of multiple spinal metastases, the SINS of all lesions within the radiation field was calculated and the highest SINS score was used for analysis. Clinical notes of the radiation oncologist or the referring specialist were reviewed to indicate whether pain was movement-related, occasional, or absent.

Pain scores were reported as a number between zero (indicating no pain) and ten (worst pain imaginable) at baseline and at fixed points in time after palliative radiotherapy. In addition, analgesic use for the preceding 24-hours was collected at time of recording the pain score. A daily total oral morphine dose was calculated from the reported opioid analgesic consumption. In case a patient did not return the pain questionnaire in time, a trained research nurse contacted the patient by phone after two weeks. The response to radiotherapy was determined four to eights weeks after palliative radiotherapy according to the international consensus criteria *[20]* which are summarized in **Table 2**. Patients were classified as overall responders if a complete or partial response was achieved. Patients with progressive pain or undetermined response were classified as non-responders. Patients who died within four weeks after radiotherapy and patients with unknown pain response were excluded from the final analysis.

Statistical analysis

Categorical variables were expressed as count and proportions; continuous variables were expressed as mean ± standard deviation or median with ranges. Chi-Square tests were used to assess differences in baseline characteristics between responders and non-responders. One-way ANOVA tests were used for continuous variables. Logistic regression was used to assess whether SINS (continuous, or binary [SINS <6 / >7]) was related to pain response. First, overall pain response (i.e., complete and partial responses combined) was assessed followed by in-depth analysis selecting only complete pain responders as

TABLE 1. SPINAL INSTABILITY NEOPLASTIC SCORE [16]

SINS component	Score
Location	
Junctional (occiput-C2, C7-T2, T11-L1, L5- S1)	3
Mobile spine (C3-C6, L2-L4)	2
Semi-rigid (T3-T10)	1
Rigid (S2-S5)	0
Pain †	
Mechanical pain	3
No (Occasional pain but not mechanical)	1
Pain-free lesion	0
Bone lesion	
Lytic	2
Mixed (lytic/blastic)	1
Blastic	0
Radiographic spinal alignment	
Subluxation/translation present	4
De novo deformity (kyphosis/scoliosis)	2
Normal alignment	0
Vertebral body collapse	
> 50% collapse	3
< 50% collapse	2
No collapse with > 50% body involved	1
None of the above	0
Posterolateral involvement of spinal elements ‡	
Bilateral	3
Unilateral	1
None of the above	0

0–6 points: stable; 7–12 points: impending unstable; 13–18 points:
unstable. In patients with a score of 7 or higher consultation of a spine surgeon is recommended.
†Pain improvement with recumbency and/or pain with movement/loading of spine
‡Facet, pedicle, or costovertebral joint fracture or replacement with tumor

TABLE 2 RESPONSE RATE TO RADIOTHERAPY ACCORDING TO THE INTERNATIONAL CONSENSUS [20]

Responders	
Complete response	Pain score of 0 and stable or reduced OMED*
Partial response	Pain reduction of 2 points on a 0–10 scale or more and/or OMED reduction by 25% or more
Non-responders	
Pain progression	Increase of 2 points on a 0–10 scale or more above baseline, and/or OMED increased by 25% or more
Indeterminate response	Any response including stable disease that is not captured by complete or partial response or pain progression

OMED, daily oral morphine equivalent

these patients may represent a group of patients with tumor pain only. Variables related to pain response, predefined based on literature and clinical experience, were entered in a multivariable logistic regression model to obtain adjusted odds ratios. These variables were gender, primary tumor (breast/prostate/lung/kidney/other) and performance score (World Health Organization 0 – 2/3 – 4). A worst-case scenario analysis was performed as sensitivity analysis, assuming that all patients who died or were lost to follow-up experienced no response. We estimated the ability of the preselected clinical variables (i.e., gender, primary tumor and performance score) to discriminate between patients with and without pain response by using the area under the receiver operating characteristics (ROC) curve (AUC), and compared this to the area under the ROC curve when SINS was added to these preselected variables. An AUC of 0.5 indicates no discriminating ability, in contrast to perfect discrimination with an AUC of 1 *[21]*. The database was analyzed using IBM SPSS statistics for Windows version 23.0 (IBM Corp., Armonk, NY, USA). Results were considered significant if $p < 0.05$.

RESULTS

Between January 2013 and September 2014, 103 patients from the European center and 52 patients from the North American center with painful thoracic, lumbar or lumbosacral metastases were included. Except for WHO performance score, no significant differences were found regarding patients and disease characteristics between responders and non-responders within the cohort (Table 3). A favorable performance score was associated with

a positive treatment response (p = 0.017). Thirteen patients (8%) died within the first four weeks after palliative radiotherapy and 18 patients (12%) were lost to follow-up. Of the patients who died within four weeks after radiotherapy, six patients had a SINS score of 7 or higher. In the lost to follow-up group, 16 patients had a SINS score of 7 or higher. Of all assessable patients, 73 (59%) patients had a SINS higher than 7 of which ten (8%) patients had a SINS higher than 13.

The association between SINS and pain response was studied in the remaining 124 patients. Of these 124 patients, 16 (13%) patients experienced a complete response, 65 (52%) patients experienced a partial response, and 43 (35%) patients did not experience a response. In the multivariate analysis **(Table 4)** relating SINS to complete versus partial and non-responders demonstrated a significant and independent association when considered as binary variable. Considering the SINS as continuous variable the association remained significant and independent yet the association may be marginal given the width of the confidence interval (adjusted odds ratio 0.78 (95%CI 0.62–0.98)). The median SINS in responders was lower compared to the median SINS in partial or non-responders (six and eight respectively, p = 0.030). Sensitivity analysis also showed a significantly and independently association between SINS and complete pain response. SINS improved the area under the ROC curve of complete response in addition to other clinical variables from 0.68 (0.53–0.82) to 0.78 (0.66–0.90) **(Figure 1A)**.

In contrast, the multivariate analysis relating SINS to overall pain response versus no response demonstrated no significant and independent association, whether considered continuous, or binary **(Table 5)**. The median SINS was similar in non-responders compared to responders (seven and eight, respectively, p = 0.449). Analyzing the six components of the SINS, no significant differences were found between the responders and the non-responders (location, p = 0.107; pain, p = 0.751; lesion, p = 0.642; alignment, p = 0.323; collapse = 0.587; and involvement, p = 0.908). Sensitivity analysis showed similar results, with no association between SINS and radiotherapy failure. SINS improved the prediction of overall response in addition to other clinical variables only marginally: the area under the ROC curve increased from 0.68 (0.60–0.79) to 0.70 (0.60–0.80) (Figure 1B).

TABLE 3 BASELINE CHARACTERISTICS FOR RESPONDERS, NON-RESPONDERS AND PATIENTS WITH AN UNKNOWN OUTCOME

	Response status			
	Responders (n=81)	**Non - Responders (n=43)**	**Unknown (n=31)**	**p-Value**
Gender				0.301*
Male	45 (56%)	24 (56%)	22 (71%)	
Female	36 (44%)	19 (44%)	9 (29%)	
Age (mean ±SD)	65±10.9	67±11.8	67±11.1	0.429†
Primary tumor				0.245*
Breast	25 (31%)	8 (19%)	4 (13%)	
Prostate	17 (21%)	15 (35%)	7 (23%)	
Lung	15 (19%)	9 (21%)	9 (29%)	
Kidney	8 (10%)	1 (3%)	2 (7%)	
Other	16 (20%)	10 (24%)	9 (29%)	
Performance score				0.017†
WHO 0-2	78 (96%)	35 (81%)	26 (84%)	
WHO 3-4	3 (4%)	8 (19%)	5 (16%)	
Location				0.143*
Thoracic spine	39 (48%)	15 (35%)	7 (23%)	
Lumbosacral spine	42 (52%)	28 (65%)	24 (77%)	
Schedule				0.273*
1 x 8 Gy	49 (61%)	33 (77%)	20 (65%)	
5 x 4 Gy	15 (19%)	5 (12%)	7 (23%)	
10 x 3 Gy	14 (17%)	2 (5%)	2 (7%)	
Other	3 (4%)	3 (7%)	2 (7%)	

WHO, World Health Organization; Gy, Gray *Pearson Chi-Square †One-way ANOVA

TABLE 4 ASSOCIATION BETWEEN SINS AND COMPLETE RESPONSE STATUS IN PATIENTS WITH SYMPTOMATIC SPINAL METASTASES

			Odds ratio			
SINS	**Compete response (n=16)**	**Partial or non-response (n=43)**	**Un-adjusted OR (95%CI)**	**p-value**	**Adjusted OR (95% CI)***	**p-value**
Continuous SINS†			0.80 (0.64–0.99)	0.040	0.78 (0.62–0.98)	0.030
Median (range)	6 (3–13)	8 (2–15)				
Mean ±SD	6.7±2.8	8.3±2.8				
Binary SINS‡, N(%)						
Stable	10 (62%)	31 (29%)	1.00		1.00	
(Impending) unstable	6 (38%)	77 (71%)	0.24 (0.08–0.72)	0.011	0.21 (0.06–0.67)	0.009

SINS, spinal instability neoplastic score; CI, confidence interval; SD, standard deviation
*Adjusted for gender, tumor, and performance status †SINS modeled as continuous variable ranging from 0–18
‡SINS modeled as binary variable 0–6 points vs. 7–18 points

FIGURE 1.

ROC curves for the discriminative value of clinical variables (gender, primary tumour and performance status, dotted line), and SINS in addition to those clinical variables (solid line) in predicting complete pain response (A) and overall pain response (B)

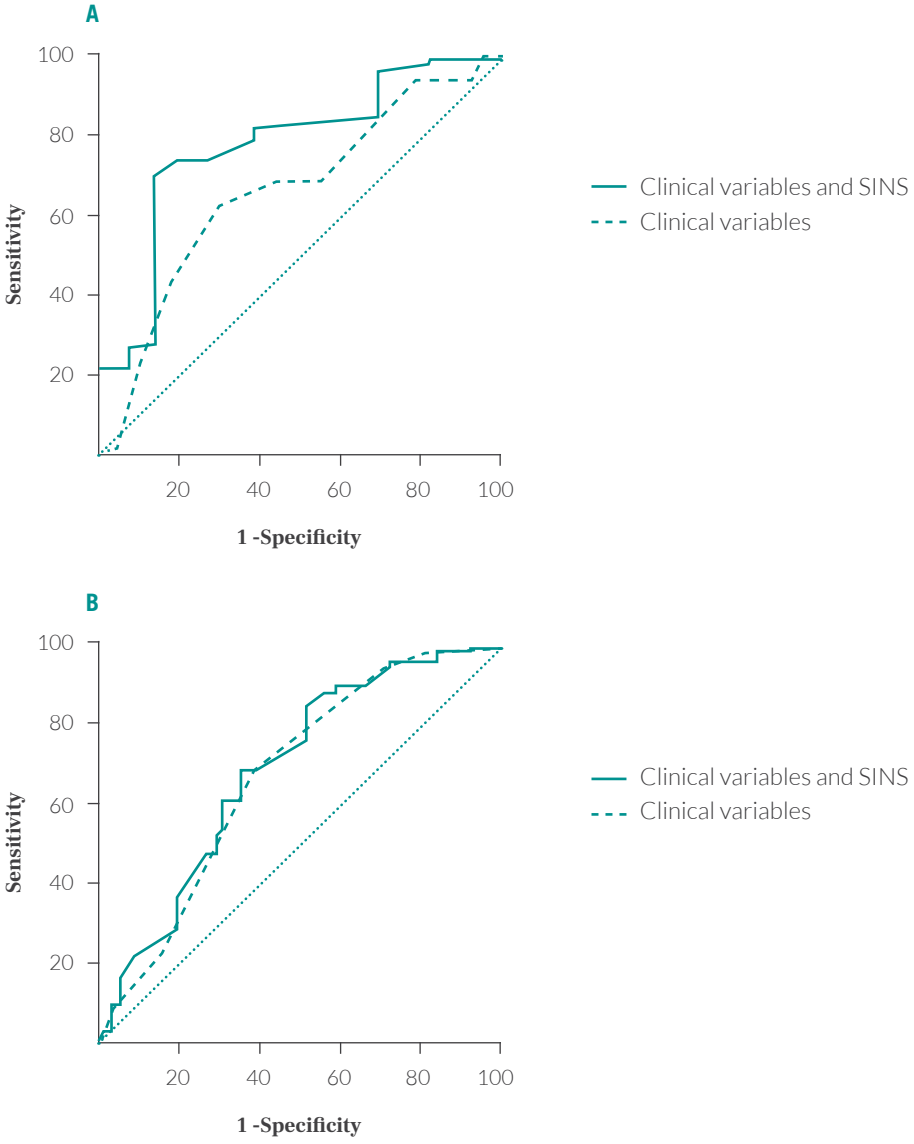

TABLE 5 ASSOCIATION BETWEEN SINS AND OVERALL RESPONSE STATUS IN PATIENTS WITH SYMPTOMATIC SPINAL METASTASES

			Odds ratio			
SINS	**response (n=81)**	**Non-response (n=43)**	**Un-adjusted OR (95%CI)**	**p-value**	**Adjusted OR (95% CI)***	**p-value**
Continuous SINS†			0.91 (0.80–1.04)	0.166	0.94 (0.81–1.10)	0.449
Median (range)	7 (2–15)	8 (2–15)				
Mean ±SD	7.8±2.8	8.6±2.9				
Binary SINS, N(%)						
Stable	29 (36%)	12 (28%)	1.00		1.00	
(Impending) unstable	52 (64%)	31 (72%)	0.70 (0.31–1.56)	0.375	0.88 (0.36–2.15)	0.782

SINS, spinal instability neoplastic score; CI, confidence interval; SD, standard deviation
*Adjusted for gender, tumor and performance status
†SINS modeled as continuous variable ranging from 0–18

DISCUSSION

In this prospective multi-institutional cohort study we found an association between spinal stability, as reflected by a SINS score lower than 7, and a complete pain response after radiotherapy. When considered as a continuous variable the association between SINS and a complete pain response might be marginally given the width of the confidence interval. However, the association of the binary SINS score with a complete pain response is more important as it is advised that patients with a SINS score of 7 or higher are to be referred to a spinal surgeon for evaluation. No association between SINS and overall pain response could be demonstrated. These results are in line with two previous retrospective studies demonstrating a statistically significant relationship between an increasing SINS score and a higher risk of radiotherapy failure *[16, 17]*. In the retrospective study of Huisman et al., the odds of radiotherapy failure for a potentially unstable (SINS 7-12) or unstable lesion (SINS 13-18) was respectively 5.9 and 12.8 times higher compared to a stable lesion *[16]*. Their study, however, used radiotherapy failure, defined as the need for retreatment on the index

site, as the main treatment outcome. Patients who did not achieve a response but were physically not fit enough to receive retreatment or patients who declined retreatment were therefore not accounted for. In the current work, a cohort study was performed with prospectively measured radiotherapy response at 4–8 weeks post-treatment according to the international consensus guidelines for palliative radiotherapy *[20]*. Therefore, all patients, even the patients with debilitating physical condition, could have been followed prospectively. Lam et al. investigated predictive factors for the occurrence of spinal adverse events (SAE) after palliative radiotherapy in a retrospective study including 299 patients *[17]*. SAEs were defined as interventions to achieve pain relief after fractures or uncontrolled pain despite radiation treatment, indicating a failed pain response after conventional radiotherapy. During the study period, 98 SAEs were reported in 51 patients. A SINS of eleven or higher was shown to be independently associated with a higher incidence of SAEs with a hazard ratio for first SAE of 2.52 (95% confidence interval 1.29–4.92) *[17]*. These results underscore the importance of the assessment of spinal instability in patients who receive palliative radiation treatment.

In contrast to the two retrospective studies, Mitera et al. investigated the relationship between radiological features on computed tomography imaging and overall pain response after conventional external beam radiotherapy prospectively *[10]*. They investigated radiological parameters partially overlapping the parameters of the SINS score, including lesion type, presence of kyphosis, vertebral body collapse and involvement of the posterior elements. A total of 33 patients were included and pain response was measured using the international consensus guidelines *[20]*. Six patients showed a response at one month, but no (significant) relationship between radiological parameters and overall pain response was found.

An impaired performance status is a known risk factor for decreased radiotherapy response *[7, 13]* as was confirmed in our study. Moreover, Yates et al. demonstrated that a lower performance status was associated with short-term survival; explained by a rapid decline in performance status within the last two months of life *[22]*. The rapid decline in performance status might be due to a widespread burden of disease in the terminal phase of cancer. The association between a low performance status and impaired radiotherapy response might therefore be explained by this widespread burden of disease; as a local treatment modality, radiotherapy will not provide systemic control and subsequently pain control. Patients with a complete pain response might differ from patients with a partial pain response in their burden of disease. This therefore might explain why we found an association between a low SINS score and complete response, but not between SINS and overall response. Another explanation why we found an association between a low SINS score and a complete response might be that these patients represent a true group of

patients without (pain due to) mechanical instability, supporting our hypothesis that pain mainly caused by mechanical instability responds less well to radiotherapy than pain caused by local tumor effects.

The current study has several methodological strengths. First, this study was conducted prospectively using an international multicenter cohort design enhancing generalizability of the results. There were some differences in fractionation schedule between the two institutions, but these are unlikely to have influenced the results, as single fraction and multi-fraction have shown to be equally effective for the treatment of spinal metastases *[6]*. Secondly, international guidelines for the measurement of radiotherapy response were used ensuring comparability to other studies. Lastly, SINS was assessed in a standardized way, by an experienced observer who was blinded for treatment outcome. One observer was deemed sufficient as the literature demonstrated excellent reproducibility of the SINS score *[23]*.

We acknowledge that this study has some limitations as well. First, there was a limited number of cases with a high SINS score indicating spinal instability (SINS ≥13), which may be due to a low incidence of spinal instability in radiotherapy practice. The low number of cases with a high SINS score limited extensive statistical analyses, yet adjusting for known the factors gender, tumor type and performance status was performed as these are known confounding factors. Adjusting for these factors demonstrated no significant difference in the confidence interval confirming the association between a low SINS score and complete radiotherapy response. Another important reason could be the introduction of the SINS in our institutions approximately two years before the start of inclusion. Recently, our group demonstrated that after introduction of the SINS the mean SINS score in a radiotherapy and surgical cohort decreased *[24]*. This can be explained by increased awareness of the radiation oncologist for spinal instability and subsequent earlier referral to a spine surgeon, resulting in fewer patients with a high SINS score in the radiotherapy cohort. However, this study sample is a realistic representation of the radiotherapy population after introduction of SINS in clinical practice. Second, a substantial number of patients died within the first four weeks after radiotherapy or did not report a pain score. Despite maximized efforts to obtain follow up information, becoming lost-to-follow up is inherent to the study population resulting in a relatively large number of patients with an unknown response. Notably, in the current study these patients had high SINS scores. However, the worst-case scenario analysis, assuming no response in all patients with an unknown pain response confirmed the results of the primary analysis. Lastly, in the current study, only patients with thoracic, lumbar or lumbosacral metastases were included limiting generalizability to these locations. The cervical spine has unique biomechanical characteristics compared to the thoracic and lumbar spine, providing stability for the

head while simultaneously allowing for a wide range of motion. As a result the current composition of the SINS score may be less reliable to detect instability of the cervical spine.

CONCLUSION

The present study used the SINS score, reflecting the degree of spinal (in)stability, as a tool to predict radiotherapy response in patients with spinal metastases. A low SINS score (<7) was associated with a complete pain response to palliative radiotherapy. However, no relation could be demonstrated between the SINS (whether continuous or binary) and overall pain response (i.e. complete and partial combined) to radiotherapy. SINS was developed to help identify spinal neoplastic related instability with the main purpose of guiding referrals and improve communication rather than providing a prognostic tool for treatment outcome. As necessary for a referral tool, the SINS score includes both components quantifying the present degree of spinal instability (e.g. spinal malalignment) as well as components reflecting the future risk of spinal instability (e.g. lytic aspect of the lesion). This decreases however the applicability of the SINS as prediction tool. Translating the results of the current study in clinical practice, patients with a low SINS score indicating no spinal instability can effectively be treated with palliative conventional external beam radiotherapy. However, it is advised that patients with a SINS score of 7 or higher be referred to a spinal surgeon to evaluate if surgical intervention is indicated as currently recommended by the SINS *[15]*. Although the majority of these patients will achieve a (partial) response after radiotherapy, some patients might benefit more from surgical intervention whether or not combined with post-operative irradiation as radiation therapy outcomes in these patients is less predictable. Future studies should be directed at optimizing the definition of spinal neoplastic related (in)stability if it is to be used as a tool to predict treatment outcome.

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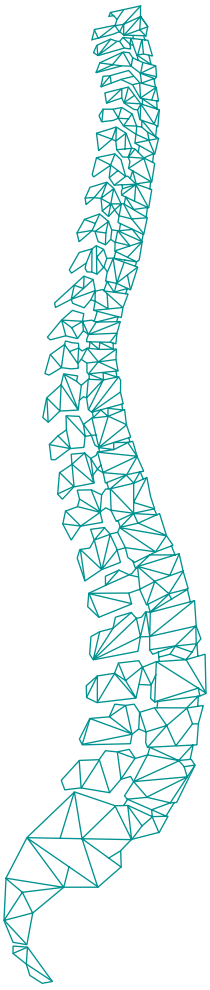
PART II

Treatment evaluation



CHAPTER 5

Psychometric evaluation and adaptation of the Spine Oncology Study Group Outcomes Questionnaire (SOSGOQ) to evaluate health-related quality of life in patients with spinal metastases

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ABSTRACT

Purpose

The Spine Oncology Study Group Outcomes Questionnaire (SOSGOQ) was developed as the first spine oncology specific health-related quality of life (HRQOL) measure. This study evaluated the psychometric properties and clinical validity of the SOSGOQ in a diverse cohort of patients with spinal metastases.

Methods

An international multicenter prospective observational cohort study including patients with spinal metastases who underwent surgery and/or radiotherapy was conducted by the AOSpine Knowledge Forum Tumor. Demographic, tumor, and treatment data were collected. HRQOL was evaluated with the SOSGOQ and SF-36 at baseline and fixed follow-up moments. Construct validity was assessed with multitrait scaling analyses; confirmatory factor analyses (CFA) and correlation with the SF-36 and NRS pain score. Test-retest reliability was assessed in a subgroup of patients between 12 weeks post-treatment and the re-test 4-9 days later.

Results

A total of 238 patients were enrolled at 9 centers across North America, 153 of these patients had HRQOL data available at 12 weeks post-treatment. Multitrait scaling analyses and CFA resulted in a refined version of the SOSGOQ with 4 domains and 4 single items. The revised SOSGOQ (SOSGOQ2.0) demonstrated strong correlations with SF-36 and the ability to discriminate between clinically distinct patient groups. Reliability of the SOSGOQ2.0 demonstrated to be good with the ICC ranging from 0.58 to 0.92 for the different domains.

Conclusion

The SOSGOQ2.0 is a reliable and valid measure to evaluate HRQOL in patients with spinal metastases. It is recommended to use the SOSGOQ2.0 together with a generic HRQOL outcome measure to comprehensively assess HRQOL and increase sensitivity and specificity.

INTRODUCTION

A diagnosis of bone metastases often represents an incurable, yet treatable disease. The population with advanced stages of cancer, including metastatic spine disease, is growing due to improved medical treatment options, which allow for better and longer disease control *[1]*. The main treatment goal for these patients is to improve or maintain health-related quality of life (HRQOL) for their remaining lifetime. Determining patient reported HRQOL is therefore important to optimize and evaluate life-extending and supportive care treatments.

Many generic and cancer-specific outcome measures including those for bone metastases exist *[2]*. Yet, these outcome measures are non-specific for spine-related functions, and thus, are less sensitive to assess changes over time due to treatment or progression of spinal disease. A disease-specific instrument in addition to a generic (cancer) HRQOL measure will increase the sensitivity and specificity of HRQOL assessments. In response to the absence of spine oncology specific outcome measures, the Spine Oncology Study Group Outcomes Questionnaire (SOSGOQ) was developed and assessed for face and content validity *[3]*. Content validity was evaluated by correlating the SOSGOQ items to the International Classification of Functioning and face validity by content expert evaluation, both demonstrated excellent results *[3]*.

With content validity confirmed, the next step is to evaluate the hypothesized structure of the SOSGOQ in a clinical setting. Therefore, the aim of this study was to examine the psychometric properties and the clinical validity of the SOSGOQ in a cohort of patients who have undergone treatment for spinal metastases.

MATERIALS AND METHODS

Design

The AOSpine Knowledge Forum Tumor initiated an international multicenter prospective observational cohort study in August 2013 at ten spine centers across North America and Europe (EPOSO), Clinical trials.gov identifier: NCT01825161. The pre-specified study objectives included the evaluation of validity and reliability of the English version of the SOSGOQ. Patients were eligible for inclusion if they had a diagnosis of metastatic spinal disease, were between 18 and 75 years old, and underwent surgery and/or radiotherapy for the treatment of spinal metastases from any primary tumor. Patients with a central nervous system tumor or a primary spinal bone tumor were excluded. The ethics board of each participating spine center approved the protocol. All patients provided written informed consent for study participation.

Demographic, medical history, diagnostic, treatment, adverse events, and quality of life data were prospectively collected. HRQOL and pain scores were evaluated at baseline and 6, 12, 24, 52, and 104 weeks post-treatment or until death with the SOSGOQ (English, version 1.0 *[3]*), SF-36 (English, version 2.0, Medical Outcomes Trust, Boston, MA, USA [5]), and the NRS pain score. All data was stored in a secure web-based application (REDCap, Vanderbilt University, Nashville, TN, USA).

The SF-36 *[6]* and the NRS pain score are widely used generic outcome instruments and have been described in detail previously. The hypothesized structure of the SOSGOQ consists of five HRQOL domains (physical function, neurological function, pain, mental health, and social function) and an additional set of questions during follow-up for evaluating treatment satisfaction. Scores for the SF-36 and the SOSGOQ were calculated if at least 50% of the items within the domain were answered. All domain scores were transformed to a 0-100 scale, where a higher score represents a better quality of life.

Statistical analysis

Demographic data were summarized by using descriptive statistics. A subject to item ratio of 1:7 *[7]* was considered sufficient power to perform a factor analysis and assess validity, the minimum required sample size was 140 subjects with 20 items in the SOSGOQ to be evaluated (excluding the post-therapy domain).

The results were first analyzed to define the structure (construct validity) of the SOSGOQ. The concurrent validity, clinical validity and reliability were determined using the modified structure of the SOSGOQ (SOSGOQ2.0). All statistical analyses were performed using SAS (version 9.4, SAS Institute Inc., Cary, NC, USA). Significance was defined as $p<0.05$.

Construct validity

The internal structure of the SOSGOQ was evaluated using multitrait scaling analysis and confirmatory factor analyses (CFA). Convergent validity was evaluated by correlating the item score with the total score of its own domain, and divergent validity by correlating the item score with the total score of the other SOSGOQ domains (Spearman's rank). A scaling success was defined as a significantly higher item correlation with its own domain compared to the other SOSGOQ domains, with a minimum correlation of 0.40 *[8]*.

CFA was first performed based on the prior hypothesized structure of the SOSGOQ *[3]* followed by testing of a modified structure on a clinical conceptual basis supported by the results of the multitrait scaling analysis and modification indices. Model fit was evaluated with the root mean square error of approximation (RMSEA (≤ 0.08)) *[9]*,

the 90% confidence interval of the RMSEA (upper bound limit of 0.1), the comparative fit index (CFI (≥ 0.90)) *[10]*, and the standardized root mean residual (SRMR (≤ 0.08)) *[11]*.

Concurrent validity was evaluated by Spearman's rank correlation of the SOSGOQ2.0 domains to the domains of the SF-36 and the NRS pain score. The domains that are conceptually related were expected to demonstrate a correlation of at least 0.40. Analyses were performed with the 12-week post-treatment data to meet the normality assumption; baseline data were used to perform sensitivity analyses of the 12-week data.

Clinical validity

Clinical validity was examined by the ability of the SOSGOQ2.0 to discriminate between patient groups. At baseline, patients with an Eastern Cooperative Oncology Group (ECOG) status of 0 or 1 were compared to patients with an ECOG score of 2 or higher. Furthermore, to assess the responsiveness to change, changes in ECOG status from baseline to 12 weeks post-treatment (stable/improved vs. deteriorated) were associated with changes in the SOSGOQ2.0 scores.

Reliability & reproducibility

The test-retest reliability of the SOSGOQ was assessed at two centers between the 12-week post-treatment assessment and the re-test 4-9 days later using the Intraclass Correlation Coefficient (ICC) *[12]*. Internal consistency of the domains of the SOSGOQ2.0 was evaluated by using Cronbach's alpha *[13]* at baseline and follow-up, the minimum acceptable alpha value was defined at 0.70 *[14]*.

RESULTS

A total of 238 patients from 9 centers across North America (Canada 4, United States 5) were enrolled in the prospective observational cohort study until November 2015. Of the 238 patients, 130 underwent surgery with or without additional radiotherapy and 108 received only radiotherapy treatment **(Figure 1)**. Breast (26%), followed by lung (18%), and renal cell (16%) were the most common primary tumor sites. A summary of the baseline characteristics is displayed in **Table 1**. At 12-weeks 172 patients had data available, 38 (16%) patients died within the first 12 weeks of follow-up, 3 patients were lost to follow-up, 11 patients did not complete the 12-week follow-up visit, and 14 (6%) patients dropped out for other reasons (withdrawal of consent, withdrawn by investigator). The SOSGOQ was complete at baseline by 224 patients (94%) and by 153 patients (63%) at 12 weeks post-treatment.

FIGURE 1.

Patient selection flow diagram

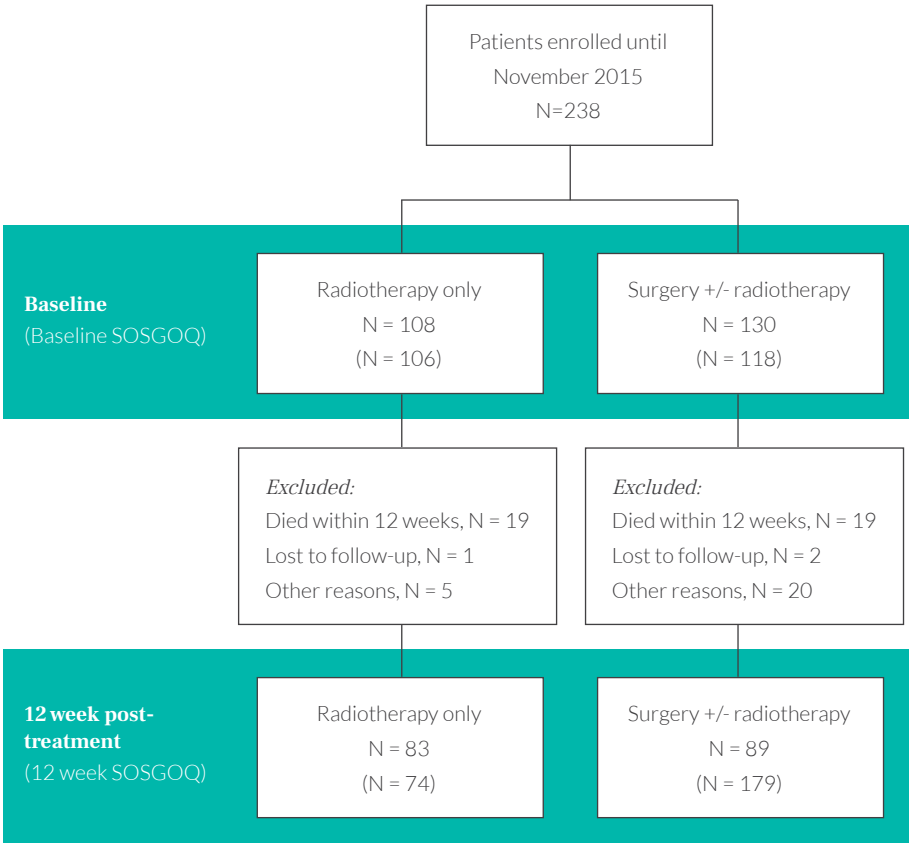

TABLE 1. SUMMARY OF BASELINE CHARACTERISTICS

	N (%)
Age at treatment (years)* (n = 238)	59 (10.3)
Gender (n = 238)	
Female	129 (54.2)
Male	109 (45.8)
Primary tumor (n = 238)	
Breast	62 (26.1)
Lung	44 (18.5)
Kidney	39 (16.4)
Prostate	21 (8.8)
Other	72 (30.3)
Time since primary diagnosis (months) (n = 238)**	26.5 (5.0 – 76.0)
ECOG (n = 234)	
0 -1	156 (66.7)
2 - 4	78 (33.3)
Location (n = 238)* **	
Cervical	38 (16)
Thoracic	152 (64)
Lumbar/Sacral	103 (43)
Presence of other metastases (n = 238)	
Visceral	80 (33.6)
Brain	23 (9.7)
ASIA	
ASIA E	181 (77.4)
ASIA D	41 (17.5)
ASIA C-A	12 (5.1)

* mean ± SD, ** median (IQR), *** multiple levels possible

At baseline, 44 (1%) items of the SOSGOQ and 47 (0.6%) of the SF-36 were missing. The item addressing bowel and bladder function (item 8) in the SOSGOQ was the most commonly reported missing item across different time points. The items addressing the strength in the arms (item 6) and bowel and bladder function (item 8) displayed positive skewness, with only 7% and 3% of the patients reporting moderate to severe symptoms.

Internal structure of the SOSGOQ

A total of 133 patients from 9 centers had complete data available to evaluate the structure of the SOSGOQ. The multitrait scaling analysis at 12 weeks post-treatment according to the prior hypothesized structure of the SOSGOQ *[3]* demonstrated that item 7 (the need for a walking aid) and item 20 (leaving the house) had a strong correlation (R = -0.71 and R = 0.65) with the physical function domain. Furthermore, item 16 (overwhelming pain) showed also a strong correlation with the pain domain (R = -0.60). Item 6 (arm strength), item 8 (bowel and bladder function), and item 15 (level of energy) showed only a moderate correlation with their own scale (R = -0.53 - 0.59). The correlation of the other items exceeded the minimum correlation of 0.40 and had a stronger correlation with their own domain than with the other domains (see supplementary material).

The CFA according to the hypothesized scale structure of the SOSGOQ confirmed the results of the multitrait scaling analysis demonstrating unacceptable model fit (RMSEA= 0.12 (90%CI: 0.10; 0.13), CFI= 0.79 and SRMR= 0.11). Based on the conceptual relation of items with other domains and the multitrait scaling analysis, the scale structure was modified. Items 7 and 20 were moved to the physical function domain and item 16 was moved to the pain domain (cross loading on mental health). Items 5 (leg strength), 6 (arm strength), and 8 (bowel and bladder function) were retained as single items, yet item 8 was split in two questions to distinctly address bowel and bladder function. Item 15 (level of energy) did not contribute new information and was removed. CFA according to the revised SOSGOQ structure confirmed the structure demonstrating adequate model fit (RMSEA= 0.074 (90%CI: 0.055; 0.092), CFI= 0.928 and SRMR= 0.06). The revised questionnaire consists of 4 domains, 4 single items, and at follow-up, a set of questions evaluating treatment satisfaction **(Table 2)**. Scoring guidelines are outlined in Appendix I (online). Results of the multitrait scaling analysis according the final structure are displayed in **Table 3**. Sensitivity analysis with the baseline data confirmed the revised structure of the SOSGOQ demonstrating adequate model fit (RMSEA= 0.08 (90%CI: 0.068; 0.095), CFI= 0.94, SRMR= 0.054).

TABLE 2. SPINE ONCOLOGY STUDY GROUP OUTCOMES QUESTIONNAIRE 2.0 (SOSGOQ2.0)

PHYSICAL FUNCTION

1. What is your level of activity?
- ☐ Full activities without restriction
- ☐ Moderate activities out of house
- ☐ Mobility limited to within house
- ☐ Bed to chair activity
- ☐ Bedridden

2. What is your ability to work (including at home)/ study?
- ☐ Unlimited
- ☐ 4-8 hours per day
- ☐ 2-4 hours per day
- ☐ Less than 2 hours per day
- ☐ Not at all

3. Does your spine limit your ability to care for yourself?
- ☐ Not at all
- ☐ A little bit
- ☐ Somewhat
- ☐ Quite a bit
- ☐ Very much

4. Do you require assistance from others to travel outside the home?
- ☐ Never
- ☐ Rarely
- ☐ Sometimes
- ☐ Often
- ☐ Very often

5. What assistance do you need with your walking?
- ☐ None
- ☐ A cane
- ☐ A walker/2 canes
- ☐ Assistance from others
- ☐ Cannot walk at all

6. Do you leave the house for social functions?
- ☐ Never
- ☐ Rarely
- ☐ Sometimes
- ☐ Often
- ☐ Very often

NEUROLOGICAL FUNCTION

7. Do you have weakness in your legs?
- ☐ None
- ☐ Mild occasionally
- ☐ Mild constantly
- ☐ Moderate constantly
- ☐ Severe constantly

8. Do you have weakness in your arms?
- ☐ None
- ☐ Mild occasionally
- ☐ Mild constantly
- ☐ Moderate constantly
- ☐ Severe constantly

9. Do you have difficulty controlling your bowel function beyond episodes of diarrhea/ constipation?
- ☐ Never
- ☐ Rarely
- ☐ Sometimes
- ☐ Often
- ☐ Very often

10. Do you have difficulty controlling your bladder function?
- ☐ Never
- ☐ Rarely
- ☐ Sometimes
- ☐ Often
- ☐ Requires catheterization

TABLE 2. SPINE ONCOLOGY STUDY GROUP OUTCOMES QUESTIONNAIRE 2.0 (SOSGOQ2.0)

PAIN

11. Overall, on average, how much back/neck pain do you have?

- ☐ None
- ☐ Very mild
- ☐ Mild
- ☐ Moderate
- ☐ Severe

12. When you are in your most comfortable position, do you still experience back/neck pain (limiting your sleep)?

- ☐ Never
- ☐ Rarely
- ☐ Sometimes
- ☐ Often
- ☐ Very often

13. How much has your pain limited your mobility (sitting, standing, walking)?

- ☐ Never
- ☐ Rarely
- ☐ Sometimes
- ☐ Often
- ☐ Constantly

14. How confident do you feel in your ability to manage your pain on your own?

- ☐ Not confident at all
- ☐ Minimally confident
- ☐ Moderately confident
- ☐ Mostly confident
- ☐ Completely confident

15. When I feel pain, it is awful and I feel that it overwhelms me.

- ☐ Never
- ☐ Rarely
- ☐ Sometimes
- ☐ Often
- ☐ Very often

MENTAL HEALTH

16. Have you felt depressed?

- ☐ Never
- ☐ Rarely
- ☐ Sometimes
- ☐ Often
- ☐ Very often

17. Do you feel anxiety about your health related to your spine?

- ☐ Never
- ☐ Rarely
- ☐ Sometimes
- ☐ Often
- ☐ Very often

SOCIAL FUNCTION

18. Does your spine influence your ability to concentrate on conversations, reading, and television?

- ☐ Never
- ☐ Rarely
- ☐ Sometimes
- ☐ Often
- ☐ Very often

19. Do you feel that your spine condition affects your personal relationships?

- ☐ Never
- ☐ Rarely
- ☐ Sometimes
- ☐ Often
- ☐ Very often

TABLE 2. SPINE ONCOLOGY STUDY GROUP OUTCOMES QUESTIONNAIRE 2.0 (SOSGOQ2.0)

20. Are you comfortable meeting new people?
- ☐ Never
- ☐ Rarely
- ☐ Sometimes
- ☐ Often
- ☐ Very often

POST-THERAPY QUESTIONS

21. Are you satisfied with the results of your spine tumor management?
- ☐ Very satisfied
- ☐ Somewhat satisfied
- ☐ Neither satisfied nor dissatisfied
- ☐ Somewhat dissatisfied
- ☐ Very dissatisfied

22. Would you choose the same management of your spine tumor again?
- ☐ Definitely yes
- ☐ Probably yes
- ☐ Not sure
- ☐ Probably not
- ☐ Definitely not

23. How has treatment of your spine changed your physical function and ability to pursue activities of daily living?
- ☐ Much better
- ☐ Somewhat better
- ☐ No change
- ☐ Somewhat worse
- ☐ Much worse

24. How has treatment of your spine affected your spinal cord and/or nerve function?
- ☐ Much better
- ☐ Somewhat better
- ☐ No change
- ☐ Somewhat worse
- ☐ Much worse

25. How has your treatment affected your overall pain from your spine?
- ☐ Much better
- ☐ Somewhat better
- ☐ No change
- ☐ Somewhat worse
- ☐ Much worse

26. How has treatment of your spine changed your depression and anxiety?
- ☐ Much better
- ☐ Somewhat better
- ☐ No change
- ☐ Somewhat worse
- ☐ Much worse

27. How has treatment of your spine changed your ability to function socially?
- ☐ Much better
- ☐ Somewhat better
- ☐ No change
- ☐ Somewhat worse
- ☐ Much worse

TABLE 3. CONVERGENT AND DIVERGENT VALIDITY AT BASELINE AND 12 WEEKS

	Surgery +/- radiotherapy		*Radiotherapy only*		*All patients*	
Scales	**Item own domain correlation**	**Item other domain correlation**	**Item own domain correlation**	**Item other domain correlation**	**Item own domain correlation**	**Item other domain correlation**
Physical function	0.68 – 0.84 *0.55 – 0.88*	0.14 – 0.50 *0.09 – 0.55*	0.70 - 0.81 *0.71 – 0.88*	0.01 – 0.68 *0.01 – 0.66*	0.72 – 0.84 *0.70 – 0.91*	0.02 – 0.55 *0.05 – 0.60*
Pain	0.60 - 0.82 *0.67 – 0.78*	0.13 – 0.59 *0.17 – 0.60*	0.67 - 0.91 *0.62 – 0.88*	0.02 – 0.65 *0.05 – 0.68*	0.64 – 0.84 *0.69 – 0.84*	0.18 – 0.61 *0.17 - 0.72*
Mental health	0.89 – 0.92 *0.84 – 0.89*	0.20 – 0.48 *0.19 – 0.50*	0.89 - 0.92 0.89 – 0.91	0.01 – 0.41 *0.09 - 0.28*	0.90 – 0.91 *0.86 – 0.90*	0.10 – 0.37 *0.12 – 0.32*
Social function	0.71 – 0.85 *0.67 – 0.87*	0.25 – 0.65 *0.09 – 0.68*	0.67 - 0.84 *0.67 – 0.87*	0.19 – 0.63 *0.21 – 0.73*	0.68 – 0.83 *0.66 – 0.88*	0.24 – 0.64 *0.16 – 0.73*
Neuro function legs	1.00	0.15 – 0.41 *0.26 – 0.52*	1.00	0.01 – 0.47 *0.14 – 0.58*	1.00	0.05 – 0.43 *0.17 – 0.58*
Neuro function arms	1.00	0.14 – 0.26 *0.23 – 0.35*	1.00	0.07 – 0.38 *0.10 – 0.44*	1.00	0.12 – 0.25 *0.17 – 0.38*
Neuro function bowel & bladder	1.00	0.13 – 0.46 *0.12 – 0.30*	1.00	0.06 – 0.29 *0.08 – 0.30*	1.00	0.11 – 0.36 *0.02 – 0.32*

Range of spearman's correlation. Italics represent correlations at baseline. Baseline N= 238, 12 weeks post-treatment N = 153.

Concurrent validity with the SF-36 and NRS pain score

Correlation between the domains of the SOSGOQ2.0 and the SF-36 and NRS pain score are displayed in Table 4. The domains of the SOSGOQ2.0 demonstrated a strong to very strong correlation with the corresponding domains of the SF-36. The SOSGOQ2.0 pain domain showed a strong correlation with the NRS pain score. The single neurological function items showed a weak correlation with the domains of the SF-36, indicating that these items assess a different aspect that is not assessed by the SF-36.

Clinical validity

At baseline, patients with an ECOG score of 0 or 1 demonstrated a significantly higher score (p<0.001) across the different SOSGOQ2.0 domains compared to patients with an ECOG score of 2 or higher. Patients with a stable or improved ECOG score at 12 weeks post-treatment showed an increase in domain scores compared to deterioration in the SOSGOQ2.0 domain scores for patients with a decline in performance status. This difference was significant for all domains except the mental health domain (Table 5).

Reliability

A total of 36 patients from two centers also completed the re-test of the SOSGOQ within 4-9 days after the assessment at 12 weeks post-treatment. Of these 36 patients, 10 underwent surgical intervention with or without additional post-operative radiotherapy and the remaining 26 received only radiotherapy treatment. There were no significant differences between patients that completed the re-test of the SOSGOQ to those included in the validity analyses for age (p=0.043), gender (p=0.873), location of primary tumor (p=0.503), and performance status (p=0.191). The ICC of the SOSGOQ2.0 domains ranged from 0.58 to 0.92, with the mental health and post-therapy domains demonstrating the lowest reproducibility with an ICC of 0.62 and 0.58, respectively (Table 6). The Cronbach's alpha at baseline and follow-up was acceptable for all domains (Table 6).

TABLE 5. SENSITIVITY TO CHANGE OF THE SOSGOQ2.0 BASED ON CHANGE IN ECOG SCORE

Change in domain	ECOG decline N=48	ECOG stable/ improved N=114	Total N=162	p-value
Physical function (N)	41	102	143	**0.001¶**
Mean (sd)	-5.7 (24.8)	8.3 (21.8)	4.3 (23.5)	
Neurological function (N)	41	102	143	**<.001¶**
Mean (sd)	-8.0 (15.7)	3.6 (15.6)	0.3 (16.4)	
Pain (N)	41	95	136	**<.001¶**
Mean (sd)	3.1 (26.5)	21.0 (29.5)	15.6 (29.7)	
Mental health (N)	41	95	136	**0.196¶**
Mean (sd)	6.4 (24.8)	11.6 (20.2)	10.0 (21.7)	
Social function (N)	41	101	142	**0.012¶**
Mean (sd)	-1.4 (22.5)	9.8 (24.1)	6.5 (24.1)	

¶ T-test

TABLE 4. CONCURRENT VALIDITY (REVISED SOSGOQ VERSION 2.0)

	SOSGOQ2.0 Physical Function		*SOSGOQ2.0 Neurological Item 5*		*SOSGOQ2.0 Neurological Item 6*		*SOSGOQ2.0 Neurological Item 8*		*SOSGOQ2.0 Pain*		*SOSGOQ2.0 Mental Health*		*SOSGOQ2.0 Social Function*	
Reference score	**n**	**r_s (p-value)**	**n**	**r_s (p-value)**	**n**	**r_s (p-value)**	**n**	**r_s (p-value)**	**n**	**r_s (p-value)**	**n**	**r_s (p-value)**	**n**	**r_s (p-value)**
SF-36v2														
Physical Functioning	153	0.85 (<.001)	153	0.46 (0.463)	153	0.26 (0.260)	153	0.30 (0.299)	146	0.58 (<.001)	146	0.14 (0.099)	152	0.51 (<.001)
Role-Physical	147	0.70 (<.001)	147	0.32 (0.321)	147	0.25 (0.247)	147	0.21 (0.210)	146	0.47 (<.001)	146	0.12 (0.135)	146	0.35 (<.001)
Bodily Pain	152	0.56 (<.001)	152	0.30 (0.300)	152	0.25 (0.253)	152	0.33 (0.332)	145	0.72 (<.001)	145	0.30 (<.001)	151	0.49 (<.001)
General Health	153	0.37 (<.001)	153	0.18 (0.184)	153	0.12 (0.122)	153	0.20 (0.200)	146	0.28 (<.001)	146	0.47 (<.001)	152	0.31 (<.001)
Vitality	147	0.34 (<.001)	147	0.18 (0.176)	147	0.25 (0.246)	147	0.20 (0.197)	146	0.33 (<.001)	146	0.44 (<.001)	146	0.37 (<.001)
Social Functioning	153	0.61 (<.001)	153	0.33 (0.332)	153	0.17 (0.167)	153	0.38 (0.381)	146	0.42 (<.001)	146	0.32 (<.001)	152	0.54 (<.001)
Role Emotional	152	0.45 (<.001)	152	0.25 (0.254)	152	0.15 (0.153)	152	0.26 (0.260)	145	0.35 (<.001)	145	0.30 (<.001)	151	0.45 (<.001)

TABLE 4. CONCURRENT VALIDITY (REVISED SOSGOQ VERSION 2.0) CONTINUED

Mental Health	148	0.23 (0.004)	148	0.16 (0.157)	148	0.15 (0.147)	148	0.23 (0.225)	146	0.37 (<.001)	146	0.72 (<.001)	147	0.49 (<.001)
Pain NRS														
Average Daily Pain	153	-0.41 (<.001)	153	-0.29 (<.001)	153	-0.26 (<.001)	153	-0.37 (<.001)	146	-0.74 (<.001)	146	-0.11 (0.197)	152	-0.39 (<.001)

TABLE 6 RELIABILITY AND INTERNAL CONSISTENCY FOR EACH OF THE SIX SUBSCALES OF THE SOSGOQ2.0

	12 Weeks (test)						*12 Weeks (test)*							
SOSGOQ2.0 Domain	**n**	**Min**	**Max**	**Mean**	**SD**	**Alpha §**	**n**	**Min**	**Max**	**Mean**	**SD**	**Alpha §**	**ICC †**	**95% CI**
Physical Function score (6 items)	36	17	100	74.0	20.7	0.77	36	13	100	76.5	20.9	0.65	0.92	0.85; 0.96
Neurological Function Legs*	36	1	4	2.1	1.1	-	36	1	5	1.9	1.2	-	0.73	0.53; 0.85
Neurological Function Arms*	36	1	5	1.5	0.9	-	36	1	5	1.4	1.0	-	0.72	0.52; 0.84
Pain score (5 items)	36	30	100	70.2	19.8	0.74	36	30	100	72.9	21.6	0.68	0.76	0.58; 0.87
Mental Health score (2 items)	36	25	100	74.1	20.1	0.85	36	13	100	80.8	23.4	0.79	0.62	0.38; 0.78
Social Function score (3 items)	36	25	100	75.1	20.2	0.74	36	42	100	80.8	18.9	0.63	0.63	0.39; 0.79
Post Therapy questions (7 items)	36	25	100	71.5	16.6	0.80	36	36	100	69.4	13.8	0.76	0.58	0.32; 0.76

† ICC = Intraclass Correlation Coefficient for item responses at 12 weeks post-treatment (re-test) calculated using an one-way random effect model.
§ Cronbach's alpha. * Reliability is only displayed for two neurological items, the item addressing bowel and bladder function is split into two questions in the SOSGOQ2.0 and therefore not displayed.

DISCUSSION

Patient reported outcomes are essential in the evaluation of long-term palliative cancer care. The value of a disease-specific questionnaire with the use of generic questionnaires has been widely acknowledged, including the development of many cancer-specific modules by the European Organization for Research and Treatment of Cancer (EORTC) *[15]*. The SOSGOQ is the first spine oncology specific HRQOL questionnaire. The objective of this study was to assess the psychometric properties and clinical validity of the SOSGOQ in a diverse cohort of spine metastases patients. Psychometric evaluation of the SOSGOQ resulted in a slightly revised structure. Evaluation of the revised SOSGOQ demonstrated that it is a clinically valid and reliable questionnaire to evaluate quality of life in patients with spinal metastases. It is recommended to use the SOSGOQ together with a generic outcome measure to comprehensively evaluate HRQOL in patients with spinal metastases.

Recently, Janssen et al. investigated the construct validity of the SOSGOQ by correlation to the EuroQol 5 dimensions 5 levels (EQ-5D-5L) and exploratory factor analyses in a convenience sample of 82 patients with spinal metastases *[4]*. Exploratory factor analyses demonstrated the association of items 7 (need for a walking aid) and 20 (leaving the house) with the physical function domain and item 16 (intensity of pain) with the pain domain. Furthermore, the neurological function items and item 15 (level of energy) demonstrated low factor loadings *[4]*. These results are in agreement with the results of our CFA analyses and the revised SOSGOQ2.0. In the current study, concurrent validity was evaluated by correlating the SOSGOQ2.0 to the SF-36 and the NRS pain score. The SF-36 is a generic, yet comprehensive, HRQOL measure as it consists of several domains, including multiple items per domain, compared to the less comprehensive EQ-5D which utilizes only single items representing the different domains. Correlation of the SOSGOQ2.0 with the SF-36 and NRS pain score demonstrated strong correlations between the domains that were conceptually related, confirming the construct validity of the SOSGOQ2.0.

In contrast to the study of Janssen et al. *[4]*, the current study also assessed the test-retest reliability. The reliability of the SOSGOQ2.0 domains were shown to be excellent, except for the post-therapy questions, mental health domain, and social function domain which demonstrated moderate to good reliability. The lower reproducibility of the mental health domain may be explained by the small size of the domain (2 questions) and the multi-factorial and dynamic nature of mental health in cancer patients. A recent study of Jim et al. *[16]* demonstrated the daily variation in depression, fatigue, activity, and sleep in women undergoing chemotherapy *[16]*. The severity of the symptoms, other aspects of the disease or other concomitant treatments (e.g. systemic therapy) may have influenced the mental health state resulting in decreased reliability. As quality of life may deteriorate quickly in patients with advanced stages of cancer, the retest was administered 4-9 days

after the initial assessment. As such, a stable health state between 12 weeks post-treatment and the retest was assumed rather than objectively assessed, which may have resulted in an underestimation of the reliability of the SOSGOQ2.0. The optimal interval between the initial assessment and the retest in patients with advanced cancer is complex and remains uncertain *[17]*. A short interval is proposed as quality of life may rapidly change in this population; however, an interval that is too short may enhance the probability of patients to recall their previous answers compromising the validity of the reliability measurement *[17]*.

The two items in the hypothesized neurological function domain assessing arm strength and bowel and bladder control showed the largest floor effect and only moderate correlation with the total domain score, which is in agreement with Janssen et al. [4]. This can be explained because most patients included in the current study were treated for metastatic disease in the thoracolumbar spine, which may affect the neurological function of the lower extremity (item 5) due to radiculopathy or metastatic spinal cord compression, and will not affect the neurological function of the upper extremity (item 6). Moreover, only 8% of the patients had diminished or no bowel or bladder control (item 8) according to physical examination. The domain score is therefore predominantly defined by the item addressing leg strength (item 5). Analysis of the missing values demonstrated that item 8 (bowel and bladder function) was the main missing item and also showed low reliability, which may be explained by the double-barreled nature of the question. As item 8 addresses two distinct, but related physical functions, answering this question may be difficult and may lead to missing values if only one of the two functions is affected. Changes to the SOSGOQ have therefore been made to ease future data analyses and interpretation. Item 8 has been split in two distinct questions addressing bowel and bladder function and rather than calculating a domain score, it is recommended to analyze these items as individual items as they address distinct functions. A domain score may be calculated to get an overall impression of the presence of impairment. In addition, a total score for the SOSGOQ2.0 may be calculated by summing the domain scores of the physical function, social function, mental health, and pain domains. The post-therapy items (21-27) should be used during follow-up together with the core items (1-20).

This study has several methodological strengths enhancing generalizability of the results. First, 9 centers across North America participated in the validation study and 2 centers in the test-retest reliability, resulting in a relatively large sample size for this difficult to study patient population. Second, both patients who underwent surgical and/or radiotherapy treatment were enrolled in the study. The different treatment modalities in combination with the wide inclusion and exclusion criteria, with no restrictions to performance status, has resulted in a heterogeneous, yet representable population of

patients who undergo treatment for spinal metastatic disease. Therefore, this instrument appears well-suited to evaluate any treatment related to metastatic spine disease.

A limitation of this study is the relatively high drop out rate (24%) within the first 12 weeks. A significant proportion (16%) of the patients died within the first 12 weeks, representing the severity of disease. Despite maximized efforts for questionnaire compliance and follow-up, a relatively high rate of lost to follow-up was encountered, which is inherent to the study population. Yet, sensitivity analyses with the baseline questionnaire responses confirmed the results of the primary analyses and the validity of the SOSGOQ2.0 across a wide range of health states. Second, physical function, including motor function and pain are assessed in greater depth compared to social function and mental health. This is reflected by the uneven number of items per domain. The instrument's bias towards physical function reflects the impact spinal metastases have on these constructs. Third, despite the multicenter approach, the demonstrated validity of the questionnaire is limited to the English version of the SOSGOQ. Translations of the SOSGOQ2.0 into other languages are currently being performed and validation of the translated versions is planned. Last, the minimal clinically important change in the SOSGOQ2.0 scores over time for a patient is important for interpretation. A study to assess the minimal clinically important difference of the SOSGOQ is currently planned.

In conclusion, this study investigated the psychometric qualities and the clinical validity of the SOSGOQ using a multicenter prospective observational study. The refined SOSGOQ2.0 demonstrated to be a valid and reliable spine oncology specific outcome measure. In future studies evaluating the management of patients with spinal metastases, it is recommended to use the SOSGOQ2.0 in addition to generic HRQOL outcome measures to achieve a more comprehensive representation of HRQOL and to increase sensitivity to change.

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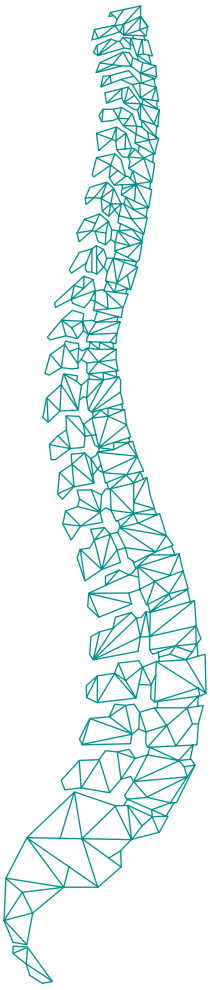

CHAPTER 6

A multicenter prospective cohort study evaluating quality of life after radiation or surgery for potentially unstable spinal metastases

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ABSTRACT

Background

The purpose of this study was to compare health related quality of life (HRQOL) outcomes for surgery and/or radiotherapy in patients with potentially unstable spinal metastases.

Methods

A multicenter prospective observational study specific to patients undergoing radiation and/or surgical intervention for the treatment of symptomatic spinal metastases was conducted. Patients with potentially unstable spinal metastases, defined as a Spinal Instability Neoplastic Score (SINS) between 7 and 12, were included. HRQOL scores were modeled and compared between treatment groups using mixed effect models with adjustment for baseline differences.

Results

In total 120 patients were treated with surgery +/- radiotherapy and 82 with radiotherapy alone. At baseline, surgically treated patients presented with worse performance status, HRQOL, numeric rating scale (NRS) pain scores and a greater median SINS score [10 versus 8 in those treated with radiotherapy alone ($p<0.001$)]. Significant differences in the distribution of individual SINS factors were also observed between both treatment groups. From baseline to 12 weeks post-treatment, surgically treated patients experienced a greater improvement in HRQOL with a 12-point increase in adjusted mean SOSGOQ2.0 score (95%CI 5.1 – 19.0, $p<0.001$) as compared to a 6.2-point gain in those treated with radiotherapy alone (95%CI 2.2 – 14.6, $p=0.352$). In addition, the gain in the SOSGOQ2.0 score exceeded the minimal clinically important difference threshold in 63% of the surgical cohort as compared to 44% in the radiotherapy alone cohort ($p=0.017$).

Conclusion

For patients presenting with potentially unstable spinal metastases, treatment with surgery +/- radiotherapy resulted in greater and clinically meaningful changes in HRQOL as compared to patients treated with radiotherapy alone. However, these results must be taken into context according to differences in individual SINS factors, and grouping of SINS factors, that comprise the individual cohorts.

INTRODUCTION

The management of patients with spinal metastases requires a multidisciplinary approach with treatment selection depending primarily on life expectancy, tumor histology, performance status, neurology, and spinal stability *[1]*. Generally, radiotherapy is the first choice of treatment for patients with symptomatic spinal metastases; however, radiotherapy alone has been shown to be inferior to surgery followed by radiation in patients with symptomatic malignant epidural cord compression (MESCC) *[2]*. In addition, the efficacy of radiotherapy in patients with mechanical instability is thought to be inferior to surgery; however, there is a lack of prospective evidence to validate this clinical observation.

The challenge with respect to instability and patient selection for surgery lies not in the patient without instability or the one with frank instability, but in those with potential instability. In these patients the choice for surgery requires careful deliberation, as the consequences of surgery can be significant with respect to complications, interruptions in systemic therapy and potential mortality. The lack of a standardized assessment tool specific to mechanical instability for the patient with spinal metastases, and comparative evidence with respect to treatment outcomes between radiotherapy and surgery specific to patients with potential mechanical instability, have been barriers to evidence-based surgical treatment algorithms.

In order to standardize the assessment of mechanical instability specific to the metastatic spine, the Spinal Instability Neoplastic Score (SINS) was developed and includes both radiographic and clinical factors thought to represent the risk of spinal instability and factors that indicate spinal instability **(Table 1)** *[3]*. Location of the lesion, bone lesion quality and involvement of the posterolateral elements are considered SINS factors representing a risk of spinal instability *[3]*, while the presence of mechanical pain, spinal misalignment and a higher degree of vertebral body collapse are considered SINS factors that indicate spinal instability *[3]*. These six factors have an assigned scoring system and when summed, a total score ranging from 0 to 6 classifies patients as stable, 7 to 12 as potentially unstable, and 13 to 18 as frankly unstable *[3]*.

The potential spinal instability group represents the largest percentage of patients with symptomatic spinal metastases and the one in which optimal treatment is most controversial. Furthermore, this cohort is challenging to define as several combinations of individual SINS factors can result in a score between 7 and 12. Although SINS represents a major advance and has been rapidly adopted within the oncologic community, it is important to note that the therapeutic impact associated with SINS has yet to be validated in a prospective study. Therefore, the primary objective of this study was to compare HRQOL outcomes at 12-weeks post-treatment for surgery +/- radiotherapy to radiotherapy alone in patients with potentially unstable spinal metastases.

TABLE 1. SINS SCORE DIVIDED IN FACTORS REPRESENTING RISK OF SPINAL INSTABILITY AND FACTORS THAT INDICATE SPINAL INSTABILITY.

Risk of spinal instability	Score	Indicating spinal instability	Score
Lesion quality		**Pain**	
Lytic	2	Mechanical pain	3
Mixed (lytic/blastic)	1	Occasional pain but not mechanical	1
Blastic	0	Pain free lesion	0
Location		**Vertebral body collapse**	
Junctional	3	>50% collapse	3
(occiput-C2, C7-T2, T11-L1, L5-S1)	2	<50% collapse	2
Mobile spine (C3-C6, L2-L4)	1	No collapse with >50% vertebral	1
Semi-rigid (T3-T10)		body involvement	
Rigid (S2-S5)	0	None of the above	0
Posterolateral involvement		**Spinal alignment**	
Bilateral	3	Subluxation/translation present	4
Unilateral	1	De novo scoliosis/kyphosis	2
None of the above	0	Normal spinal alignment	0

Total SINS score is sum of all six factors. 0-6 point represent spinal stability, 7-12 points represent indeterminate spinal instability and 13-18 points represent spinal instability.

METHODS

Design

An international multicenter prospective observational cohort study (Epidemiology, Process and Outcomes of Spine Oncology (EPOSO), Clinical trials.gov identifier: NCT01825161) including patients between the ages of 18 and 75 years who underwent surgery and/or radiotherapy for symptomatic spinal metastases was performed, and sponsored by the AOSpine. Between August 2013 and May 2017, patients were enrolled at ten spine centers across North America and Europe. For this analysis, patients with a SINS score between 7 and 12 (potentially unstable) were included. Those potentially unstable patients presenting with neurologic deficits secondary to malignant spinal cord compression as the primary indication for treatment were excluded as these patients are

often treated urgently with stability a secondary objective. The ethics board of each of the participating centers approved the study protocol. All patients provided written informed consent for study participation.

Patient demographics, primary tumor diagnosis, treatment, adverse events (AE) and HRQOL data were prospectively collected. HRQOL including numeric rating scale (NRS) pain scores, the Spine Oncology Study Group Outcomes Questionnaire (SOSGOQ2.0) *[4]*, the short-form 36 (SF-36v2) *[5]* and EuroQol five dimensions (EQ-5D-3L) were evaluated at baseline and during follow-up at fixed time points until 2 years post-treatment or death. A secure web-based application was used to store all data (REDCap, Vanderbilt University, Nashville, TN, USA).

The SF-36v2 and EQ-5D-3L are widely used generic HRQOL measures *[6, 7]*, while the SOSGOQ2.0 is a spine oncology specific HRQOL measure, which has been recently validated *[8]*. The minimal clinically important difference (MCID), representing a clinically meaningful change in the total score for a patient, was estimated for the SOSGOQ2.0 total score based on a distribution based method using half the standard deviation of the SOSGOQ2.0 total score at baseline *[9]*. Accordingly, an increase in the SOSGOQ2.0 total score of 9 points or higher within the first three months compared to the baseline value was considered clinically meaningful.

Statistical analysis

Descriptive statistics were used to represent demographic and HRQOL baseline data. Student's t-tests, Wilcoxon rank sum tests, chi-square tests, and Fisher's exact tests were used to compare differences in continuous variables and proportions between patients who underwent surgery and/or radiotherapy. The distribution of the SINS factors representing the risk of spinal instability and factors indicating spinal instability were compared between both treatment groups. Mixed effect models were used to model changes in HRQOL outcomes over time between the surgery and/or radiotherapy group. The models were adjusted for baseline differences to minimize the effect of confounding. P-values were adjusted for multiple testing by Tukey-Kramer. The log-rank test was used to compare survival up to six months between both treatment groups. Significance was defined as $p<0.05$. All statistical analyses were performed using SAS (version 9.4, SAS Institute Inc., Cary, NC, USA).

RESULTS

A total of 228 patients with a SINS score between 7 and 12 were enrolled in this prospective cohort, of whom 26 were excluded from the analyses because neurologic deficits were the primary indication for surgery. Of the 202 patients included in this analysis, 120 underwent surgery with or without radiotherapy, and 82 were treated with radiotherapy alone. With respect to general baseline characteristics, patients who underwent surgery had a lower performance status ($p<0.001$), were less often breast cancer patients as compared to other tumor histologies ($p=0.004$), and more often had radiographic signs of epidural disease ($p<0.001$) **(Table 2)**.

Among patients who underwent surgery, 37 underwent only surgery, 20 had a prior history of radiotherapy and 63 underwent surgery with adjuvant radiotherapy. Adjuvant conventional external beam radiotherapy (EBRT) was given in 27 patients, with a median total dose and number of fractions of 30Gy and 5 (range, 1-30 fractions) and adjuvant stereotactic body radiotherapy (SBRT) in 30 patients with a median total dose and number of fractions of 24Gy and 2 (range, 1-12 fractions). The radiotherapy technique was unknown for 6 patients. Of the 82 patients who underwent radiotherapy alone, 38 received EBRT with a median total dose and number of fractions of 20Gy and 5 (range, 1-14 fractions), and 44 were treated with SBRT with a median dose and number of fractions of 24Gy and 2 (range, 1-5 fractions). Thirteen intra-operative and 67 post-operative AEs occurred in 12 (10%) and 36 (30%) patients, respectively. A total of 140 radiation or chemotherapy related AEs were observed in 44 (58%) surgically treated patients, and 128 events in 29 (35%) patients treated with radiotherapy alone. No difference in overall survival up to 6 months between the two treatment groups was observed ($p=0.314$).

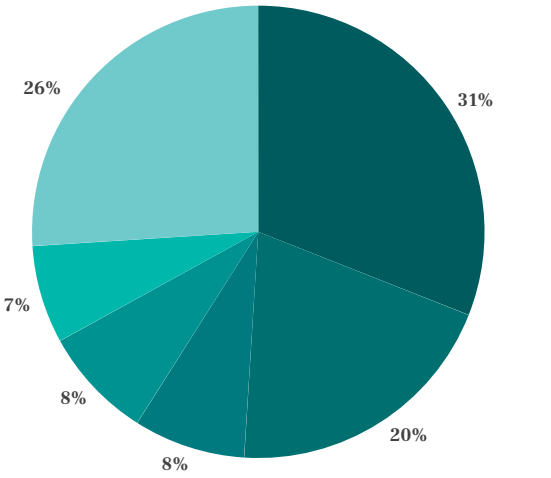
Spinal instability

A greater median SINS score of 10 (IQR 8 - 11) was observed in the surgical cohort, as compared to a median SINS score of 8 (IQR 7 - 9) in the radiotherapy alone cohort ($p<0.001$). Within the surgical cohort, mechanical pain, lytic bone lesion quality, and spinal misalignment as individual SINS factors were more often observed compared to the radiotherapy cohort **(Table 3)**. The dominant combinations of SINS factors that indicate spinal instability were mechanical pain with <50% or >50% vertebral body collapse and normal alignment (31%) or mechanical pain with >50% vertebral body involvement without collapse and normal alignment (20%) (Figure 1). In contrast, within the radiotherapy alone cohort, pain free status and mixed (blastic/lytic) tumor as individual SINS factors were more often observed compared to the surgical cohort. The most frequently observed combinations of SINS factors that indicate instability in the radiotherapy alone cohort were a pain free lesion with <50% or >50% vertebral body collapse and normal alignment (16%) or occasional pain and >50% vertebral body involvement without collapse and normal alignment with (15%) **(Figure 1)**.

FIGURE 1.

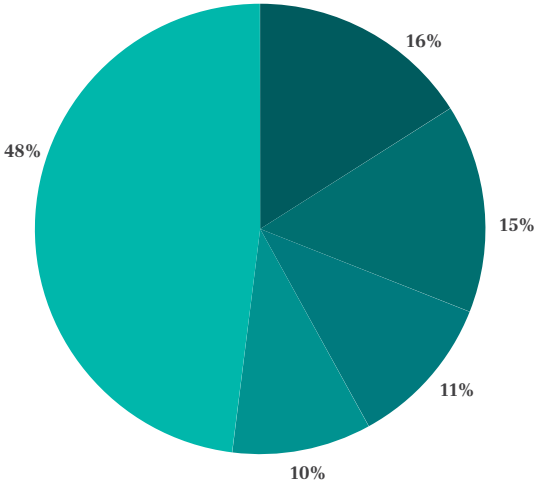
Representation of the distribution of combinations of SINS factors indicating spinal instability
A) within the surgical cohort B) radiotherapy alone

SURGERY +/- RADIOTHERAPY



- Mechanical pain + any degree of vertebral body collapse + normal alignment (31%)
- Mechanical pain + >50% vertebral body involvement without collapse + normal alignment (20%)
- Mechanical pain + <50% vertebral body involvement without collapse + normal alignment (8%)
- Mechanical pain + <50% vertebral body collapse + de novo deformity (8%)
- Mechanical pain + >50% vertebral body collapse + normal alignment (7%)
- other combinations (N=10) (26%)

RADIOTHERAPY ALONE



- Pain free lesion + any degree of vertebral body collapse + normal alignment (16%)
- Occassional pain + >50% vertebral body involvement without collapse + normal alignment (15%)
- Mechanical pain + >50% vertebral body involvement without collapse + normal alignment (11%)
- Mechanical pain + <50% vertebral body involvement without collapse + normal alignment (10%)
- Other combinations (N=14) (48%)

TABLE 2. BASELINE CHARACTERISTICS

Characteristic	Surgery (+/- radiotherapy) N=120	Radiotherapy alone N=82	P -value
Age at Surgery/ Radiotherapy (years)	120	82	0.181¶
Mean (sd)	58.5 (10.3)	60.4 (9.4)	
Gender, n (%)	120	82	0.030†
Female	56 (46.7)	51 (62.2)	
Male	64 (53.3)	31 (37.8)	
ECOG Classification, n (%)	120	78	<.001‡
0	13 (10.8)	22 (28.2)	
1	60 (50.0)	50 (64.1)	
2	29 (24.2)	3 (3.8)	
3	16 (13.3)	3 (3.8)	
4	2 (1.7)	0 (0.0)	
Site of the primary cancer, n (%)	120	82	0.004†
Breast	20 (16.7)	31 (37.8)	
Lung	23 (19.2)	13 (15.9)	
Prostate	4 (3.3)	6 (7.3)	
Kidney	26 (21.7)	13 (15.9)	
Other	47 (39.2)	19 (23.2)	

TABLE 2. CONTINUED

Characteristic	Surgery (+/- radiotherapy) N=120	Radiotherapy alone N=82	P -value
ASIA Impairment Scale, n (%)	120	80	0.005‡
A - C	1 (0.8)	0 (0.0)	
D	14 (11.7)	1 (1.3)	
E	105 (87.5)	79 (98.8)	
Bilsky epidural spinal cord compression scale	113	76	<.001†
0 – 1c	62 (54.9)	71 (93.4)	
2 – 3	51 (45.1)	5 (6.6)	
Pre-operative observed SOSGOQ total score, n	111	79	0.003¶
Mean (sd)	53.5 (17.0)	61.0 (17.0)	
Pre-operative observed EQ-5D, n	110	77	<.001§
Mean (sd)	0.51 (0.26)	0.66 (0.22)	
Pre-operative observed SF-36 physical component score, n	111	78	<.001¶
Mean (sd)	29.7 (8.5)	34.9 (9.9)	
Pre-operative observed SF-36 mental component score, n	111	78	0.116¶
Mean (sd)	43.0 (11.9)	45.8 (11.7)	
Pre-operative observed NRS pain score, n	111	80	<.001§
Mean (sd)	6.2 (2.7)	4.7 (2.5)	

TABLE 3. DISTRIBUTION OF SINS ITEMS

SINS factors	Surgery (+/- radiotherapy) N=120	Radiotherapy alone N=82	P -value
Spine Location, n (%)			0.091‡
Junctional (occiput-C2, C7-T2, T11-L1, L5-S1)	47 (39.2)	43 (52.4)	
Mobile spine (C3-C6, L2-L4)	26 (21.7)	20 (24.4)	
Semi-rigid (T3-T10)	45 (37.5)	18 (22.0)	
Rigid (S2-S5)	2 (1.7)	1 (1.2)	
Pain, n (%)			<.001†
Mechanical pain	87 (72.5)	35 (42.7)	
Occasional pain but not mechanical	32 (26.7)	29 (35.4)	
Pain-free lesion	1 (0.8)	18 (22.0)	
Bone Lesion Quality, n (%)			0.031†
Mixed (lytic/blastic)	21 (17.5)	26 (31.7)	
Lytic	91 (75.8)	48 (58.5)	
Blastic	8 (6.7)	8 (9.8)	
Radiographic Spinal Alignment, n (%)			0.085‡
Subluxation/translation present	1 (0.8)	0 (0.0)	
De novo deformity (kyphosis/scoliosis)	25 (20.8)	9 (11.0)	
Normal alignment	94 (78.3)	73 (89.0)	
Vertebral Body Collapse, n (%)			0.318†
>50% vertebral body collapse	23 (19.2)	13 (15.9)	
≤50% vertebral body collapse	50 (41.7)	26 (31.7)	
>50% vertebral body involvement without collapse	29 (24.2)	27 (32.9)	
None of the above (<50% vertebral body involvement without collapse)	18 (15.0)	16 (19.5)	
Posterolateral Involvement of Spinal Elements, n (%)			0.846†
Bilateral	39 (32.5)	28 (34.1)	
Unilateral	56 (46.7)	35 (42.7)	
None of the above	25 (20.8)	19 (23.2)	
Total SINS score			<.001¶
Mean (SD)	9.7 (1.7)	8.5 (1.4)	
Median (Q1;Q3)	10.0 (8.0;11.0)	8.0 (7.0;9.0)	

The combinations of SINS factors representing the risk of spinal instability were similar for the two cohorts consisting of a lytic lesion in a non-rigid spine location with unilateral or bilateral involvement of the posterolateral elements **(Figure 2)**. Of note, for the surgical cohort these combinations also grouped consistently with 'mechanical pain' or '<50% or >50% vertebral body collapse'. In contrast, these combinations of risk factors in the radiotherapy alone cohort were observed in nearly all patients in the absence of mechanical pain.

Pain scores

At baseline, patients who underwent surgery presented with a higher mean NRS pain score compared to patients who underwent radiotherapy alone, 6.2 (SD 2.7) and 4.7 (SD 2.5), respectively (p<0.001) (Table 2). After adjusting for baseline differences, both treatment groups demonstrated a significant decrease in NRS pain scores within the first six weeks post-treatment, with a greater magnitude of decrease in NRS pain score in the surgical cohort (-2.5, 95%CI -3.6 – -1.4, p<0.001) compared to those treated with radiotherapy alone (-1.4, 95%CI -2.7 – -0.1). The decrease in NRS pain score in the surgical cohort sustained (-2.6, 95%CI -3.8 – -1.4), while the pain scores in patients treated with radiotherapy alone slightly increased by 26 weeks post-treatment (-1.1, 95%CI -2.7 – 0.6) **(Table 4)**.

HRQOL

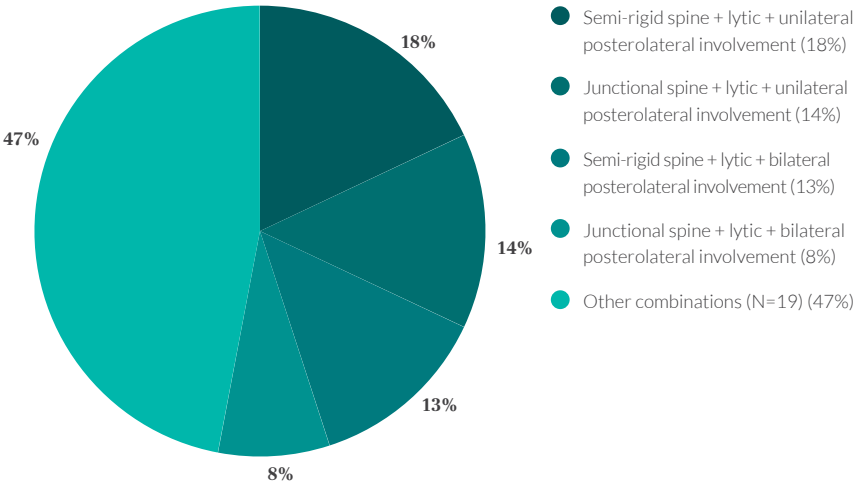
Patients who underwent surgery +/- radiotherapy presented with lower baseline SOSGOQ2.0 total, EQ-5D-3L and SF-36 physical component scores (SF-36 PCS) compared to those treated with radiotherapy alone **(Table 2)**. The adjusted mean SF-36 PCS for surgically treated patients was significantly improved at 26 weeks post-surgery (+5.7, 95% CI 0.5 – 10.9, p=0.020); however, improvements during the first 12 weeks post-surgery were non-significant (+3.3, 95% CI -0.6 – 7.1, p=0.164). SF-36 mental components scores (SF-36 MCS) were similar for both treatment groups at baseline. A trend was observed for an increase in the adjusted mean SF-36 MCS from baseline to 26 weeks post-surgery (+5.4, 95% CI -0.5 – 11.3, p=0.104). Patients treated with radiotherapy alone demonstrated no significant changes in adjusted mean SF-36 PCS and SF-36 MCS during the follow-up period **(Table 4)**.

Greater and significant improvements in mean adjusted EQ-5D-3L scores at 12 weeks were observed in surgically treated patients (+0.21, 95%CI 0.12 – 0.29, p<0.001), as compared to those treated with radiotherapy alone (+0.09, 95%CI -0.02 – 0.19, p=0.168). Improvements in mean EQ-5D-3L scores were sustained during follow-up for both treatment groups **(Table 4)**.

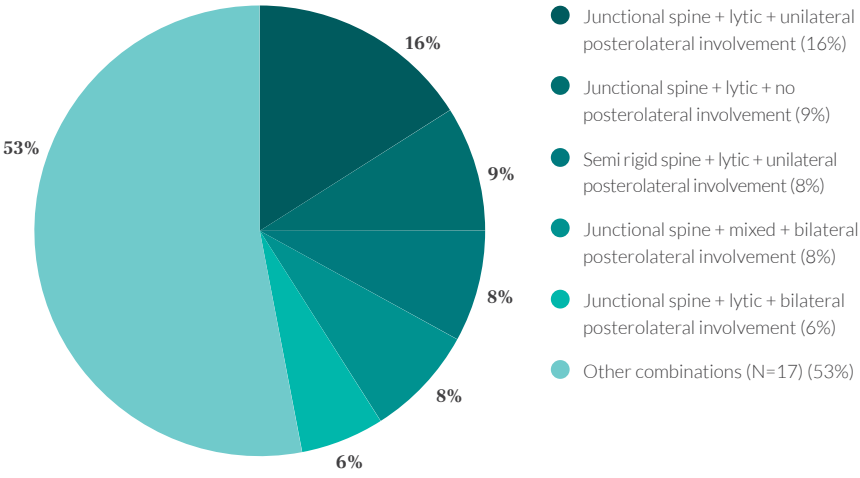
FIGURE 2.

A representation of the distribution of combinations of SINS factors representing risk of spinal instability within A) surgical cohort B) radiotherapy alone cohort.

SURGERY +/- RADIOTHERAPY



RADIOTHERAPY ALONE



After adjusting for baseline differences, patients who underwent surgical treatment demonstrated greater and significant improvements in the SOSGOQ2.0 total score at 12 weeks post-treatment (+12.0; 95% CI 5.1 – 19.0, p<0.001), as compared to patients treated with radiotherapy alone (+6.2; 95% CI -2.2 – 14.6, p=0.352). Up to 12 weeks post-surgery, 61 (63%) surgically treated patients demonstrated an increase in the SOSGOQ2.0 total score that exceeded the MCID, representing a clinically meaningful improvement in HRQOL, compared to 29 (44%) of the patients treated with radiotherapy alone (P=0.017). At 12 weeks post-surgery, 9 patients were deceased, 9 were lost to follow-up and 5 had missing SOSGOQ2.0 values. At 12 weeks post-radiotherapy, 7 patients were deceased, 6 were lost to follow-up and 3 had missing SOSGOQ2.0 values. The percentage of patients experiencing a clinically meaningful difference in HRQOL improved to 71% (N=37/52) up to 6 months post-surgery, compared to a decrease to 36% (N=15/41) of those treated with radiotherapy alone. At 6 months post-surgery, 10 patients had missing SOSGOQ2.0 values, 30 were deceased and 28 were lost-to follow-up (p<0.001). At 6 months post-radiotherapy, 12 patients had missing SOSGOQ2.0 values, 15 were deceased and 14 were lost to follow-up. Patients who experienced a clinically meaningful difference in HRQOL, after surgery +/- radiotherapy or radiotherapy alone, had lower unadjusted baseline HRQOL scores than those who did not experience a meaningful difference **(Table 5)**.

DISCUSSION

In this first multicenter international prospective cohort study evaluating patients with potentially unstable spinal metastases treated with either surgery +/- radiotherapy or radiotherapy alone, a greater and clinically significant gain in HRQOL was observed in the surgical cohort compared to those treated with radiotherapy alone. In addition, the improvements in HRQOL sustained over time in the surgical cohort.

Important differences in the individual SINS factors, grouping of SINS factors and the total SINS score were observed between the two cohorts. First, the median SINS score was higher at 10 in the surgical cohort, as compared to 8 in the radiotherapy alone cohort. Second, higher scores in those SINS criteria regarding mechanical pain and presence of vertebral body collapse were observed in the surgical cohort as compared to a more heterogeneous distribution of factors in the radiotherapy alone cohort (Figure 1 and 2). Third, patients treated with surgery had a lower baseline performance status and HRQOL scores, which likely reflects greater functional impairment related to their spine symptoms rather than overall physical fitness. By appreciating the differences in the baseline characteristics that compromise the cohorts, the results of this study are put into context with respect to the gains observed in HRQOL measures following surgery and/or radiotherapy.

TABLE 4. ADJUSTED HRQOL OUTCOMES OVER TIME PER TREATMENT GROUP

		Surgery +/- radiotherapy			*Radiotherapy*		
	n	**Mean (95% CI)**	**Change (95% CI)**	**Adj. p-value †**	**Mean (95% CI)**	**Change (95% CI)**	**Adj. p-value †**
SOSGOQ2.0							
Baseline	174	54.5 (50.0; 59.1)			59.6 (53.9; 65.2)		
6 weeks	135	65.3 (60.5; 70.0)	10.7 (4.2; 17.2)	**<.001**	63.6 (57.7; 69.6)	4.1 (-4.0; 12.1)	0.854
12 weeks	114	66.6 (61.7; 71.5)	12.0 (5.1; 19.0)	**<.001**	65.8 (59.8; 71.8)	6.2 (-2.2; 14.6)	0.352
26 weeks	90	70.7 (65.6; 75.8)	16.1 (8.8; 23.5)	**<.001**	64.9 (58.7; 71.1)	5.3 (-3.3; 13.9)	0.623
52 weeks	65	70.6 (64.6; 76.6)	16.1 (6.7; 25.5)	**<.001**	61.0 (53.9; 68.1)	1.4 (-9.5; 12.4)	1.000
SF-36v2 PCS							
Baseline	174	31.3 (28.8; 33.8)			35.2 (32.1; 38.3)		
6 weeks	131	34.4 (31.7; 37.1)	3.1 (-0.3; 6.4)	0.096	35.8 (32.5; 39.2)	0.7 (-3.4; 4.8)	1.000
12 weeks	113	34.5 (31.8; 37.3)	3.3 (-0.6; 7.1)	0.164	36.2 (32.9; 39.6)	1.1 (-3.5; 5.7)	1.000
26 weeks	89	37.0 (33.5; 40.5)	5.7 (0.5; 10.9)	**0.020**	34.1 (29.9; 38.3)	-1.1 (-7.0; 4.9)	1.000
52 weeks	63	38.1 (34.1; 42.0)	6.8 (0.8; 12.7)	0.013	34.5 (29.9; 39.0)	-0.7 (-7.4; 6.0)	1.000
SF-36v2 MCS							
Baseline	174	43.5 (40.3; 46.6)			45.2 (41.2; 49.1)		
6 weeks	131	46.1 (42.8; 49.3)	2.6 (-1.5; 6.7)	0.583	43.7 (39.7; 47.7)	-1.5 (-6.5; 3.5)	0.997
12 weeks	113	47.1 (43.8; 50.4)	3.7 (-1.0; 8.4)	0.277	45.9 (41.9; 49.9)	0.7 (-4.9; 6.3)	1.000
26 weeks	89	48.8 (45.0; 52.7)	5.4 (-0.5; 11.3)	0.104	46.9 (42.3; 51.4)	1.7 (-5.1; 8.4)	0.999
52 weeks	63	49.1 (45.1; 53.0)	5.6 (-0.6; 11.8)	0.112	44.2 (39.7; 48.8)	-0.9 (-7.9; 6.0)	1.000

TABLE 4. CONTINUED

		Surgery +/- radiotherapy			*Radiotherapy*		
	n	**Mean (95% CI)**	**Change (95% CI)**	**Adj. p-value †**	**Mean (95% CI)**	**Change (95% CI)**	**Adj. p-value †**
EQ-5D-3L							
Baseline	172	0.53 (0.47; 0.58)			0.64 (0.57; 0.71)		
6 weeks	135	0.66 (0.61; 0.72)	0.14 (0.05; 0.22)	**<.001**	0.70 (0.63; 0.76)	0.06 (-0.05; 0.16)	0.801
12 weeks	115	0.73 (0.68; 0.78)	0.21 (0.12; 0.29)	**<.001**	0.73 (0.67; 0.79)	0.09 (-0.02; 0.19)	0.168
26 weeks	88	0.71 (0.65; 0.77)	0.19 (0.08; 0.29)	**<.001**	0.71 (0.64; 0.79)	0.07 (-0.05; 0.20)	0.706
52 weeks	65	0.71 (0.65; 0.78)	0.19 (0.07; 0.31)	**<.001**	0.72 (0.64; 0.80)	0.08 (-0.06; 0.22)	0.748
Pain NRS							
Baseline	175	5.7 (5.0; 6.3)			4.3 (3.5; 5.1)		
6 weeks	136	3.2 (2.5; 3.8)	-2.5 (-3.6; -1.4)	**<.001**	2.9 (2.1; 3.7)	-1.4 (-2.7; -0.1)	**0.033**
12 weeks	119	2.9 (2.2; 3.6)	-2.7 (-3.9; -1.5)	**<.001**	2.9 (2.0; 3.7)	-1.4 (-2.9; 0.0)	**0.053**
26 weeks	90	3.1 (2.4; 3.8)	-2.6 (-3.8; -1.3)	**<.001**	3.4 (2.5; 4.3)	-0.9 (-2.3; 0.5)	0.584
52 weeks	64	2.6 (1.9; 3.4)	-3.0 (-4.4; -1.6)	**<.001**	3.2 (2.3; 4.2)	-1.1 (-2.7; 0.6)	0.569

TABLE 5. UNADJUSTED BASELINE HRQOL SCORES BY TREATMENT GROUP AND RESPONSE TO TREATMENT AT 12 WEEKS POST-TREATMENT. RESPONSE TO TREATMENT BASED ON MCID OF 9 POINTS OR HIGHER INCREASE IN SOSGOQ2.0 TOTAL SCORE.

	Surgery +/- radiotherapy			*Radiotherapy*		
	Improvement exceeding MCID N = 61 Mean (SD)	**No improvement or improvement less than MCID N = 36 Mean (SD)**	**p-value**	**Improvement exceeding MCID N = 29 Mean (SD)**	**No improvement or improvement less than MCID N = 37 Mean (SD)**	**p-value**
SOSGOQ2.0 total score	48.2 (16.7)	61.3 (13.2)	<.001¶	53.2 (12.3)	69.9 (14.9)	<.001¶
SOSGOQ2.0 physical function	45.7 (25.3)	66.4 (21.8)	<.001¶	63.9 (21.4)	77.1 (18.6)	0.007§
SOSGOQ2.0 pain	31.1 (19.6)	42.9 (17.1)	0.002§	36.0 (15.1)	61.8 (19.0)	<.001§
SOSGOQ2.0 mental health	58.2 (25.0)	65.5 (20.3)	0.180§	54.0 (18.8)	64.4 (25.0)	0.050§
SOSGOQ2.0 social function	57.3 (25.8)	69.8 (18.0)	0.016§	58.3 (20.5)	75.7 (19.1)	<.001§
SF-36v2 PCS	27.9 (7.7)	33.4 (9.4)	0.002¶	32.5 (8.1)	37.9 (9.9)	0.025¶
SF-36v2 MCS	42.5 (12.5)	43.6 (11.4)	0.667¶	44.0 (10.5)	46.4 (11.9)	0.395¶
EQ-5D-3L	0.45 (0.27)	0.62 (0.23)	0.004§	0.59 (0.24)	0.74 (0.18)	0.003§

We used the disease specific SOSGOQ2.0, and generic SF-36 and EQ-5D questionnaires to measure the impact of treatment on HRQOL. The SOSGOQ2.0 is the first validated disease specific HRQOL instrument sensitive to changes in symptoms of patients with spinal metastases [8]. The observed gains in HRQOL in our surgery +/- radiotherapy cohort suggest that surgery is more effective as compared to radiotherapy alone for potentially unstable spinal metastases. This is supported by the greater and significant increase SOSGOQ2.0, EQ-5D and SF-36 PCS in the surgical cohort. Surgically treated patients also experienced the greatest improvement in SOSGOQ2.0 and EQ-5D within the first six weeks after treatment with further improvements over time. This is likely explained by the immediate impact of surgery on mechanical stability of the spine considering that surgical patients were more likely to have mechanical pain and vertebral compression fracture at baseline (Figure 1). Mechanical pain and vertebral fracture are associated with pain aggravated by movement or loading of the spine and decreases with recumbence *[4]*. This type of pain is associated with functional impairment and surgical stabilization has been shown to enable rapid improvement in pain and daily functioning *[11]*.

Patients treated with radiotherapy alone had lower SINS scores and were at baseline less compromised in their functional ability as reflected by higher baseline HRQOL values compared to those treated with surgery. The improvements in SOSGOQ2.0 and EQ-5D were only moderate, and did not improve over time. In fact, the SOSGOQ2.0 scores decreased over time and no improvements in SF-36 PCS were observed. The lack of significant gains in HRQOL following radiotherapy alone in this potentially unstable patient population suggest that efficacy is limited in the absence of surgery.

Interpretation of patient reported HRQOL scores are generally challenging. A change in HRQOL scores that reflects a clinically meaningful change to the patient aids in the interpretability of patient reported outcomes. The current study shows that a greater proportion of patients treated with surgery +/- radiotherapy experienced a clinically meaningful improvement in HRQOL as compared to those treated with radiotherapy alone, as indicated by the SOSGOQ2.0 score exceeding the MCID threshold in 63% of the surgical cohort as compared to 44% in the radiotherapy alone cohort (p=0.017). Additionally, the proportion of patients experiencing a clinically meaningful change after radiotherapy alone decreased over time suggesting only a temporary effect of radiotherapy. It is important to note, that in those patients who experienced a clinically meaningful change after treatment with surgery and/or radiotherapy presented with lower baseline HRQOL scores as compared to those not experiencing a meaningful change. Further research to identify other factors that are associated with a clinically relevant response after treatment is warranted.

Our analyses also demonstrates that both surgery +/- radiotherapy and radiotherapy alone result in a decrease in pain within the first 6 weeks post-treatment. These results are expected, as both modalities are effective in reducing pain. Pain is complex to analyze and thought to be caused by tumor related factors (biological pain) and pain resulting from mechanical instability. The greater and sustained decrease in pain observed in the surgical cohort as compared to radiotherapy alone might be explained by the greater proportion of patients presenting with mechanical pain and fracture, which is suggested to be less responsive to radiotherapy and analgesics, and more to immediate surgical stabilization *[12]*. Furthermore, there could be a synergistic effect from surgery plus radiation on improving outcomes. Insight into the specific role of the distribution of SINS factors within a patient on outcome is beyond the capacity of this study; however, future studies with larger cohorts should enable answers to these questions, leading to improved evidence based care.

Despite this being the first prospective multicenter study that compares outcomes in SINS potentially unstable spinal metastases, there are limitations to consider. This study is an observational cohort, rather than a randomized trial. The choice of treatment was determined by the individual physician according to their clinical judgment as opposed to an assigned treatment, Although this enhances generalizability and effectiveness, we are limited in determining the true efficacy of these interventions. As a result of the study design baseline differences between the two treatment groups were observed, mixed effects model adjusting for baseline differences were used to minimize these imbalances. However, differences with respect to the distribution and grouping of SINS factors remained, and although this serves to inform the results it limits a direct comparability. Furthermore, the MCID value of the SOSGOQ2.0 has not yet been determined. Instead, an approach of an MCID threshold of 0.5SD was chosen because other studies have shown that 0.5SD is associated with a clinically significant improvement in HRQOL *[10]*.

In conclusion, surgery +/- radiotherapy and radiotherapy alone were both associated with improvements in HRQOL measures, however, surgically treated patients demonstrated greater and clinically significant improvements. Distinct differences in the combination of SINS factors were observed between the two treatment groups, despite all patients being classified as potentially unstable, and need to be considered when interpreting the results. The results of this study should improve future communication and patient referral between specialists and improve patient counselling on the effect of treatment and HRQOL.

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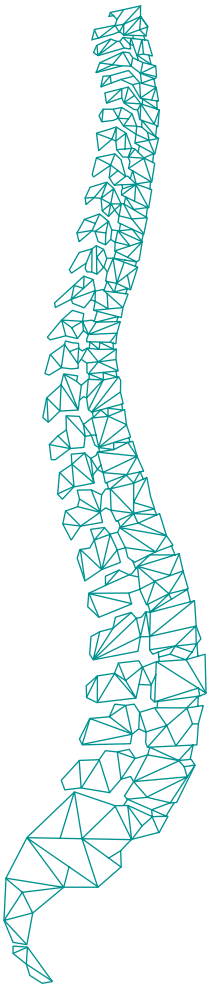

CHAPTER 7

Adverse events in emergency oncological spine surgery: a prospective analysis

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ABSTRACT

Objective

Most descriptions of spine surgery morbidity and mortality in the literature are retrospective. Emerging prospective analyses of adverse events (AEs) demonstrate signi cantly higher rates, suggesting underreporting in retrospective and prospective studies that do not include AEs as a targeted outcome. Emergency oncological spine surgeries are generally palliative to reduce pain and improve patients' neurology and health-related quality of life. In individuals with limited life expectancy, AEs can have catastrophic implications; therefore, an accurate AE incidence must be considered in the surgical decision-making process. The purpose of this study was to determine the true incidence of AEs associated with emergency oncological spine surgery.

Methods

The authors carried out a prospective cohort study in a quaternary care referral center that included consecutive patients admitted between January 1, 2009, and December 31, 2012. Inclusion criteria were all patients undergoing emergency surgery for metastatic spine disease. AE data were reported and collected on standardized AE forms (Spine AdVerse Events Severity System, version 2 [SAVES V2] forms) at weekly dedicated morbidity and mortality rounds attended by attending surgeons, residents, fellows, and nursing staff.

Results

A total of 101 patients (50 males, 51 females) met the inclusion criteria and had complete data. Seventy- six patients (76.2%) had at least 1 AE, and 11 patients (10.9%) died during their admission. Intraoperative surgical AEs were observed in 32% of patients (9.9% incidental durotomy, 16.8% blood loss > 2 L). Transient neurological deterioration occurred in 6 patients (5.9%). Infectious complications in this patient population were signi cant (surgi- cal site 6%, other 50.5%). Delirium complicated the postoperative period in 20.8% of cases.

Conclusions

When evaluated in a rigorous prospective manner, metastatic spine surgery is associated with a higher morbidity rate than previously reported. This AE incidence must be considered by the patient, oncologist, and surgeon to determine appropriate management and preventative strategies to reduce AEs in this fragile patient population.

INTRODUCTION

Historically, most reports on adverse events (AEs) in the literature are retrospective in nature or are from studies that do not include AE compilation as a primary outcome. Emerging prospective studies with AEs as the targeted outcome *[3,17]* suggest that when prospectively collected, AE rates are significantly higher than previously reported. This discrepancy is multifactorial but explained primarily by complication studies that relied on hospital-based administrative databases that lack sufficient detail and are populated retrospectively.

Street et al. reported on 942 consecutive patients admitted to a quaternary care referral center undergoing spinal surgery and found that 87% had at least one documented AE *[17]*. The patient population represented all admissions undergoing any type of spine surgery, either emergency or elective. Campbell et al. *[3]* prospectively studied 128 patients undergoing thoracic and/or lumbar spine surgery at the neurosurgical spine unit of a university hospital and documented AEs occurring within the first 30 days of the operative procedure. They found that 59.4% of the patients experienced at least one AE *[3]*.

Fourteen percent of cancer patients will develop symptomatic spine metastasis, and this number is likely to increase as systemic treatments continue to improve. Surgery has become an evidence-based and integral part of the treatment paradigm for these patients, with indications including high-grade epidural spinal cord compression, neurological compromise, spinal instability, and tumor progression after radiation therapy *[2, 5, 11, 19]*. The goals of surgical management are preservation of neurological function, ensuring spinal stability, and achieving local tumor control. Surgical intervention is not without risk, however, and the benefits must be weighed against the mortality and morbidity pro les of the procedure. AE occurrence has the potential to be catastrophic in this fragile oncological population for whom quality of life is so paramount in their remaining time. The societal costs of these AEs for this palliative intervention is also an important consideration *[6, 18]*.

The primary purpose of this study was to determine the true incidence of AEs in this specific population of patients undergoing emergency spine surgery for metastatic epidural spine disease and to compare the results of an AE-targeted prospective study to the best available literature. We hypothesized that AE rates would be higher when collected prospectively compared to retrospectively. The secondary objectives of this study were the evaluation of the impact of AEs on the length of stay and overall patient survival.

METHODS

Design

This study was a prospective observational analysis of consecutive patients admitted to our academic quaternary referral center over a 4-year period between January 1, 2009, and December 31, 2012. All patients discharged within this 4-year period with a primary or secondary diagnosis of metastatic spine disease who required an emergency surgery were included. No specific time frame was defined to meet the emergency criteria. Rather, emergency surgery was defined as surgery on patients admitted through the emergency department or seen in an outpatient clinic emergently for acute symptom onset who required immediate surgical attention either for neural structure compression or instability. Intradural metastases and primary bone tumors were excluded. Ethics committee approval was obtained according to the institutional standards.

Data Collection

Every patient's case was discussed at weekly morbidity and mortality rounds attended by all attending surgeons, residents, fellows, and nursing staff. All the AEs encountered in the previous week are discussed and coded during these rounds. The statuses of each in-hospital patient and all patients discharged since the last meeting were reviewed by all attendees. In addition, a dedicated research nurse completed daily rounds on every in-hospital patients with the purpose of identifying and documenting all AEs. In an effort to ensure that all AEs were identified, patients were also discussed at daily ward rounds, where any new AE was also recorded, and each patient was again discussed with the discharge coordinator at the time of discharge. If a patient was discharged without a completed Spine AdVerse Events Severity System, version 2 (SAVES V2) *[14]* form, the form was returned to the responsible attending surgeon within 1 week of discharge for completion. These multiple quality-assurance checks were developed to ensure maximal accuracy of our AE recording system and to ensure that no AEs were missed. All AEs were prospectively recorded using the SAVES V2 collection form *[13, 14]* which was previously tested for reliability and validity in both elective degenerative and emergency traumatic populations. The SAVES form contains a list of common intra- and postoperative AEs and was developed specifically for spinal surgery. The occurrence of any one discrete AE in this study did not necessarily imply a measurable adverse consequence. This form was used to ensure accurate and reliable AE data identification and collection, which is critical to the development of clinical care guidelines and standards, to resource and funding allocation, and to facilitate meaningful multicenter and multidisciplinary collaboration.

Data

Demographic data, including age, sex, primary tumor histology, and comorbidities (Charlson Comorbidity Index [CCI]), were collected from a local prospective spine database. Admission motor score was calculated by the surgical team using the International Standards for Neurological and Functional Classification of Spinal Cord Injury by the American Spinal Injury Association (ASIA). The type of surgical intervention was not standardized and was left to the discretion of the treating surgeon based on the specific clinical scenario for each patient. AEs occurring after discharge were collected again prospectively. Because this is the only referral center for spine-related cancer treatment within the region, all patients requiring readmission were admitted back to our institution.

Statistical Analysis

Statistical analysis was conducted using logistic regression and forward selection models to define the impact of these variables on the overall AE rate. All AE analyses were adjusted for age. The Hosmer-Lemeshow goodness-of- t test for logistic regression models was performed to confirm adequate model fit on the forward selection models. We also performed length of stay analyses and generated Kaplan-Meier survival curves.

RESULTS

A total of 101 patients met our inclusion criteria, including 50 males (49.5%) and 51 females (50.5%). Complete data were available for analysis in all 101 patients (100%). The median age at admission was 62 years (range 33–85 years). The mean CCI score *[4]* was 8. The primary tumor distribution and patient characteristics are shown in Table 1. The main clinical presentation was myelopathy in 39 patients (38.6%), mechanical pain in 38 patients (37.6%), and radiculopathy in 24 patients (23.8%). Forty-four patients (43.6%) had visceral metastases on initial presentation. The mean motor score was 88 (range 0–100), and 53 patients (52.5%) had motor function intact on admission.

Spinal metastases were distributed as follows: cervical spine in 16 cases (15.8%), thoracic in 63 (62.3%), lumbar in 20 (19.8%), and sacral in 2 (2%). The mean time from admission to surgery was 78 hours, and the mean operating time was 4.6 hours. The types of surgical approaches are listed in Table 2.

Seventy-six patients (76.2%) had at least 1 AE during their admission (Table 3). There was a mean of 1.8 AEs per patient. One-quarter of our population (n = 27) experienced 3 or more AEs. There were several factors that significantly influenced the total number of AEs in the forward selection model. These included the time between admission and surgery (p = 0.002), surgeon load (p = 0.009), and the mode of presentation. Surgeon load was defined as the number of cases a specific surgeon performed during the

study period, and the results demonstrated that patients operated on by a surgeon who per- formed more of these procedures had fewer overall AEs. Also, patients who presented with myelopathy had more AEs than patients who presented with only radicular symptoms, and the latter group suffered more complications than patients without neurological deficit who presented with mechanical pain only (p = 0.001). Interestingly, neither the CCI score (p = 0.104) nor the motor score on admission (p = 0.175) reached statistical significance as factors influencing the total rate of AEs in multivariate analysis.

TABLE 1. CHARACTERISTICS OF 101 PATIENTS UNDERGOING EMERGENCY ONCOLOGICAL SPINE SURGERY

Factor	Value
Demographics	
Male sex (%)	49.5
Median age (yrs)	61.9
Mean CCI score	8
Primary tumor%	
Breast	21.8
Non-small cell lung	19.8
Kidney	16.8
Colorectal	10.9
Prostate	6.9
Lymphoma	5.0
other	18.8
Clinical presentation	
Mechanical pain	37.6
Radiculopathy	23.8
Myelopathy	38.6
Pre-operative radiotherapy	19.8
ASIA impairment grade	
A	2.0
B	1.0
C	8.9
D	46.5
E	41.6

TABLE 2. SURGICAL APPROACH BY LEVEL

Factor	No. of Cases
Cervical	18
Posterior	7
Anterior	7
Anterior/posterior	4
Thoracolumbar	83
Posterolateral vertebrectomy	24
Decompression and fusion	50
Decompression only	6
Fusion only	3

Thirty-two percent of the emergency oncology patients in our study suffered from at least 1 intraoperative AE; the most common was significant blood loss (> 2 L) in 17 patients (16.8%). An iatrogenic dural tear occurred in 10 patients (9.9%), and malposition of instrumentation requiring revision occurred in 6 patients (5.9%). One patient (1%) had an intraoperative cardiac event, and 2 had an unplanned nerve root injury (2%). The length of surgery ($p = 0.029$) was the strongest predictor of intraoperative AEs. Two-thirds of our patients developed postoperative complications. Two factors had a statistically significant unfavorable impact on these complications in the forward selection models: longer duration of time from admission to surgery ($p = 0.021$) and age at admission ($p = 0.035$).

Two-thirds of our patients developed postoperative complications. Two factors had a statistically significant unfavorable impact on these complications in the forward selection models: longer duration of time from admission to surgery ($p = 0.021$) and age at admission ($p = 0.035$). Twenty-one patients (20.8%) developed delirium, making it one of the most common AEs complicating the postoperative course of our study population. Delirium was more common in male patients ($p = 0.031$). Transient neurological deterioration occurred in 6 patients (5.9%). No patients suffered from permanent neurological deterioration. Infectious complications occurred in a significant number of patients. Thirty-five (34.7%) had a urinary tract infection, 12 (11.9%) developed pneumonia, and 4 patients (3.9%) developed systemic sepsis. Surgical site infection was documented in 6 patients: 4 (3.9%) developed deep wound infections and 2 (2.0%) developed superficial infections. Twenty patients (19.8%) received pre- operative radiation therapy and subsequently had surgery because of radiation treatment failure; however, neither pre- nor postoperative

radiation therapy influenced the rate of wound complications in our study (p = 0.968). The deep wound infection rate was increased by the presence of an iatrogenic dural tear (p = 0.024) and if the patient required another surgery during the same admission (p = 0.002). Three patients required revision surgery during their index admission: 2 for wound infection and 1 for hardware revision. Four patients (4.0%) developed pressure sores during their hospitalization. The presence of pressure sores was influenced by the motor score on admission (p = 0.031) and the time from admission to surgery (p = 0.037).

TABLE 3. SUMMARY OF AES IN 101 PATIENTS

Factor	% of patients
AEs	
Any AEs	76.2
Mean no. AEs/patient	1.8
In-hospital death	10.9
Intraoperative AEs, overall	31.7
Blood loss > 2L	16.8
Iatrogenic dural tear	9.9
Revision of instrumentation	5.9
Nerve root injury	2.0
Cardiac event	1.0
Postoperative AEs, overall	66.3
Delirium	20.8
Transient neurological deterioration	5.9
Pressure sores	4.0
Deep vein thrombosis	4.0
Early construct failure	2.0
Electrolyte imbalance	11.0
arrythmyia	4.0
dysphagia	5.0
Infection	
Urinary tract infection	34.7
Pneumonia	11.9
Systemic sepsis	3.9
Deep wound infection	3.9
Superficial wound infection	2.0

Four subjects had a deep vein thrombosis (4%), and 2 had an early construct failure (2%). Other AEs, which by themselves did not have significant clinical impact but are worth mentioning for completeness, were electrolyte imbalance (11%), hematological complication (2%), transient cardiac arrhythmia (4%), and short-lived postoperative dysphagia (5%).

The median length of stay was 21 days (range 4–100 days). The presence of any AE clearly affected the length of stay ($p < 0.0001$). As we would expect, the need for a second operation was also significant in the multivariate analysis ($p = 0.006$) for increased length of stay. Motor score on admission ($p < 0.0001$) and postoperative deep venous thrombosis ($p = 0.0013$) were also significant in the multivariate analysis for increased length of stay. Eight patients (8%) required readmission for an AE: 4 for a deep wound infection, 2 for failure of instrumentation, and 2 for pain management.

Twenty-four patients (23.8%) were still alive at the last follow-up. The median survival after spinal surgery was 8.4 months; the Kaplan-Meier survival curve is shown in Fig. 1. There were 11 in-hospital deaths (10.9%). These were not necessarily related to postoperative AEs but rather to a more palliative orientation and withdrawal of aggressive treatment according to patient and family wishes. Overall survival was statistically influenced by the surgery duration, number of AEs, male sex, primary disease, surgeon load, and the initial ASIA impairment scale score. In addition, overall survival was also influenced by the presence of postoperative delirium. Yet, in our study, overall survival was not influenced by the CCI score or the extent of disease.

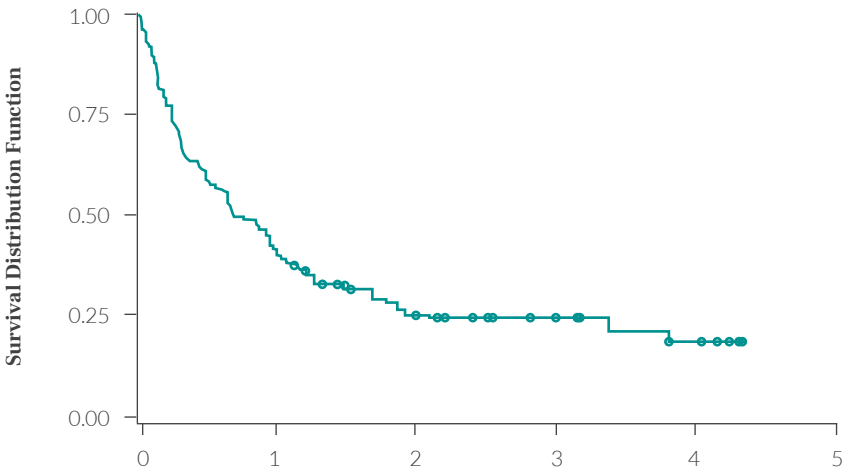
DISCUSSION

Using a detailed prospective data collection method and the validated AE data collection form, SAVES V2, we examined 101 consecutive patients undergoing emergency surgery for spinal metastases and found an overall AE rate of 76.2%. This is significantly higher than previously reported in the spine literature. Historically, the complication rates range from 15% to 39% *[9, 10. 12. 15]*. Wise et al. conducted a retrospective analysis on complications, survival rates, and risk factors of surgery for metastatic disease of the spine and found a complication rate of 25% in 80 patients *[20]*. The likelihood of having a complication in their study was strongly related to the Harrington classification of spinal metastatic disease, presence of neurological deficits, and preoperative radiation therapy.

Although the presence of myelopathy or radiculopathy was associated with an increased overall AE rate, we did not find similar association between the preoperative motor score and AE rate. Also, preoperative radiation therapy did not seem to have a

FIGURE 1.

Kaplan-Meier survival curve. The line shows the product-limit estimate curve. Censored observations are indicated with circles.



significant impact on wound complications in our study. This is in contrast to what was previously published on this subject *[7]*.

However, their study was a retrospective chart review including patients from 1970 through 1996 who underwent surgical decompression for spinal cord compression after irradiation *[20]*. Advancements in radiation treatments, surgical techniques, and postoperative care might explain the difference in the influence of radiation on wound complications. Another reason for this discrepancy may be that our study was underpowered to assess this outcome.

Wang et al. *[19]* reported a combined major complication and reoperation rate of 25.3% in patients undergoing single-stage posterolateral decompression for epidural metastatic disease. Like most other studies, this was a retrospective analysis investigating a specific procedure. In a retrospective study of 200 patients surgically treated for pine metastases, Arrigo et al. found that 34% of their patients had at least one AE *[1]*. The CCI

score4 was the most significant predictor of AE occurrence in their study. We did not adjust for oncological factors in our statistical analysis, which may explain why we did not reproduce these findings. Similarly Arrigo et al. and Shehadi et al. did not find a positive correlation between perioperative radiation therapy and wound complications *[1, 15]*.
Our total AE rates are not significantly different from those reported by Street et al., *[17]* who published a study of 942 consecutive patients undergoing spinal surgery for all indications. This may suggest that, despite having metastatic disease, this population is not significantly more prone to developing AEs. Interestingly, another study by Street et al.*[16]* at the same institution reported AEs in 47% of the patients who underwent a posterolateral vertebrectomy for spinal metastatic disease. This retrospectively collected AE rate was significantly lower than the rate reported in their prospective study, even though both were conducted at the same spine unit, once again reinforcing the superiority of prospective AE collection.

Accurate AE rates are important to both patients and physicians. They allow the patient to have all the necessary information to provide more precise informed operative consent. For the surgeon, it provides quality assurance and a useful basis to develop preventive and risk reduction measures with the ultimate goal of improved patient care. It also assists in the decision-making process and improves the treatment algorithm employed by the multidisciplinary team of physicians caring for these patients by confronting a known risk pro le to an expected benefit. Having a disease-specific AE profile is even more useful because it allows physicians to apply it to real-life, day-to-day clinical scenarios.

AEs are inevitable in any type of surgical intervention. To be able to recognize them in a timely fashion and react accordingly is certainly very important. More important is the use of valid AE data to initiate preventative strategies. As expected based on other prospective studies on AEs, our AE rate was higher than that reported in retrospective studies. This may be due to the prospective nature of the data collection as well as the rigorous methodology we employed. In addition, we collected all potential AEs, not only the ones considered medically relevant, which may be different from the approach used in previous publications and likely contributes to the higher AE rate. This resulted in the recording of AEs that are not necessarily direct postoperative complications but rather secondary to the primary diagnosis. Recording all of these AEs provides a more accurate picture of what can be expected during the admission of a patient with a spinal metastasis, and it also contributes to surprisingly high rates of AEs. The assumption that the clinical impact of some AEs may be of questionable significance and there- fore may be ignored has never been studied before. It is imprudent to assume that there is no effect of an AE; in- deed, in combination with other AEs, it can potentially influence patient outcome. Furthermore, there is the perception that minor AEs are insignificant, but recent data suggest that they are responsible for one-third of total AE

costs *[8]*. Increased length of stay contributes to increased cost and negatively impacts patient quality of life. It is therefore important to limit the occurrence of even the most benign AEs.

CONCLUSIONS

To the best of our knowledge, this study is the first detailed, prospective analysis using a validated data collection instrument specifically looking at AEs in an emergency oncological setting. The results revealed that when evaluated in a rigorous prospective manner, metastatic spine surgery is associated with a higher morbidity than previously reported. This AE incidence must be considered by the patient, oncologist, and surgeon in determining appropriate management and preventative strategies to reduce AEs in this fragile patient population. Quality of life and health economic impact studies related to AEs in patients with metastatic spine disease are lacking and are much needed to improve patient outcomes.

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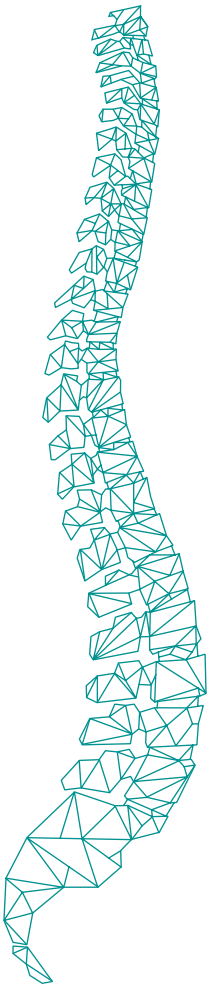

CHAPTER 8

Complications after percutaneous pedicle screw fixation for the treatment of unstable spinal metastases

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ABSTRACT

Background

Complications after surgical stabilization for the treatment of unstable spinal metastases are common. Less invasive surgical procedures are potentially associated with a lower risk of complications, however little is known regarding the complications after less invasive surgical procedures for the treatment of spinal metastases. The primary objective is to determine the characteristics and rate of complications after percutaneous pedicle screw fixation (PPSF) for the treatment of mechanically unstable spinal metastases. The secondary objective is to identify factors associated with the occurrence of complications and survival.

Methods

A retrospective multicenter cohort study of patients who underwent PPSF between 2009 and 2014 for the treatment of unstable spinal metastases was performed. Patient data pertaining to demographics, diagnosis, treatment, neurological function, complications, and survival were collected.

Results

A total of 101 patients were identified, 45 males (45%) and 56 females (55%) with a mean age of 60.3 (±11.2) years. The median operating time was 122 minutes (range 57-325) with a median blood loss of 100ml (based on N=41). Eighty-eight patients (87%) ambulated within the first three days postoperative. An overall median survival of 11.0 months (range 0-70 months) was found with 79% of the patients being alive at three months post-treatment. Eighteen patients suffered a total of 30 complications; nonsurgical complications were most commonly encountered. Prolonged operating time was independently associated with an increased risk of complications.

Conclusion

A complication rate of 18% was found after PPSF for unstable spinal metastases. Potential advantages of less invasive treatment are limited blood loss and high early ambulation rate.

INTRODUCTION

The life expectancy of patients diagnosed with metastatic disease can vary from several weeks or months for patients with unfavorable aggressive primary tumors with bone and visceral involvement to several years for patients with exclusively bone metastases *[1, 2]*, with the spinal column being the most common location for bone metastases *[3]*. Radiotherapy has been the standard of care for the treatment of symptomatic spinal metastases *[4, 5]*. However, if spinal metastases compromise the mechanical integrity of the spine, surgical stabilization is the preferred treatment option followed by radiotherapy for local tumor control *[6]*.

Surgical stabilization has traditionally been performed through open procedures necessitating extensive soft tissue dissection associated with significant blood loss, lengthy hospital stays and a substantial risk of complications *[7]*. Invasive procedures are, considering the limited life expectancy and comorbidities of the majority of patients with spinal metastases, often undesirable and unfeasible *[8]*.

Advancements in surgical techniques have led to the development of the concept of less invasive surgical (LIS) procedures with the aim to achieve the same clinical results with less morbidity related to the surgical approach *[8]*. Benefits of less invasive techniques include decreased blood loss, less post-operative pain, and shortened recovery time *[8]*. Moreover, LIS procedures allow earlier initiation of post-operative adjuvant treatments due to faster wound healing *[9]*. The ability to perform LIS procedures for the treatment of unstable spinal metastases may enable surgeons to offer surgical intervention to patients who were not deemed surgical candidates for conventional open surgery *[8]*.

LIS procedures have been shown to be safe and have resulted in good clinical outcomes in patients with traumatic and degenerative spinal disorders *[10-12]*. Only a few studies have investigated the clinical outcome of less invasive techniques for the treatment of spinal metastases, with improved pain scores and functional status being reported *[13-16]*. However, a paucity of literature exists regarding the safety of less invasive surgery for the treatment of symptomatic spinal metastases. Therefore the primary objective of this study was to determine the characteristics and rate of complications after percutaneous pedicle screw fixation (PPSF) for the treatment of mechanically unstable spinal metastases. The secondary objective was to identify factors associated with the occurrence of complications and survival.

METHODS

A multicenter retrospective observational cohort study of patients who underwent PPSF for the treatment of unstable spinal metastases was performed. The local institutional review board approved the research protocol. Patients were eligible for inclusion if they had histological proof of malignancy (including multiple myeloma) and were treated with PPSF, with or without cement augmentation, between January 2009 and December 2014. An (impending) unstable pathologic fracture and/or intractable mechanical pain due to an impending pathologic fracture were indications for surgical intervention. In addition, a life expectancy of at least three months, as assessed by the referring oncologist, was required. Assessment of the degree of spinal instability was based on the clinical experience of the surgeon and/or the recent Spinal Instability Neoplastic Score (SINS)*[17]*. To enhance homogeneity of the procedure and study population, patients were excluded if diagnosed with a primary spinal tumor or if additional minimal access spine surgery (e.g. mini open decompression, laminectomy) was performed.

Data pertaining to demographics, primary tumor diagnosis, surgical treatment, neurological status, performance status, complications, and survival were collected from medical charts, and institutional databases. Governmental databases were accessed to retrieve information about vital statistics. The definitions and scales of the outcome parameters are listed in Table 1.

Statistics

Continuous data were described using mean, median, standard deviation and range. Frequencies were used to describe categorical data. Univariate logistic regression was performed to identify predictive factors for the occurrence of complications. Linear regression analysis was conducted to determine variables related to length of stay. The Kaplan-Meier analysis and log-rank tests were used to investigate factors that influenced survival, followed by multivariate cox regression analysis to determine the impact of the variables. $P<0.05$ defined significance. IBM SPSS statistics for windows version 21.0 was used for the analysis (IBM Corp., Armonk, NY, USA).

RESULTS

Demographics

A total of 101 patients were identified in the five participating centers; 45 patients were male (45%) and 56 were female (55%) with a mean age of 60.3±11.2 years. Patient characteristics are listed in Table 2. Breast cancer (25%) and multiple myeloma (25%) were the most frequent primary tumors. Fifty percent of the patients had exclusively metastatic

TABLE 1. DEFINITIONS OF OUTCOME PARAMETERS

Parameter	Definition	Scale/ unit	Time points
Neurological status	Degree of neurological deficit	ASIA scale [24]	Pre- and post-operative, first follow-up visit.
Performance status	Level of daily functioning	Karnofsky [25]	Pre-operative
Consultation time	Time from first surgical consultation until date of surgery	Days	n.a.
Ambulatory function	Able to walk at least four steps [20].	Days	n.a.
Blood loss	Estimated blood loss	Milliliters	n.a.
Complication	Any unexpected and undesirable medical event that required additional intervention.	n.a.	Peri- and post-operative.
Operating time	Time from first incision until wound closure ('skin-to-skin')	Minutes	n.a.
Hospital stay	Date of surgery until date of discharge	Days	n.a.
Follow-up time	Date of surgery until date of death	Months	n.a.

bone disease, 42% of the patients had bone and visceral metastases, and the remaining 8% of the patients had bone and lymph node metastases. Ninety-four of the patients (93%) were neurologically intact pre-operatively (ASIA E), six patients (6%) had minimal motor impairment (ASIA D) without progression and one patient (1%) had severe motor impairment (ASIA C).

Operative characteristics

Median time from first surgical consultation to surgical intervention was nine days (range 0-377 days). The most commonly treated areas were the thoracolumbar (T10-L2, N=39) and thoracic (N=38) regions followed by the lumbar (N=22) and lumbosacral (L4-S2, N=2) region. The median operating time was 122 minutes (range 57–325 minutes) with

TABLE 2. BASELINE CHARACTERISTICS

Variables	N%
Gender (N = 101)	
Female	56 (55%)
Male	45 (45%)
Age at Surgery (years) (N = 101)	60.3 (SD11.2)
Primary tumor type (N = 101)	
Breast	25 (25%)
Multiple myeloma	25 (25%)
Lung	13 (13%)
Kidney	10 (10%)
Prostate	5 (5%)
Other	23 (22%)
Clinical presentation (N =101)	
Back pain	53 (52%)
Radicular pain	7 (7%)
Combined radicular and back pain	20 (20%)
Impending fracture without significant pain	21 (21%)
Karnofsky performance scale (N = 98)	
100%	4 (4%)
80-90%	46 (47%)
60-70%	28 (28%)
40-50%	20 (21%)
<30%	0 (0%)
Pre-operative ASIA scale (N = 101)	
ASIA E	94 (93%)
ASIA D	6 (6%)
ASIA A/B/C	1 (1%)

a median blood loss of 100 ml (range 50–500 ml) based on data available for 41 patients. Five vertebral bodies or more were bridged in 65 patients (64%); four vertebral bodies in 9 patients (9%) and three vertebral in 27 patients (27%). Vertebroplasty was performed in six patients (6%), kyphoplasty in ten patients (10%), and vertebral body stenting in 19 patients (19%). Cement augmentation of pedicle screws was performed in three patients (3%).

Eighty-seven percent of the patients (N=88) were ambulatory within the first three days post-operative (median: one day) and overall median length of hospital stay was seven days (range 1–43 days). Patients who suffered a complication had a median length of hospital stay of 11.5 days, which was significantly longer compared to a median length of hospital stay of seven days for patients without complications (P=0.002). The overall presence of complications (P=0.003), the need for re-operation (P<0.001), the presence of neurological deterioration (P=0.015), the presence of construct failure (P<0.001) and the presence of nonsurgical complications (P=0.026) were associated with increased length of hospital stay. The most common form of adjuvant treatment was post-operative radiotherapy in 56 patients (55%). Fifteen patients (15%) had received radiotherapy prior to surgery, 11 patients (11%) received both pre- and post-operative radiotherapy and 17 patients (16%) did not receive additional radiotherapy.

Complications

A total of 30 complications occurred **(Table 3)**, with 18 patients suffering at least one complication. Prolonged operating time (P=0.041) was the only factor significantly associated with the occurrence of complications. Non-surgical adverse events were common including delirium (N=3), pneumonia (N=2), ileus (N=1), urinary tract infection (N=1) and bladder retention (N=1). Furthermore, one patient developed a perioperative acute coronary syndrome. This patient was transported to the ICU post-operatively and died three days later due to cardiac failure.

A wound-healing disturbance occurred in four patients of which two were deep wound infections. Four patients experienced construct failure, two patients had a pedicle screw pullout of which one required a re-operation, and one patient had a broken pedicle screw (S1) causing pain and requiring reoperation 1.5 years after the index surgery. In one patient secondary screw pullout occurred caused by tumor progression, which required revision surgery within one month of the index surgery. After the second surgery the patient developed a superficial wound infection and suffered neurological deterioration due to tumor growth into the spinal canal; neither preoperative nor postoperative radiotherapy was administered. Local tumor progression was also the cause for neurological deterioration in two other patients, both within four months after index surgery. Neurological deterioration occurred also in two other patients, one patient suffered permanent complete paraplegia due to too medial placement of a pedicle screw, revision surgery was performed without postoperative neurological improvement. Cement extravasation resulting in an incomplete spinal cord lesion (ASIA C), which recovered fully (ASIA E) after reoperation was the cause in the other patient. A total of six patients (7%) required revision surgery. One patient experienced transient neurological deterioration immediately post-operative at the recovery unit but recovered spontaneously within 6 hours. The neurological status over time is displayed in **Table 4**.

TABLE 3. COMPLICATIONS (N (%) OF 101 PATIENTS)

Superficial wound infection	2 (2%)
Deep wound infection	2 (2%)
Neurological deterioration	
Transient deterioration	1(1%)
Surgical Permanent deterioration	2 (2%)
Secondary Permanent deterioration	3 (3%)
Construct failure	
Within three months	1 (1%)
After three months	3 (3%)
Malposition of screw	1 (1%)
Re-operation	6 (6%)
Other complications	9 (9%)

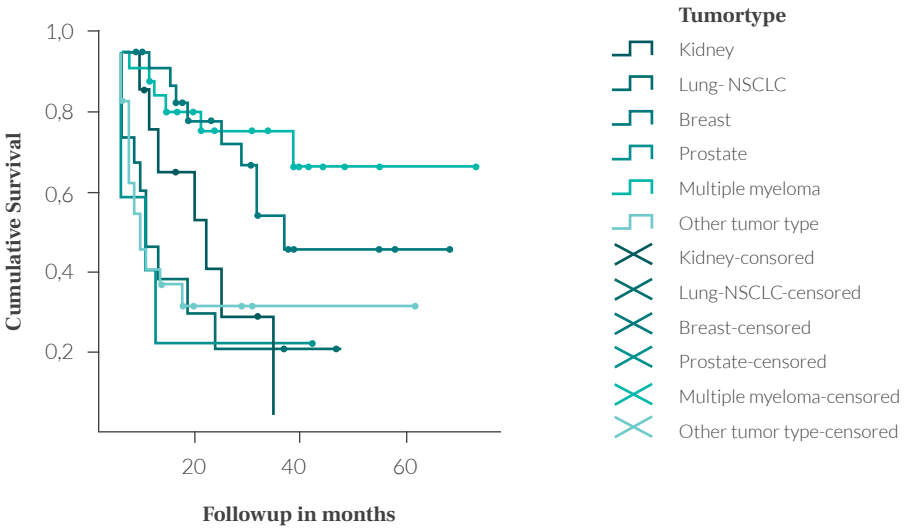
TABLE 4. NEUROLOGICAL STATUS OVER TIME

ASIA score	Pre-operative	Post-operative	Follow-up*
E	94	94	93
D	6	3	3
C	1	1	1
B	0	1	1
A	0	1	1

Total SINS score is sum of all six factors. 0-6 point represent spinal stability, 7-12 points represent indeterminate spinal instability and 13-18 points represent spinal instability.

FIGURE 1.

Kaplan Meier survival curve. Differences in survival between different tumor types was testes with the Log-rank test P< 0.001. Excluding multiple myeloma = P<0.001.



Survival

The overall median survival was 11.0 months (range 0 – 70 months), with 39 (39%) patients still alive in March 2015. Seventy-nine patients (78%) were alive three months after surgery. Kaplan Meier analysis showed that breast carcinoma and multiple myeloma had significantly better survival compared to other primary tumor types **(Figure 1)**. Univariate analysis demonstrated that lower performance status (P=0.043), primary tumor type (P<0.001), the presence of node and/or organ metastases (P=0.019) and no administration of post-operative chemotherapy (P=0.007) negatively influenced three months survival. Using multivariate analysis only no administration of post-operative chemotherapy (P=0.017, HR 5.8, 95%CI 1.79 – 18.77) demonstrated to be independently associated with mortality within three months postoperative.

Overall survival was negatively influenced by higher age (P<0.001), primary tumor type (P<0.001) and the presence of node and/or or visceral metastases (P<0.001) in the univariate analysis. Multivariate analyses demonstrated that two factors were independently associated with impaired overall survival: a diagnosis of primary tumor type other than breast, prostate, lung or renal carcinoma, (P=0.006, HR 3.94, 95%CI 1.4 – 8.1) and the presence of lymph node and/or visceral metastases (P<0.005, HR 2.9, 95%CI 1.37 – 6.1).

DISCUSSION

Advancements in surgical techniques and implants have led to the development of less invasive surgical (LIS) procedures. Thus far, studies reporting the clinical outcomes after minimal invasive procedures for the treatment of spinal metastases have been scarce *[13-16]*. These studies reported promising clinical results in terms of decreased post-operative pain levels and early recovery of ambulatory function *[13-16]*. To the best of our knowledge, this is the largest cohort of patients who underwent percutaneous pedicle screw fixation, with or without cement augmentation, for the treatment of spinal metastases and the first with a specific focus on the characteristics and rate of complications. In addition, factors that could predict the occurrence of complications or influenced survival were analyzed.

This study demonstrated that 18% of the patients suffered at least one complication with an increased risk for complications with longer operation duration. Seven patients required revision surgery for construct failure, neurological deterioration or surgical debridement of a deep wound infection. Two different studies reporting on outcomes after percutaneous pedicle screw fixation, but without specific focus on complications, reported complication rates of 9% (4/46) and 17% (2/12) *[13, 14]*. In comparison, several retrospective studies have investigated complications rates after open surgical procedures for the treatment of spinal metastases with complication rates reported between 15% and 47% *[7]*. Furthermore, Dea et al. *[7]* conducted a prospective study on the adverse events after emergency spine surgery for spinal metastases. A complication rate of 76% was found, with a mean of 1.8 adverse events per patient *[7]*. Both, prospective and retrospective studies report high complication rates after surgical intervention for spinal metastases *[7]*. The high risk for complications does not only reflect the surgical demand of these procedures but also reflects the fragility of this patient category *[18]*. Our reported complication rate of 18% falls in the lower range of previous published complication rates suggesting that PPSF for the treatment of spinal metastases may result in fewer complications compared to conventional open procedures. However, the retrospective design of this study may also account for this lower complication rate. Minor complications may not have been registered in the patient's medical chart. In

addition, only patients who underwent PPSF were included for analysis. This limits a direct comparison of complication rates between different surgical approaches. However, by including only patients who underwent isolated PPSF we aimed to create homogeneity regarding the surgical procedure thereby facilitating more accurate interpretation of the complications associated with PPSF. The multicenter research approach has resulted in a relatively large number of patients, thereby increasing the generalizability of the results. It should, however, be noted that PPSF, in regular practice, is frequently combined with decompressive techniques as a LIS procedure.

Three (3%) of our patients experienced neurological deterioration caused by local tumor progression. This rate is similar to other studies reporting decreased ambulatory and/or neurological function due to local disease progression resulting in spinal cord compression *[13, 14]*. Although this rate is relatively low, the impact of this complication on quality of life is substantial and is also associated with decreased survival rates *[19, 20]*. Symptomatic spinal cord compression is best treated with the combination of surgical decompression, stabilization and radiotherapy *[21]*. Percutaneous pedicle screw fixation techniques can successfully be combined with mini-open decompressive techniques in patients with symptomatic spinal cord compression. However, because the benefits of percutaneous surgical procedures, compared to conventional open techniques, quickly diminish when decompressive techniques are required due to the increased risk of complications, the presence of symptomatic spinal cord compression may be regarded as a relative contraindication for percutaneous pedicle screw fixation techniques.

Although LIS procedures have potential benefits there are also some limitations. First, LIS procedures depend on accurate intraoperative visualization of the bony anatomy to minimize the risk of screw malposition and to prevent cement leakage. Second, the implants used in LIS procedures serve as an internal brace as bony fusion is not achievable with most LIS procedures *[11, 16]*. However, considering the limited life expectancy of most patients with spinal metastases the main goal is to improve quality of life by stabilizing the spine rather than achieving fusion, as is the goal with traumatic fractures *[16]*. Third, only limited sagittal correction can be achieved using current LIS procedures compared to an open procedure *[11]*. It should be noted that the term LIS procedure does not encompass one surgical technique but rather is a surgical concept including a wide variety of surgical procedures including minimal access decompression of the spinal cord.

The most frequent complications in our study were neurological deterioration (6%) and revision surgery (6%), with 3 patients requiring revision surgery as a result of neurological deterioration. In contrast, studies reporting on adverse events after open surgical procedures report infection (including wound infections), pneumonia and

hematoma *[7, 18]* as frequent complications. Four of our patients experienced a wound complication consisting of two deep and two superficial wound infections. No excessive blood loss or hematomas were reported. The differences in complication types between open surgical procedures and percutaneous procedures can be explained by the difference in surgical approach, with PPSF having several potential advantages over the open approach. First, PPSF is performed through small stab incisions. The combined total length of the incisions may be the same or longer compared to open surgery but the smaller incisions limit soft tissue dissection, minimize blood loss, decrease post-operative pain and decrease the risk of wound healing disturbances. Less post-operative pain also results in less analgesics use, earlier ambulation and shorter hospital stay. This study reported a median length of hospital stay of seven days and 78% of the patients were ambulatory within the first three days post-surgery. A significant difference was found between the length of stay of patients with and without complications. Finally, PPSF is associated with less blood loss with a median blood loss of 100ml in the present study. Significant blood loss has been associated with lengthy hospital stays, and increased morbidity and mortality rates *[8]*. Furthermore, significant blood loss often requires blood transfusions associated with immunosuppression and a subsequent increased risk for infections and progression of disease *[22]*.

Most of the patients who require surgical intervention for the treatment of spinal metastases are subsequently treated with radiotherapy for local control. In addition, chemotherapy and/or immunotherapy are often initiated as systemic treatment. Improved wound healing caused by the smaller incisions allows for earlier initiation of post-operative adjuvant therapies *[9]*. Earlier initiation or continuation of adjuvant therapies is important in the palliative phase to maximize tumor control *[23]*. Fewer complications and shortened rehabilitation time therefore LIS procedures may also enable surgical intervention for patients who were not considered to be good surgical candidates for extensive open surgery on the bases of their life expectancy and physical status *[8]*.

To summarize, this is the first study to specifically focus on complications after PPSF for the treatment of spinal metastases. A complication rate of 18% was found suggesting that PPSF may lead to fewer complications compared to complication rates of open surgical procedures that have been reported in the literature *[7]*. Prolonged operating time demonstrated to be associated with an increased risk of complications. In addition, the absence of postoperative administration of chemotherapy was associated with mortality at three months post surgery. Potential advantages of LIS procedures consist of decreased need for blood transfusions, decreased need for analgesics, early ambulatory function, shorter hospital stay and earlier initiation of post-operative adjuvant therapies. Future prospective studies are needed to improve insight in the frequency and types of complications following different types of LIS procedures.

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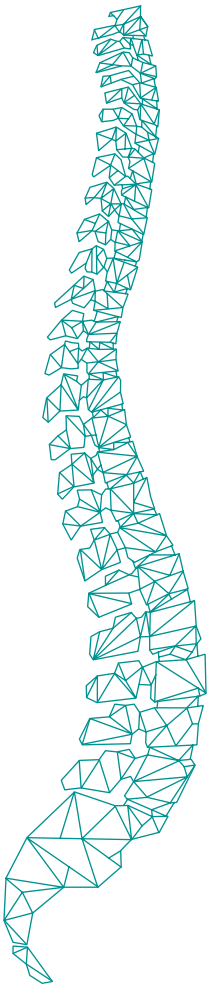
PART III

Advances in treatment strategy



CHAPTER 9

Sparing the surgical area with stereotactic body radiotherapy for combined treatment of spinal metastases; a treatment planning study

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ABSTRACT

Introduction

Decreasing the radiation dose in the surgical area is important to lower the risk of wound complications when surgery and radiotherapy are combined for the treatment of spinal metastases. The purpose of this study was to compare the radiation dose in the surgical area for spinal metastases between single fraction external beam radiotherapy (EBRT), single fraction stereotactic body radiotherapy (SBRT) and single fraction SBRT with active sparing (SBRT-AS) of the posterior surgical area.

Methods

Radiotherapy treatment plans for EBRT, SBRT and SBRT-AS of the posterior surgical area were created for 13 patients with spinal metastases. A single fraction of 8Gy was prescribed to the spinal metastasis in the EBRT plan. For the SBRT treatment plans, a single fraction of 18Gy was prescribed to the metastasis and 8Gy to the rest of the vertebral body. For the SBRT plan with active sparing the dose in the designated surgical area was minimized without compromising the dose to the organs at risk.

Results

The median dose in the surgical area was 2.6Gy (range 1.6Gy – 5.3Gy) in the SBRT plan with active sparing of the surgical area compared to a median dose of 3.7Gy (range 1.6Gy – 6.3Gy) in the SBRT plan without sparing and 6.5Gy (range 3.5Gy – 9.1Gy) in the EBRT plans ($p < 0.001$). The radiation doses to the spinal metastases and organs at risk were not significantly different between the SBRT plan with and without sparing the surgical area.

Conclusion

The radiation dose to the surgical area is significantly decreased with the use of SBRT compared to EBRT. Active sparing of the surgical area further decreased the mean radiation dose in the surgical area without compromising the dose to the spinal metastasis and the organs at risk.

INTRODUCTION

The combination of surgery and radiotherapy has been shown to be effective in achieving pain relief, maintaining ambulatory function and improving quality of life in patients with symptomatic spinal metastases *[1, 2, 3]*. Optimal timing of surgery and radiotherapy is however crucial as radiotherapy may impair wound healing *[4, 5]*. Surgical intervention for spinal metastases is typically followed by conventional 2D external beam radiotherapy (EBRT) for local tumor control and additional pain relief. The dose distribution with EBRT is non-conformal; consequently the radiation dose to the spinal metastasis is limited by the radiation tolerance of the spinal cord and the dose received by the skin and underlying soft tissues is high due to the photon energy attenuation *[6]*. The administration of post-operative EBRT is therefore deferred 1-2 weeks post-operative to allow for initial wound healing *[4]*.

Advances in radiotherapy techniques have led to the development of conformal radiation techniques such as stereotactic body radiotherapy (SBRT). The conformal dose distribution of SBRT permits dose escalation to ablative radiation doses to the spinal metastasis while limiting the dose to the spinal cord and other surrounding tissues, including the skin *[7, 8]*. Post-operative use of SBRT, rather than EBRT, is therefore likely associated with a lower risk of wound complications *[5]*. The use of SBRT after surgical stabilization is, however, challenging as the metallic spinal implants cause imaging artifacts and radiation backscattering prevents accurate target delineation, treatment planning and delivery *[9]*. Reversing the order of surgery and SBRT may overcome some of these technical challenges. Active dose sparing of the surgical area may eliminate the need for the time interval between the two treatment modalities as wound healing is no longer impaired by the damaging effects of high-dose irradiation.

The purpose of this study was to investigate the effect of active sparing of the surgical area with SBRT on the radiation dose in the surgical area as compared to routine single fraction SBRT and single fraction EBRT.

METHODS

The imaging studies of thirteen patients treated in a recently conducted phase I/II study (ClinicalTrials.gov identifier: NCT02622841 [Versteeg 2017]) for symptomatic unstable spinal metastases in the thoracic or lumbar spine requiring surgical stabilization and radiotherapy were included in this study. Patients with symptomatic or radiographic high-grade spinal cord compression (Bilsky 2 or 3 *[10]*) were not included in this cohort.

Treatment planning

Patients were immobilized in a vacuum mattress (BlueBAGTM Vacuum Cushion, Elekta, Stockholm, Sweden) with arms in abduction above the head. Computed Tomography (CT) simulation was performed prior to radiotherapy treatment in radiotherapy position on a Philips large bore CT Scanner (slice thickness 1.2 mm, Philips Medical Systems, Cleveland, OH). In addition, all patients underwent a MRI-scan (1.5 Tesla, slice thickness 1.1–4 mm, Ingenia; Philips Medical System, Best, The Netherlands) also in treatment position. The MRI sequences were registered to the CT by rigid mutual information registration on a box around the tumor. The attending radiation oncologist contoured the gross tumor volume (GTV), the clinical target volume (CTV), the organs at risk (OAR), and the posterior surgical area using in-house delineation software on MRI imaging *[11]*. The GTV consisted of the visible volume of the spinal metastasis and the CTV of the vertebra containing the spinal metastasis. The GTV and CTV were expanded with 2mm to create the planning target volume (PTV), respectively the PTV-boost and the PTV-elective. The posterior surgical area was cranially and caudally bordered by the upper, respectively, lower endplate of the vertebral body adjacent to the planned lower and upper level of pedicle screw instrumentation, laterally by the tips of transverse processes, anteriorly by the vertebral body contour and posteriorly by the outermost skin layer **(Figure 1)** as described previously [Versteeg 2017]. Organs at risk (OAR) in close proximity to the tumor were delineated as well. A 2 mm planning OAR volume (PRV) margin was applied to the spinal cord to account for geometrical uncertainties and variations in spinal cord position *[12, 13]*

EBRT treatment plans

For EBRT treatment planning, a routine single fraction of 8Gy to the spinal metastasis and the adjacent upper and lower vertebral body was prescribed **(Figure 1)**. A single postero-anterior field with a 100% iso-doseline at 6cm or 7cm for a 6MV or 10MV, photon beam was planned using the Monaco treatment planning system version 5.1 (Elekta, Stockholm, Sweden). Adequate coverage was achieved if the vertebral body harbouring the spinal metastasis received at least 80% of the prescribed dose. An anteroposterior field was added to achieve sufficient coverage, if adequate coverage with a single postero-anterior field alone could not be achieved.

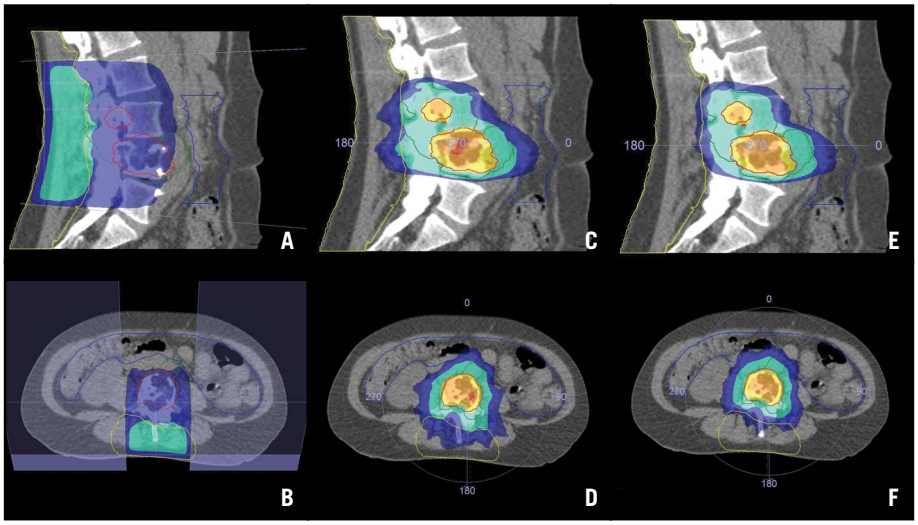
SBRT treatment plan

Volumetric arc therapy (VMAT) treatment plans were generated for all patients in the Monaco treatment planning system version 5.1. The plans were designed for an Elekta Synergy linear accelerator equipped with a 5 mm multi-leaf collimator (Elekta Inc., Crawley, UK). Two 10 MV photon beam posterior partial arcs with an average arc length of 115° were employed. The maximum number of control points per arc was set to 144, the minimum segment width to 0.5 cm, the collimator angle to 0°. The dose calculation grid resolution

was 2 x 2 x 2 mm. A simultaneous integrated boost strategy was adopted prescribing 18Gy to the PTV-boost and 8Gy to the PTV-elective. A single fraction of 18Gy to the spinal metastasis was prescribed, as studies have shown pain response rates in over 80% of the patients with a dose of 16Gy or higher *[14]*. Additionally, 18Gy single fraction SBRT has been shown to result in less vertebral compression fractures (VCFs) compared with a fraction of 24Gy (21% vs. 39% respectively) *[15, 16]*. The PTV-elective was prescribed 8Gy to treat any bony subclinical disease, which is in line with the dose administered when single fraction EBRT is used to treat spinal metastases in a palliative setting. Adequate coverage of the PTV was defined as at least 90% of the target volume receiving 90% of the prescribed dose. The dose constraints for the OAR were based on local institutional guidelines. The spinal cord tolerance (maximum 12 Gy) was the primary concern during treatment planning. If necessary, a lower dose to the GTV was accepted to meet the dose constraint of the spinal cord.

FIGURE 1.

Different radiotherapy treatment plans for one patient. A&B) Sagittal and transverse image of conventional EBRT treatment plan C&D) Sagittal and transverse image of SBRT treatment plan without sparing of surgical area E&F) Sagittal and transverse image of SBRT treatment plan with sparing of the surgical area. The yellow line denotes the surgical area. The dark blue area receives 8Gy, the turquoise area 9Gy, the yellow area 16.2Gy and the orange area 18Gy.



SBRT treatment plan with active dose sparing of the surgical area

The SBRT plan with sparing of the surgical area was created in the same way as described in the SBRT treatment plan above. In addition, the dose to the surgical area was minimized without compromising the constraints of the OAR and/or target volume coverage (Figure 1).

Statistical analysis

The non-parametric Wilcoxon signed rank test and Friedman test for paired data were used to compare the dosimetric differences between the plans generated for single fraction EBRT, single fraction SBRT and SBRT with dose sparing of the surgical site and. Statistical analyses were performed with RStudio (Version 0.99.903). Significance was defined as $p<0.05$.

RESULTS

The demographic and tumor characteristics of the included patients are displayed in Table 1. The majority of the tumors were located in the thoracolumbar junction or lower lumbar area, the median distance of the tumor to the skin was 4.1 cm (range 1.0 – 8.1 cm). The dosimetric parameters of the EBRT and SBRT treatment plans are summarized in Table 2. The median PTV boost dose for the SBRT plans with and without dose sparing was 17.9Gy (range 16.4Gy – 18.6Gy) and 17.5Gy (range 16.8Gy – 18.3Gy) respectively. The median percentage of the PTV boost receiving at least 16.2Gy was similar for the SBRT plan with and without active sparing of the surgical area (83%, range 67% - 93%; vs. 82%, range 70% - 96%). The median percentage of the PTV elective receiving at least 7.2Gy or higher was 62% (range 25% – 75%) for the EBRT plan. Median delivery time of the EBRT plan (88 seconds (sec), range 84 – 95) was significantly shorter compared to the SBRT plan with dose sparing (714sec, range 583 – 1046) and the SBRT plan without dose sparing (815sec, range 516 – 922) ($p<0.001$). There were no significant differences in the radiation dose to the OAR between the SBRT plan with and without sparing of the surgical area.

The median radiation dose in the surgical area was significantly lower in the SBRT treatment plan with active sparing of the surgical area (2.6Gy, range 1.6Gy – 5.3Gy) and the SBRT plan without sparing (3.7Gy, range 1.6Gy – 6.3Gy) compared to the EBRT plan (6.5Gy, range 3.5Gy – 9.1) ($p<0.001$). The volume of the surgical area receiving 7.2Gy or higher was 21cc (range 4 – 148cc) in the SBRT plan with active sparing and 46cc (range 16 – 138cc) in the SBRT plan without sparing and significantly lower than the 209cc (range 117 - 568cc) in the EBRT treatment plan ($p <0.001$).

TABLE 1. PATIENT AND TUMOR CHARACTERISTICS

Sex	Primary tumor	Location	PTVb volume in cc	PTVe volume in cc	Volume overlap with surgical area in cc	PTVb distance to skin (cm)	Surgical area volume in cc
M	Renal cell	L2	81	224	1.7	3.7	308
F	Breast	L3	99	181	0.0	8.1	888
M	Lung	T9	121	136	9.7	1	441
F	Breast	T10	64	222	11.3	3	243
M	Prostate	L4	107	144	0.0	5.3	252
F	Breast	L3	74	155	10.6	2.9	481
M	Prostate	T1	45	62	0.0	5.6	375
M	Renal cell	T6	42	79	0.0	5.4	567
F	Melanoma	L4	61	147	0.1	5.3	801
F	Breast	T11	29	48	0.0	4.8	300
F	Lung	T9	76	257	3.3	4	344
M	Lung	T10	130	356	30.0	2.7	360
F	Renal cell	L3	55	356	20.0	4.1	566

TABLE 2. DOSIMETRIC PARAMETERS

	EBRT		*SBRT*		*SBRT with sparing*		*P-value*
	Median	**Range**	**Median**	**Range**	**Median**	**Range**	
Target overage							
V16.2Gy PTVb (%)	-	-	82	70-96	83	67-93	0.72§
V7.2Gy PTVe (%)	62	25-75	100	99-100	100	97-100	<0.001#
Target dosimetry							
D2% in PTVb (Gy)	-	-	20.1	19.5 – 22.3	20.5	19.5 – 23.1	0.15§
D2% in PTVe (Gy)	-	-	19.7	19.1 – 22.1	20.3	19.1 – 22.7	0.2§
Dmean PTVb (Gy)	-	-	17.5	16.8 – 18.3	17.9	16.4 – 18.6	0.4§
Dmean PTVe (Gy)	-	-	15	11.5 – 16.9	14.7	11.6 – 16.7	0.27§
Conformity index* PTV_b	-	-	0.74	0.57 – 0.87	0.75	0.51 – 0.89	0.4§
OAR							
D1cc Spinal cord PRV (Gy)	-	-	9.5	0.3 – 9.6	9.2	0.2 – 9.6	0.23§
V10Gy Spinal cord (cc)	-	-	0.27	0.0 – 0.32	0.24	0.0 – 0.34	0.14§
D1cc Cauda equina (Gy)	-	-	12.75	11.8 – 12.8	12.7	11.9 – 13	1.0§
V13Gy Cauda equina (cc)	-	-	0.6	0.2 – 0.9	0.6	0.2 – 1.0	1.0§
D0.1cc Nerve roots (Gy)	-	-	17.3	15.5 – 17.4	17.4	14.2 – 17.5	0.93§
Dmean Bowel	-	-	1.9	0.5 – 3.3	1.9	0.4 – 3.2	1.0§
V11.2Gy Bowel (cc)	-	-	0	0.0 – 2.4	0.0	0.0 - 2.5	0.42§

TABLE 2. CONTINUED

	EBRT		*SBRT*		*SBRT with sparing*		*P-value*
	Median	**Range**	**Median**	**Range**	**Median**	**Range**	
OAR							
Dmean Oesophagus	-	-	4.9	2.8 – 8.1	4.3	2.9 – 9.1	0.62§
V11.9Gy Oesophagus (cc)	-	-	0.8	0.0 – 3.2	1.5	0.0 – 2.9	0.58§
Dmean Aorta	-	-	5.2	2.4 – 9.6	5.2	2.1 – 8.8	0.23§
V12Gy Aorta (cc)	-	-	3.8	1.5 – 4.8	3.0	1.0 – 4.8	0.13§
Surgical area							
Dmean	6.5	3.5 – 9.1	3.7	1.6 – 6.3	2.6	1.6 – 5.3	**<0.001#**
D2cc	9.8	8.9 – 10.2	11.9	8.9 – 18.3	9.9	7.4 – 17.6	**0.023#**
Volume							
V7.2Gy cc	209	117 - 568	46	16 – 138	21	4 – 148	**<0.001#**
Delivery time (s)	88	84 - 95	815	516 - 922	714	583 - 1046	**<0.001#**
Monitor units	880	844 - 948	6375	4026 - 7336	5524	4110 – 8036	**<0.001#**

§ Wilcoxon signed rank test, # Friedman test

DISCUSSION

This planning study compared single fraction EBRT (8Gy) to single fraction SBRT (18Gy) dose distributions, the latter technique with and without active sparing of the posterior surgical area, to explore the feasibility of reducing the radiation dose to the surgical area without compromising the dose to the spinal metastasis and the organs at risk. The use of SBRT compared to EBRT resulted, as expected, in a significant decrease in mean radiation dose to the surgical area. Active sparing of the surgical area with SBRT further decreased the mean dose to this area without compromising the planning quality.

The occurrence of wound complications is one of the primary concerns when radiotherapy and surgery are combined in a short time frame, regardless of the order of execution. Wound complication rates of up to 46% have been reported when EBRT and surgery were combined less than a week apart *[4]*. Considering the increased application of SBRT as adjuvant radiotherapy treatment Itshayek et al. *[5]* conducted a systematic review investigating the effect of timing of SBRT and surgical treatment on the risk of wound complications. The authors concluded that due the conformal dose distribution SBRT is likely associated with a lower risk of wound complications *[5]*. Yet, considering the sensitivity of the early phases of the wound healing process in tissues exposed to radiation, a time interval of at least 1 week between surgery and SBRT is still recommended [5]. Besides the time interval between surgery and radiotherapy other factors including incision size, radiation dose, number of fractions and patient related factors are important for the risk of wound complications *[17]*. Kumar et al. *[18]* investigated the effect of different radiation doses on wound healing in albino mice with surgical wounds. They demonstrated that a dose of 2Gy to the wound already resulted in delayed healing compared with a wound without exposure to radiation *[18]*. Wound healing time increased, although non-significantly, with increasing doses of radiation *[18]*. Other authors also demonstrated a dose-dependent relation between radiation exposure and impaired wound healing with higher radiation doses *[19]*. In addition, several studies have demonstrated that the mean dose rather than the maximum dose to the surgical area is associated with acute radiation toxicity *[20, 21]*. As the risk of wound complications is multifactorial no definitive radiation dose threshold could be determined for the occurrence wound complications. It is currently unknown whether the additional decrease in mean radiation dose with active sparing of the surgical area as observed in this planning study has a clinically significant impact on the risk of wound complications. The results of the different studies however emphasize the importance of decreasing the radiation dose to a surgical area to minimize impairment of the normal wound healing process.

The use of SBRT for the treatment of spinal metastases is increasing, however the number and quality of studies evaluating the effectiveness of SBRT in the post-

operative setting is still limited *[22, 23, 24]*. The first studies show high pain response rates and long-term control but the time interval between surgery and post-operative SBRT remains present *[8, 22, 23, 24]*. Post-operative SBRT is not only delayed by the waiting time for wound healing but also by SBRT treatment preparation requirements. The precise delivery of high radiation doses requires up-to-date and accurate MRI imaging, which is challenging in the postoperative setting for the patient and with the spinal implants causing imaging artifacts *[8, 25]*. Additional invasive imaging techniques such as a CT myelogram are therefore often needed to ensure accurate target delineation in treatment planning. Furthermore, the spinal implants cause backscattering of electrons increasing the dose in front of the material while limiting the dose behind the spinal implants *[8]*. Yazci et al. *[25]* demonstrated that the dose to the spinal cord increased up to 18.6% when spinal implants were present in the SBRT treatment field. Avoiding interaction between the radiation beam and the spinal implant to prevent high doses to the spinal cord is therefore important but also complicates post-operative SBRT planning *[25]*. Reversing the order of surgery and SBRT may overcome these technical challenges. The patients included in this study were treated in a phase I/II study investigating the safety of SBRT followed by surgical stabilization within 24 hours for the treatment of unstable spinal metastases [Versteeg 2017]. A planning strategy with active sparing of the surgical area was used for the administered SBRT treatment. One of the additional inclusion criteria for the phase I/II study was the absence of a history of surgery and/or radiotherapy to the treatment site as these are known risk factors for wound complications. None of the patients experienced disturbed wound healing. Reversing the order of surgery and radiotherapy, and minimizing the radiation dose to the surgical area with SBRT enabled elimination of the traditional required time interval between surgery and radiotherapy.

We acknowledge some limitations of the present study. First, the radiotherapy treatment plans in this study were created by an experienced spine radiotherapy planner potentially limiting the generalizability of the results. Radiotherapy planning is operator dependent and many acceptable-but-different radiotherapy plans can be created for the same patient. Second, to be able to maintain an adequate dose coverage to the metastasis, the radiation dose that is decreased in the surgical area has to be distributed to other areas of the body potentially compromising other OAR. However, in this study the radiation dose to the surgical area could be decreased for all patients without compromising the OAR dose.

Single fraction SBRT with single fraction EBRT was compared instead of multifraction (e.g. 10x 3Gy) EBRT as previous studies have shown no difference in pain response between single fraction or multifraction EBRT *[26]*. Single fraction EBRT has been associated with higher rates of retreatment compared to multifraction EBRT although it has been speculated that this may be attributed to selection bias. Radiation oncologists may

be more reluctant to retreat patients with a history of multifraction EBRT considering the total dose to the spinal cord. Furthermore, comparing single fraction SBRT to multifraction EBRT requires complex calculations for a genuine comparison of the dosimetrics. It can be expected that a multifraction EBRT regimen results in even higher mean total radiation doses to the surgical area when compared to a single fraction EBRT technique.

In conclusion, compared to EBRT, use of SBRT significantly decreases the dose to the posterior surgical area thereby likely decreasing the risk of impaired wound healing after surgery. Active sparing of the surgical area further decreases the dose without significantly compromising the dose to the spinal metastasis and organs at risk. Considering the dose-dependent relationship between radiation exposure and impaired wound healing, it may be recommended to actively spare the surgical area in an SBRT plan for patients who recently underwent surgery or are scheduled for surgery as it might be beneficial in reducing the incidence of wound complications. Using SBRT, instead of EBRT, in combination with surgery may enable innovation of treatment strategies.

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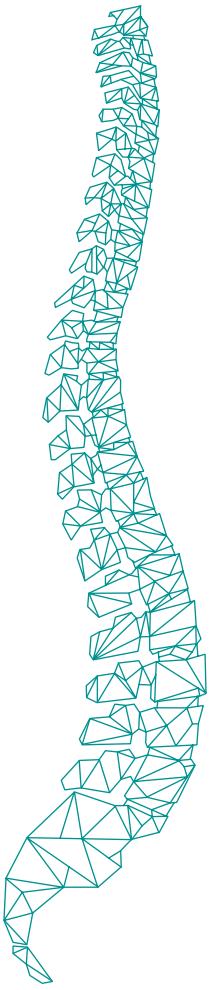

CHAPTER 10

Stereotactic radiotherapy followed by surgical stabilization within 24hours for unstable spinal metastases; a stage I/IIa study according to the IDEAL framework

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ABSTRACT

Background

Routine treatment for unstable spinal metastases consists of surgical stabilization followed by external beam radiotherapy (EBRT) or stereotactic body radiotherapy (SBRT) after a minimum of 1-2 weeks to allow for initial wound healing. Although routine treatment, there are several downsides. First, radiotherapy induced pain relief is delayed by the time interval required for wound healing. Second, EBRT often requires multiple hospital visits and only 60% of the patients experience pain relief. Third, spinal implants cause imaging artefacts hindering SBRT treatment planning and delivery. Reversing the order of surgery and radiotherapy, with dose sparing of the surgical area by SBRT, could overcome these disadvantages and by eliminating the interval between the two treatments, recovery and palliation may occur earlier.

Design

The safety of SBRT followed by surgical stabilization within 24-hours for the treatment of unstable spinal metastases was investigated. Safety was evaluated using the Common-Toxicity-Criteria-Adverse-Events-4.0, with the occurrence of wound complications within 90-days being the primary concern.

Results

Between June-2015 and January-2017, 13 patients underwent SBRT followed by surgical stabilization for unstable spinal metastases. The median time between SBRT and surgery was 17-hours (IQR 5–19). None of the patients experienced wound complications. Improvements in pain and quality of life were observed over time for all patients.

Conclusion

SBRT followed by surgical stabilization within 24-hours for the treatment of unstable spinal metastases is safe. Palliation may be experienced earlier and with both treatments being performed in one hospital admission the treatment burden decreases.

INTRODUCTION

More than half of the newly diagnosed cancer patients suffer from a tumor that frequently metastasizes to the bones *[1]*, with the spine being the most frequent site *[2]*. In addition to pain, spinal metastases can cause mechanical instability and/or spinal cord compression. The combination of surgery and radiotherapy is increasingly being used in the management of patients with symptomatic spinal metastases. Surgery is used for stabilization of the spinal column and/or to decompress neurological structures while post-operative radiotherapy aims for additional pain relief and local tumor control. This approach has shown to be effective to reduce pain and maintain or improve functional status and quality of life *[3, 4]*.

While conventional external beam radiation therapy (EBRT) has been the mainstay of post-operative adjuvant radiotherapy, there are several concerns regarding its use in patients with spinal metastases. Precise targeting is limited with conventional EBRT and, as a consequence, the tolerance of the spinal cord limits the radiation dose to the vertebral body with pain relief achieved in only 60% of patients and local tumor control in only 30% of the patients after 1 year *[5, 6, 7]*. Furthermore, to reach adequate radiation doses to the metastasis, hotspots of >120% of the prescribed dose are common in the subcutaneous tissues, which impairs wound healing [8]. As such, a minimum time interval of 1-2 weeks between surgery and EBRT is considered necessary but thereby also delays radiotherapy-induced pain relief *[8]*.

Stereotactic body radiotherapy (SBRT) allows for the delivery of ablative radiation doses while actively limiting the dose to the spinal cord and other areas at risk due to steep dose gradients *[9]*. SBRT has shown to achieve durable pain relief, as well as high long-term local control rates independent of tumor histology and is subsequently increasingly being used to treat patients with spinal metastases *[10, 11]*. The use of SBRT in the post-operative setting is, however, technically challenging. Precise planning and delivery of ablative radiation doses rely on accurate imaging including magnetic resonance imaging (MRI) and computed tomography (CT) examinations *[9]*. Post-operatively, spinal implants cause imaging artefacts and prevent accurate delineation of the neural structures [9]. Furthermore, radiation backscattering caused by spinal implants limits the biologically effective dose behind the implants, resulting in changed, and difficult to correct for, dosimetrics *[12, 13]*.

Reversing the order of surgery and SBRT could overcome the abovementioned technical challenges. Moreover, the ability with SBRT to actively limit the radiation dose to the posterior surgical area may eliminate the need for a time interval between the two treatment modalities. When both treatments would be administered within one hospital admission, SBRT induced pain relief could be experienced earlier, the treatment burden

decreases and the start of adjuvant systemic therapies may be advanced.
Although both surgery and SBRT have proven to be safe and effective for the treatment of spinal metastases [14], the safety and feasibility of executing both modalities within a 24-hour timeframe is yet unknown and was therefore investigated in this study.

METHODS

Study design & patients

A non-randomised, single arm, single center, IDEAL stage I/IIa (see below) intervention study including patients with spinal metastases was conducted at the University Medical Center Utrecht, The Netherlands. Patients were eligible for inclusion if they were aged 18 years or older, had histological proof of malignancy, had symptomatic unstable spinal metastases in the thoracic or lumbar spine requiring surgery (based on clinical and imaging features, including the Spinal Instability Neoplastic Score (SINS) *[15]*), had a Karnofsky performance status of 50% or higher, and provided written informed consent. Patients were not eligible for inclusion if they had a diagnosis of a primary spinal bone tumour, had a history of prior radiation or surgery for the target spinal metastasis, required surgical stabilization of more than five adjacent spinal levels, had radiographic or symptomatic spinal cord compression (Bilsky 2 and 3 *[16]*), presented with rapidly deteriorating neurological deficits defined as the decline of one or more ASIA scale within 24 hours, or had a life expectancy of less than three months. An orthopaedic surgeon and radiation oncologist together evaluated the eligibility of all patients. The local ethics board approved the study protocol.

This study was designed and conducted according to the IDEAL recommendations for the evaluation of complex surgical interventions *[17]*. In stage I, the new treatment was used for the first time in three patients with a minimum time interval of 6 weeks between each patient to allow for identification of early major safety and/or feasibility issues. In stage IIa, 10 patients were enrolled to further evaluate the safety/feasibility of the new treatment strategy and allow for technical modifications if necessary.

Study procedures

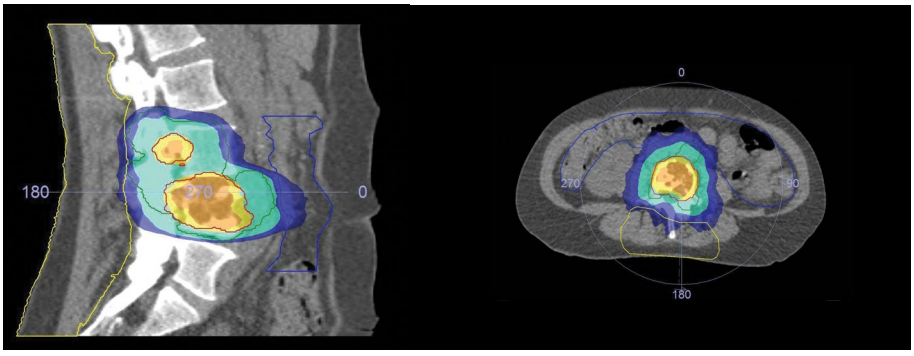
After obtaining informed consent patients underwent a planning CT (Philips Medical Systems, Cleveland, OH) and 1.5 Tesla MRI scan (Ingenia; Philips Medical System, Best, The Netherlands) in SBRT treatment position. A single dose of 18Gy was prescribed to the macroscopic volume of the spinal metastasis. The bony compartment harbouring the spinal metastasis was prescribed 8Gy to treat any subclinical disease. The macroscopic tumour volume, surrounding bony compartment, the organs at risk and the posterior surgical area were delineated using MRI data. The posterior surgical area was delineated cranially and

caudally by the lower, respectively the upper endplate of the vertebral body adjacent to the upper and lower level of pedicle screw instrumentation; anteriorly by the contour of the vertebral body, laterally by the tips of the transverse processes, and posteriorly by the outermost layer of the skin **(Figure 1)**. The dose to the surgical area was actively limited during planning using a rotating beam technique. Dose constraints for the spinal cord and other organs at risk were of primary concern while preparing the SBRT treatment plan and violations of these constraints were not accepted. A detailed description of the radiotherapy planning is described elsewhere [AL Versteeg 2017, manuscript in preparation]. Administration of dexamethasone was at the discretion of the treating radiation oncologist. SBRT treatment was delivered on a priority base within 24 hours prior to the planned surgical procedure.

The surgical technique, either a percutaneous (Longitude, Medtronic) or conventional open (Universal Spine System, Depuy Synthes) approach, was determined by the surgeon depending on the need for decompression of neurological structures and the spinal level(s) affected. If indicated, vertebral body stenting with poly methyl methacrylate was used to reinforce the anterior spinal column. Intraoperative and post-operative care was performed according to the local standard of care.

FIGURE 1.

Planning CT showing a L4 metastases. The surgical area is depicted with the yellow lines. The dark blue area receives 8Gy, the turquoise area 9Gy, the yellow area 16.2Gy and the orange area 18Gy.



Outcomes

The primary outcome of this study was safety of the combined procedure (SBRT and surgery with 24 hours) within 90 days following treatment, with the occurrence of wound complications being the primary concern. Adverse events were evaluated and classified according to the Common Toxicity Criteria Adverse Events 4.0 (CT-CAE 4.0) during hospital stay on a daily basis by a researcher and during follow-up in the outpatient clinic. The secondary outcomes were evaluated at baseline and 4, 8, 12 weeks post-treatment and included pain response measured with the Brief Pain Inventory *[20]* according to the International Bone Metastases Consensus Endpoints for Clinical Trials [18], length of hospital stay (days), neurological status as defined by the ASIA scale [19] and quality of life using the EQ-5D, the EORTC QLQ-C15-PAL, the EORTC QLQ-BM22 and the Spine Oncology Study Group Outcomes Questionnaire (SOSGOQ) *[21]*. Patients were contacted by a researcher in case the questionnaires were not returned in time. Patients returned to routine clinical follow-up every six months after completion of the study.

Statistical analysis

A sample size of 13 patients was predefined based on the IDEAL recommendations for stage I and IIa. An independent data safety monitoring board (DSMB) consisting of content experts was established before the start of the study. Results were presented to the DSMB after the third and eight patients, stopping criteria were predefined based on the occurrence of wound complications. Descriptive statistics were used to describe demographic and treatment data, using RStudio (Version 0.99.903). This study was registered in the ClinicalTrials.Gov database (NCT02622841).

RESULTS

Fifteen patients with symptomatic unstable spinal metastases were recruited between June 2015 and January 2017. Two patients were excluded before SBRT treatment due to development of mild neurological deficits at the time of hospital admission and inconclusive preoperative pathology. Thirteen patients were treated according to the study protocol and underwent SBRT followed by surgical stabilization. The most common primary tumor was breast carcinoma followed by lung carcinoma and renal cell carcinoma **(Table 1)**. For eight patients, painful spinal metastases were the first symptom of their primary tumor. At the time of surgery two patients had evidence of lymph node metastases and three patients had evidence of visceral and lymph node metastases.

All patients underwent surgery within 24 hours after SBRT; the median time between SBRT and surgery was 17 hours (IQR 5 – 19 hours) with four patients receiving both treatments on the same day. All patients underwent single fraction SBRT with a mean

TABLE 1. BASELINE CHARACTERISTICS OF TREATED PATIENTS

Sex	Age at time of surgery	Primary tumor	Affected level	Karnofsky	SINS	Pain score	ASIA
M	79	Renal cell	L2	60	9	4.0	E
F	44	Breast	L3	60	13	5.4	E
M	64	Lung	T9	90	9	3.4	E
F	57	Breast	T10	70	9	2.8	E
M	68	Prostate	L4	80	11	5.3	D
F	55	Breast	L3	80	9	4.6	E
M	58	Prostate	T1	60	12	4.7	E
M	63	Renal cell	T6	90	10	1.6	E
F	64	Melanoma	L4	90	7	5.7	E
F	44	Breast	T11	60	11	9.1	E
F	72	Lung	T9	70	10	1.2	E
M	41	Lung	T10	80	8	4.7	E
F	82	Renal cell	L3	70	10	5.3	E

dose to the target metastasis of 17.7Gy (range 16.4 - 18.6Gy) and a mean radiation dose of 2.9Gy (range 1.6 – 5.3Gy) to the surgical area (Table 2). Eleven patients underwent percutaneous pedicle screw fixation and two patients underwent an open procedure including decompression of neurological elements. The median operation time (incision until wound closure) was 68 minutes (IQR 60 – 90 minutes) with a median blood loss of 50 ml (range 50 – 300). All patients were able to ambulate on the first day after surgery. The median length of hospital stay was five days (IQR 4 – 6 days) measured from the day of SBRT until discharge.

Adverse events

In the interval between SBRT and surgery we observed two grade 1 adverse events; nausea and radiation dermatitis (erythema). Cement leakage outside the vertebral body was observed intra-operatively with fluoroscopy in three patients. In one patient, this caused grade 3 radiculitis due to compression of the exiting left L3 nerve root requiring re-operation to decompress the root. The re-operation was performed 2 weeks after the initial treatment and resolved the complaints. Postoperatively, we observed the following grade 1-2 adverse events; nausea (1 event), diarrhoea (2 events), constipation (2 events), transient urinary retention unrelated to cauda equina/spinal cord function (1 event),

transient paresthesia of the leg (1 event), anemia not requiring transfusion (1 event) and transient radiculitis (1 event). One grade 3 syncope occurred post-operatively. None of the patients experienced disturbed wound healing or wound infection.

TABLE 2. SBRT DOSIMETRICS

Mean dose to macroscopic tumour volume	17.7 Gy (range 16.4 – 18.6Gy)
Mean coverage macroscopic tumour volume	82% (range 67 – 93.4%)
Mean coverage of vertebral body	99% (range 97 – 100%)
Mean D1cc of the spinal cord §	7.8Gy (range 0.2 – 9.6Gy)
Mean D1cc of the cauda§	12.5Gy (range 11.9 – 13Gy)
Mean dose to the surgical area	2.9Gy (range 1 – 5.3Gy)
Mean volume of surgical area (cc)	455 (range 243 – 888cc)

* % of GTV that received 16.2Gy or higher, †% of CTV that received 7.2Gy or higher
§ maximum dose in Gy to 1cc of the volume

Clinical outcomes

At the time of study completion, the median clinical follow-up time was 13 months (IQR 10 – 17 months), one patient died due to systemic disease progression 14 months after the procedure. The mean BPI severity score at baseline was 3.8 (range 1 - 7) and decreased to 2.7 (range 0 - 5) at 4 weeks post-treatment, with all but one patient reporting a decrease in pain. All patients experienced a partial pain response during follow-up according to the consensus criteria. At 4 weeks post-treatment substantial improvements were reported in all domains of the SOSGOQ, BM-22, QLQ-C15 and the EQ-5D with further improvement over time (Table 3).

Thirteen months post-operatively one patient presented with neurological deficit based on recurrence of disease in the cranial level adjacent to the index level requiring emergency surgical decompression.

TABLE 3. QUALITY OF LIFE AND PAIN SCORES OVER TIME

	Baseline (95%CI)	4 weeks (95%CI)	8 weeks (95%CI)	12 weeks (95%CI)
BPI				
Intensity*	4.5 (3.2 – 5.7)	3.3 (2.0 – 4.7)	2.0 (0.8 – 3.2)	2.6 (1 – 4.2)
Severity*	3.8 (2.7 – 4.8)	2.8 (1.8 – 3.8)	2.4 (1.2 – 3.5)	2.9 (1.4 – 4.3)
BM22				
Painful Site*	29.2 (17.0 – 41.4)	20.0 (13.8 – 26.2)	16.4 (10.6 – 22.5)	21.1 (11.2 – 30.9)
Painful Characteristics*	38.9 (24.9 – 52.8)	24.8 (14.1 – 35.45)	24.8 (13.1 – 35.4)	24.2 (13.8 – 34.7)
Social aspects	54.6 (41.4 – 68.1)	60.7 (47.3 – 74.0)	66.7 (56.8 – 76.5)	69.2 (57.9 – 80.4)
Functional Interference	56.4 (38.8 – 74.0)	71.9 (55.1 – 88.6)	76.4 (67.6 – 85.2)	75.0 (63.0 – 87.0)
QLQ-C15				
Pain*	56.9 (38.6 – 75.2)	38.5 (27.3 – 49.6)	29.2 (16.3 – 42.0)	22.2 (10.0 – 34.4)
Physical	45.6 (22.9 – 68.1)	66.7 (52.9 – 80.4)	76.4 (65.3 – 87.5)	78.9 (68.2 – 89.5)
Global	44.9 (25.9 – 63.9)	69.2 (60.2 – 78.3)	71.8 (61.4 – 82.2)	68.1 (55.7 – 80.4)
SOSGOQ				
Pain	48.1 (34.4 – 58.7)	64.2 (53.8 – 74.6)	69.2 (58.5 – 80.0)	77.1 (63.9 – 90.3)
Physical function	51.3 (31.6 – 70.9)	60.8 (51.3 – 70.2)	65.1 (56.0 – 74.1)	71.2 (59.5 – 82.8)
Social function	53.5 (46.2 – 60.7)	50.0 (40.4 – 59.6)	50.1 (41.1 – 60.2)	52.1 (43.9 – 60.3)
Mental health	65.4 (51.2 – 78.9)	70.2 (55.2 – 85.2)	75.0 (61.9 – 88.0)	77.1 (64.5 – 89.7)
EQ-5D	0.46 (0.25 – 0.65)	0.69 (0.6 – 0.8)	0.74 (0.64 – 0.82)	0.77 (0.68 – 86)

*decrease in score corresponds with improvement of symptoms

DISCUSSION

In this first-in-man study we demonstrated the safety and feasibility of single fraction SBRT, with active dose-limiting of the surgical area, followed by surgical stabilization within 24 hours for the treatment of symptomatic unstable spinal metastases. Substantial improvements in pain and quality of life scores were observed for all patients over time. Minimal clinically important difference (MCID) values have previously been reported for the BM-22 and the QLQ-15 *[22]*. The biggest improvements in quality of life were observed in the first 4 weeks following treatment with further improvement at 8 and 12 weeks post-treatment, improvements in all BM-22 domains and in the pain, physical and global quality of life domain of the QLQ-15 were greater than or equal to the previously reported MCID's.

This new treatment strategy has several advantages. First, with both procedures being performed within one hospital admission the treatment burden for the patient is substantially decreased. Second, by eliminating the time interval between treatments the radiation induced pain relief is experienced earlier as Ryu et al. demonstrated a median time to pain response after SBRT treatment of 14 days with a response achieved as early as 24 hours after treatment *[23]*. Moreover, complete response rates of up to 39% at 4 weeks post-SBRT treatment have been reported *[23, 24]*. Third, pre-operative SBRT treatment planning is less challenging compared to post-operative treatment planning and delivery with its associated imaging artefacts and radiation scattering due to spinal implants. Furthermore, obtaining accurate imaging is physically demanding for the patient in the first days following surgery. Fourth, adjuvant therapies may be initiated earlier as these are often delayed until irradiation and initial wound healing is completed. Lastly, another potential advantage of pre-operative SBRT is the potential to decrease the spread of vital tumor cells due to surgical manipulation. Experimental animal studies have shown that single high doses of radiation (15-20Gy), as achieved with SBRT, result in tissue damage as early as 1-6 hours after irradiation *[25, 26]*. The vitality of tumor cells that are spilled into the bloodstream and neighbouring tissues by surgical manipulation *[27]* and the subsequent potential acceleration of tumour spread and progression of disease, may therefore be reduced with reversing the order of surgery and SBRT.

We observed one serious adverse event, which was a grade 3 radiculitis requiring re-intervention. However, the DSMB regarded this as an isolated surgical incident secondary to cement extravasation rather than the result of combining SBRT with surgery. One patient developed neurological deficits 13 months post-SBRT based on recurrence of disease in the adjacent vertebra. This was in line with the study of Koyfman et al reporting 12.5% recurrence in the adjacent level at a median time of 7.7 months after SBRT *[28]*. Other adverse events were consistent with known reported adverse events associated with surgery and SBRT *[9, 29]*.

One of the primary concerns of combining surgery and radiotherapy within a short timeframe is the occurrence of wound complications, which were not observed in any of our patients. The first phase of wound healing is particularly vulnerable for radiation exposure and with the use of conventional EBRT, the dose to the skin and underlying soft tissues is high *[25, 26]*. Disturbed wound healing rates up to 46% have been reported when surgery and EBRT were performed within one week and a minimum time interval between surgery and EBRT of 1-2 weeks was therefore recommended *[3, 30]*. The use of SBRT likely decreases the risk of wound complications as the conformal dose distribution allows for active sparing of healthy tissues overlying the surgical field. A recent systematic review investigated the effect of the timing of SBRT on the occurrence of wound complications [5]. The evidence is limited to small observational studies and none of the studies considered wound complications as primary outcome *[5]*. No time intervals of less than a week between surgery and SBRT were reported and considering the normal wound healing process an interval of at least 1 week was recommended *[5]*.

Despite the conformal dose distribution, a distance between the spinal cord and tumor is necessary to deliver an ablative radiation dose while limiting the dose to the cord. The concept of separation surgery was therefore introduced *[31]*. Tumor resection is limited to decompression of the spinal cord to allow for the use of post-operative SBRT to achieve local tumour control. Laufer et al. demonstrated in a series of 186 patients treated with separation surgery a 1-year local control rate of 90% to 96% depending on the SBRT fractionation schedule *[31]*. Although these results are promising, it should be noted that SBRT was administered 2-4 weeks after surgery and an additional CT myelogram was required for accurate treatment planning increasing the treatment burden for the patient. The majority of 186 patients presented with cord compression (Bilsky 2 & 3 *[16]*) warranting separation of the tumor and the cord, but 25% of the patients presented with limited epidural disease, similar to our patients, and potentially could have been treated with the treatment strategy investigated in the current study.

We acknowledge the possible limitations of this study. Inherent to the study design, only a few and selected patients were included and subsequently the study is underpowered to detect any potential adverse advents with a low incidence. However, the main safety concern for the combination of radiotherapy and surgery within a short time frame is disturbed wound healing with substantial wound complication rates previously reported *[3, 30]*. Furthermore, only patients without radiological or symptomatic spinal cord compression (Bilsky 1a-1c) were included as a distance between the spinal cord and the tumor is necessary for the safe delivery of an ablative dose and to avoid emergent treatment planning in this safety study. Lastly, although only one patient demonstrated a local recurrence 13 months after treatment, the true imaging-based local control rate for all

patients is unknown. Patients were followed clinically, including routine follow-up imaging of the spine, but without specific imaging for the early detection of local recurrence.
In conclusion, this study demonstrated the safety and feasibility of SBRT, with active sparing of the surgical area, followed by surgical stabilization within 24 hours for the treatment of symptomatic unstable spinal metastases with none of the patients demonstrating disturbed wound healing. Combining the two treatments within 24 hours decreases the treatment burden for the patient, as no return visits for radiotherapy are necessary, and may result in earlier and improved pain response and local control rates compared to the current standard of care of surgery followed by EBRT. An IDEAL stage IIb study is currently planned to evaluate the effectiveness of the new treatment strategy and to obtain additional data to potentially change the standard of care for patients with symptomatic unstable spinal metastases.

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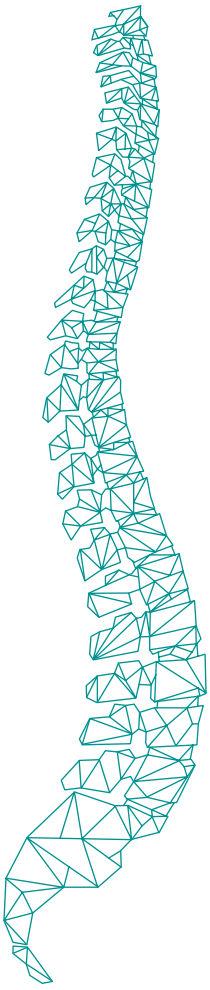

CHAPTER 11

Summary and discussion

SUMMARY AND DISCUSSION

Enhancements in diagnostic methods and systemic treatment options have improved the life expectancy of cancer patients in the past decades *[1]*. With the improved survival, patients have the time to develop symptomatic metastatic disease, including spinal metastases *[2]*. With these patients living longer it is imperative to maintain or improve their quality of life for their remaining time. The management of patients with spinal metastases is often complex with treatment selection depending on many factors. Together with advances in surgical and radiotherapy techniques, treatment strategies for spinal metastases have dramatically evolved over the last decades. Surgery and radiotherapy are increasingly being used to complement each other to improve outcomes for patients *[3, 4, 5]*. Although effective, combining surgery and radiotherapy is time consuming, as a time interval between surgery and radiotherapy is necessary for wound healing *[6, 7]*. Considering the palliative intent of the procedures, it would be desirable to further optimize patient selection but also to decrease the treatment burden while maintaining or even improving treatment outcomes. The research presented in this thesis has filled some of the knowledge gaps regarding patient selection, treatment outcomes and reduction of treatment burden. The implications of the research in this thesis for patient selection, treatment strategies and treatment evaluation will be discussed below.

PATIENT SELECTION

Accurate patient selection for radiotherapy or surgical treatment for symptomatic metastatic spinal disease is critical considering the consequences of inadequate management. For example, patients with spinal instability may develop irreversible neurological deficits when treated non-surgically. Treatment decision making for patients with spinal metastases is complex and challenging. In 2006, Bilsky et al. introduced the NOMS framework to provide a systematic approach for treatment decision making for patients with spinal metastases *[8]*. NOMS is an acronym that represents the four fundamental pillars of treatment decision making in patients with spinal metastases; Neurology, Oncology, Mechanical instability and Systemic disease. Consistent use of the framework enhances the systematic evaluation of patients and improves communication between treating physicians. The decision for surgical or radiotherapy treatment, alone or in combination, or other medical treatment is based on selecting the treatment modality that best serves the patient's needs by preserving or restoring neurological function, performance status and alleviation of pain to maintain or improve quality of life *[8]*.

The NOMS neurology and oncology factors are considered together and include the clinical and radiographic degree of spinal cord compression, and the sensitivity of the tumor to radiation or systemic therapy *[8]*. The systemic disease pillar considers the

overall clinical picture of the patient including the evaluation of systemic disease status, performance status and life expectancy *[8]*. Generally, a life expectancy of at least three months is considered necessary for a patient to be considered for surgery. An impaired performance status has been associated with short-term survival in several studies *[9, 10]*. Yet, rating performance status is challenging in patients with spinal metastases. A patient with mechanical instability may be bedridden due to severe mechanical pain but otherwise be in good clinical condition. An impaired performance status based on functional impairment should therefore be distinguished from an overall impaired physical status.
Mechanical spinal instability is an indication for surgical intervention, regardless of the degree of metastatic epidural spinal cord compression (MESCC). Historically, evaluation of mechanical instability was mainly based on the presence of mechanical pain, which was defined as movement related pain with specific symptoms depending on the involved spinal level [8]. The introduction of the NOMS was a big step forward in the systematic and algorithmic decision-making approach for patients with spinal metastases, but the mechanical instability pillar remained ill defined.

Outside the NOMS framework, several authors used the presence of movement related pain with relief by recumbence as the key-identifying symptom of spinal instability. In addition, several radiographic criteria and scoring systems for spinal instability were proposed. However, none of these radiographic criteria were comprehensive. Implementation of the scoring systems in clinical practice failed due to the absence of thresholds to categorize patients as high risk of spinal instability as well as the lack of validation **(Chapter 2)** *[11]*.

In response to the lack of a standardized scoring system for spinal instability due to spinal metastatic disease, the Spine Oncology Study Group used a Delphi method to develop a classification system for neoplastic related spinal instability *[12]*. The Spinal Instability Neoplastic Score (SINS) was introduced in 2010 as a tool to evaluate the degree of spinal instability, and to improve communication and referral between medical specialists taking care of patients with spinal metastases *[12]*. In prospective studies, the SINS demonstrated to be a reliable tool for the assessment of spinal instability by spine surgeons, radiation oncologists and radiologists *[13, 14, 15]*.

With the SINS a need in the evaluation of patients with symptomatic spinal metastases is met, especially for non-spine experts. Early identification of (impending) spinal instability and timely referral for surgical consultation can prevent unnecessary neurological and functional deterioration. The aim of the study presented in **Chapter 3** was to determine the effect of introducing the SINS in routine clinical practice on referral of patients with spinal metastases. The SINS scores of patients who underwent surgery and/or

radiotherapy for spinal metastases before and after the introduction of the SINS in clinical practice were compared. As expected, the mean SINS scores of surgically treated patients were significantly higher compared to the SINS scores of patients who were treated with radiotherapy alone. Interestingly, the SINS scores in both treatment groups decreased significantly after the introduction of the SINS in daily practice. This decrease in SINS score was regarded as the reverse of the "Will-Rogers" phenomenon, which describes the result of migration of one group to another group resulting in an increased average in both groups, or decrease in case of the reversed phenomenon *[16]*. The introduction of the SINS in daily practice has likely increased the awareness of spinal instability and reduced the threshold for referring patients with evidence of (potential) spinal instability for surgical consultation. The timely referral of patients resulted in a decrease of mean SINS score in the surgery group as surgical intervention was likely performed before spinal instability progressed to overt spinal instability with high risks of neurological compromise. Subsequent, the average SINS score in the radiotherapy cohort decreased due to the referral of these patients with higher SINS scores for surgical consultation. It remains however unclear, if the earlier referral of patients has also resulted in improved outcomes for patients.

Several authors have suggested that mechanical pain, as opposed to biological pain, does not respond well to radiotherapy *[8, 17, 18]*. Although the SINS was designed as a referral tool, several authors have attempted to use the SINS as a surrogate measure of spinal instability, to investigate the relation between spinal instability and radiotherapy outcomes. In a retrospective study, our group demonstrated an association between an increasing SINS score and increasing odds of radiotherapy failure after conventional external beam radiotherapy *[17]*. Radiotherapy failure was defined as re-irradiation *[17]*. In **Chapter 4** we prospectively assessed the association between spinal instability, according to SINS, and the response to palliative radiotherapy for spinal metastases. An international multicenter study including neurologically intact patients with symptomatic spinal metastases who underwent conventional external beam radiotherapy (EBRT) was conducted. Response to radiotherapy was measured according to the international consensus criteria based on changes in Numeric Rating Scale (NRS) pain scores and analgesic use. SINS was independently and positively associated with a complete pain response to EBRT. It is important to acknowledge that the majority of the treated patients were diagnosed with widespread metastatic disease, which likely contributed to the NRS pain score and required analgesic use. The consensus guidelines recommend evaluating a site-specific response, however rating site-specific pain levels is difficult *[19]*. A response to radiotherapy might therefore be overshadowed by revealing pain at other sites *[20]*. This distorting effect is not only problematic in research but also in daily clinical practice, when one aims to determine the effect of treatment. The number of patients with a high SINS score (13 or higher), which is hypothesized to have the highest risk of non-response

to radiotherapy, was low. This is likely the (welcome) result of implementation of the SINS score in our daily clinical practice, which resulted in the referral and subsequent surgical treatment of patients with high SINS scores. Although this low number of patients with high SINS scores limited the statistical power of the study, this will be difficult to overcome in future studies, as it would be unethical to treat patients with overt spinal instability with radiotherapy only if surgery is warranted.

Besides spinal instability, a dose-effect relation may also play a role in the risk of response and non-response to radiotherapy *[20, 21]*. The radiation dose delivered to the spinal metastasis with EBRT is non-conformal and the maximum dose is limited by the tolerance of the spinal cord and surrounding organs at risk. Stereotactic body radiotherapy (SBRT) allows for a conformal dose delivery and the dose to the metastatic lesion can be increased to ablative levels whereas radiation to the spinal cord can be largely avoided.

In a multicenter study, including 410 spinal segments, Sahgal et al. evaluated the prognostic value of the individual SINS parameters for the occurrence of vertebral compression fracture (VCF) after SBRT *[22]*. An independent association between a lytic lesion, spinal malalignment, baseline vertebral body collapse, radiation dose and the progression or de novo occurrence of VCF was demonstrated *[22]*. The presence of mechanical pain was not associated with the occurrence of VCF; the authors noted that this could be explained by referral of patients with an overt history of mechanical pain for surgical consultation *[22]*. Similar results were found in a single center study by Lee et al. *[23]*. The results of both studies underscore the importance of the assessment of spinal instability with the SINS. However, these studies focussed on radiographic outcomes rather than patient reported outcomes on pain and health related quality of life (HRQOL). A future study including the evaluation of the association between SINS and patient reported outcomes in patients who undergo radiotherapy, either EBRT or SBRT, may improve insight in the role of spinal instability and the dose effect relation in response to radiotherapy.

It should be emphasized that SINS was not developed as a prognostic tool but as a referral tool, which is reflected by the different parameters of the SINS. Both, factors that represent an increased risk of spinal instability and factors that indicate current spinal instability are included in the SINS. Location of the lesion, bone lesion quality and the degree of involvement of the posterolateral elements represent SINS factors that express the risk of spinal instability *[14]*. The presence of mechanical pain, a higher degree of vertebral body collapse and spinal misalignment reflect SINS factors that indicate spinal instability *[14]*. The use of the total SINS score in daily practice should therefore be used to improve communication and referral between medical specialists rather than to predict treatment

results. Moreover, as mentioned above, spinal instability is only one of many factors that should be considered in the treatment decision-making process for patients with spinal metastases

TREATMENT OUTCOMES AND TREATMENT EVALUATION

Treatment of patients with symptomatic spinal metastases has changed over the last decades. Historically, patients were either treated with extensive tumor resection and fixation, or with isolated decompression of the neurological structures (e.g. spinal cord, nerve roots) [18]. Yet, several studies comparing surgical decompression followed by EBRT for the treatment of metastatic epidural spinal cord compression (MESCC) demonstrated no difference in the proportion of patients who regained or sustained ambulatory function after treatment *[24, 25, 26]*. The results of these studies resulted in treatment strategies shifting away from surgical intervention towards radiotherapy only *[18]*. In 2005, Patchell et al. published a landmark paper demonstrating the superiority of surgery with post-operative radiotherapy versus radiotherapy alone for the treatment of MESCC *[27]*. The combination of surgical stabilization and/or decompression with post-operative radiotherapy was associated with improved neurological outcomes and ambulatory status *[27]*. This paper in combination with advances in surgical techniques and instrumentation resulted in a second treatment paradigm shift back towards surgical interventions for patients with spinal metastases *[3]*. Today, patients with MESCC, spinal instability and/or progression of (neurological) symptoms after recent radiotherapy are considered for surgical intervention *[4]*. Over the past two decades, numerous studies have reported outcomes of different surgical procedures, including stabilization and/or decompression *[28, 29, 30]*. Historically, studies focussed on physician reported outcomes *[29, 30]*, while recently a combination of physician and patient reported outcomes are considered to be important *[28]*.

In order to accurately assess patient reported HRQOL, it is imperative to use outcome instruments that are specific and sensitive to changes within the patient population and/or condition that is evaluated. Historically, HRQOL in patients with spinal metastases who underwent surgery was most commonly evaluated with the generic short-form 36 (SF-36) and the EuroQol-5-dimensions (EQ-5D) outcome instruments *[31]*. Studies investigating the effect of radiotherapy on HRQOL often grouped patients with spinal metastases together with patients with other bone metastases *[32, 33]*. Spinal metastases are however distinctly different in terms of symptom burden and treatment consideration compared to other bony metastatic sites.

The Spine Oncology Study Group Outcomes Questionnaire (SOSGOQ) was introduced in 2010 as the first spine oncology specific outcome *[34]*. The SOSGOQ

assesses five domains including physical function, pain, social function, mental health and neurological function *[34]*. In addition to these five domains, post-therapy treatment items are included to evaluate satisfaction with treatment *[34]*. **Chapter 5** describes the results of an international multicenter study evaluating the construct validity and test-retest reliability of the SOSGOQ. Multi-trait scaling analyses and factor analyses suggested re-ordering of some items of the SOSGOQ and the structure of the SOSGOQ was modified accordingly (SOSGOQ2.0). Subsequently, the validity and test-retest reliability of the refined SOSGOQ2.0 were established. The SOSGOQ2.0 is the first spine oncology specific HRQOL instrument that has been validated in a heterogeneous cohort of patients with spinal metastases. Use of the SOSGOQ2.0 in the assessment of HRQOL in patients with spinal metastases has an added value because for an accurate and comprehensive evaluation of HRQOL it is recommended to use both a disease specific and a generic HRQOL instrument. Improved insight in HRQOL may help in the counselling of patients and treatment decision-making between surgery and/or radiotherapy, or other medical treatment when treatment selection is not clear cut.

As mentioned earlier, overt spinal instability is an indication for stabilizing surgery, but the majority of patients present with "indeterminate spinal instability", represented by a SINS score between 7 and 12. The optimal treatment of patients with indeterminate spinal instability is unknown. The aim of the study described in **Chapter 6** was two-fold. First, to compare the effect of surgery (+/- radiotherapy) and radiotherapy alone on HRQOL in patients with indeterminate spinal instability. Second, to investigate the differences in individual SINS factors and combinations of SINS factors between both treatment groups. As part of the international multicenter observational cohort study described in **Chapter 5**, 228 patients with indeterminate spinal instability (SINS 7-12) were included. Patients with neurologic deficits as primary indication for surgery were excluded from the analyses to reduce treatment selection bias. Both, treatment with surgery (+/- radiotherapy) or radiotherapy alone improved quality of life. Yet, patients who underwent surgery demonstrated a greater gain in HRQOL compared to patients treated with radiotherapy alone. The greatest improvements were observed within the first six weeks after treatment, with slight improvements afterwards. Important differences in the SINS score and the composition of the SINS score were detected between the two treatment groups. Surgically treated patients had a significantly higher median SINS compared to patients who underwent radiotherapy alone, 10 and 8 respectively. Patients who underwent surgery had higher scores on the SINS factors regarding vertebral body collapse, mechanical pain and spinal misalignment. No differences in the distribution location of the lesion, bone lesion quality and involvement of the posterolateral elements were observed. The results of this study require careful interpretation and the limitations of this study should be considered. The study was a prospective observational cohort study

representing best clinical practice.
Due to the nonrandomized design, baseline differences between the two treatment groups were observed. Multivariate mixed effect models were used to adjust for these baseline differences, however residual confounding (by indication) remained.

The interpretation of the observed changes in HRQOL can be challenging. The observed changes in **Chapter 6** are statistically significant for the surgical group, but are these changes also clinically relevant? This question can be addressed by assessing the minimal clinically important difference (MCID). The MCID reflects the minimum change in a HRQOL measure that is associated with a clinically meaningful change for an individual patient *[35]*. The MCID for the SOSGOQ2.0 was estimated based on an increase in SOSGOQ2.0 equal or greater than 0.5 a standard deviation. Based on the estimated MCID value, a greater proportion of surgically treated patients experienced a clinically meaningful difference than those treated with radiotherapy alone. The limited numbers prohibited an analysis relating the combinations of SINS factor to treatment outcome. A follow-up prospective observational study including 26 centers is currently planned and may enable these analyses in the future including adjustment for other known factors related to treatment response such as performance status and age. In addition, a study to determine the MCID for the SOSGOQ2.0 based on an anchor-based method is currently being performed and will facilitate improved interpretation of the results.

Surgical interventions are inherently associated with the risks of adverse events and in the treatment decision-making process it is therefore important to weigh the potential benefits of the surgical intervention to the risk of adverse events. **Chapter 7** displays the results of a single center prospective observational study evaluating the incidence of adverse events in patients who underwent surgery for spinal metastases. Adverse events were collected on a daily basis by a trained research nurse and discussed by all surgeons in a weekly meeting. An incidence of adverse events of 76.2% was found, with an average of 1.8 adverse events per patient. This high rate of adverse events is partially the result of the rigorous method of adverse events collection; all adverse events were collected including grade 1 events without any clinical adverse effect such as electrolyte imbalances. The time between admission and surgery demonstrated to be positively associated with the risk of adverse events. This can be explained by an increased risk of adverse events with immobilization; the majority of patients were confined to bed between admission and surgery due to the severity of symptoms or to prevent progression of symptoms. The most common post-operative adverse events were urinary tract infection (35%), delirium (21%) and pneumonia (12%), which may be preventable when patients are closely evaluated and ambulated as soon as possible. Improved insight in the adverse event profile of patients with spinal metastases is imperative for treatment decision-making, when weighing the

benefits of surgery to the associated risks. Future studies assessing the relation between the occurrence of adverse events, HRQOL, and associated costs are required.

Advances in surgical techniques have led to the development of less invasive surgical techniques. The potential advantages of less invasive spine surgery include a decreased risk of complications, reduced loss of blood and improved recovery time as a result of less post-operative pain due to the smaller incisions and less soft tissue dissection *[36]*. The literature regarding less invasive surgical procedures in patients with spinal metastases is however still limited. Chapter 8 assessed the incidence of adverse events following percutaneous pedicle screw fixation for spinal metastases. A multicenter retrospective review of 101 neurologically intact patients who underwent percutaneous pedicle screw fixation for spinal metastases was performed. A total of 30 adverse events in 18 patients were identified. The lower incidence of adverse events suggests a benefit of using a less invasive surgical approach in this patient population. However, it should be noted that less impactful adverse may not have been accounted for in this retrospective review, which also contributes to the lower incidence.

Controversy exists regarding the indication for less invasive spine surgery in patients with spinal metastases. Some authors propose that less invasive surgery should be limited to patients in bad clinical shape. Others, including the author's current institution, feel that a less invasive approach should be used whenever possible to decrease the risk of complications and enhance patient recovery. A future study comparing the difference in adverse events between minimal invasive surgery and conventional open surgery should therefore consider the potential influence of selection bias.

ADVANCES IN TREATMENT STRATEGY

Currently, standard of care for patients with unstable spinal metastases consists of stabilizing surgery followed by EBRT, or SBRT, after a minimum of two weeks. The time interval between surgery and radiotherapy is considered necessary based on the high incidence of wound healing complications that were reported when surgery and EBRT were combined within a week *[6]*. The wound healing process is a complex cascade of inflammation, proliferation and tissue-maturation, which is vulnerable for disruption due to radiation exposure, especially in the early phases *[7]*.

Dose delivery with EBRT is non-conformal and is performed with a single posterior-anterior beam or with a two-beam approach with a posterior-anterior and anterior-posterior beam. The maximum dose to the spinal metastasis with EBRT is limited by the radiation tolerance of the surrounding organs at risk. Moreover, due to dose

attenuation the radiation dose delivered to structures present in the pathway in front of the spinal metastasis, including soft tissues in the surgical field, is higher compared with the dose delivered to the spinal metastasis [9]. SBRT, on the other hand, allows highly conformal delivery of the radiation dose. The radiation dose to the spinal metastases can be increased up to ablative radiation doses while limiting the dose to the surrounding tissues. The conformal dose delivery with SBRT also substantially reduces the radiation dose to the posterior surgical area, and may be even further decreased with active sparing of the surgical area during treatment planning. The aim of the study described in **Chapter 9** was to compare the radiation dose to the surgical area with EBRT, standard SBRT, and SBRT with active sparing of the surgical area. As expected, the mean radiation dose in the surgical area was significantly lower with the use of SBRT, with and without active sparing of the surgical area, compared to the use of EBRT. Active sparing of the surgical area with SBRT resulted in a further decrease in mean radiation dose to the surgical area. It is presently not known if the additional sparing of the surgical area with SBRT has a clinically relevant impact on the risk of wound complications compared to SBRT without active sparing of the surgical area. However, considering the feasibility of active sparing of the surgical area without compromising the radiation dose to the target spinal metastasis and other organs at risk, we tentatively recommend to use this type of SBRT planning strategy to minimize the risk of wound complications due to radiation injury.

The current standard practice, i.e. surgery followed by radiotherapy after a two-week interval, has several downsides. First, the time interval between surgery and radiotherapy delays the time until radiotherapy-induced pain relief. Second, the surgical implants induce scatter artifacts on planning computed tomography (CT) and magnetic resonance imaging (MRI) examinations, which prohibit accurate planning and delivery of radiation *[37]*. Third, in case of postoperative SBRT additional invasive imaging procedures, such as a CT myelogram, are necessary for accurate treatment planning. Fourth, in case of EBRT, multiple hospital visits are often needed for the administration of hyper-fractionated radiation schemes. Finally, only in about 60% of the patients, pain relief is achieved [38]. An alternative treatment strategy, which could potentially lead to faster pain relief in a higher proportion of patients with less hospital visits, is described in **Chapter 10**. Here, safety and feasibility of SBRT followed by stabilizing surgery within 24 hours for patients with symptomatic unstable spinal metastases is demonstrated. Combining SBRT and surgery within 24 hours has several advantages for the patient. Both treatments can be performed within one hospital admission and the radiotherapy induced pain relief may be experienced (approximately two weeks) earlier. If necessary, systemic treatment can also be initiated earlier. In addition, the use of pre-operative SBRT may reduce the vitality of malignant cells, thereby decreasing the risk of tumor spread as a result of surgical manipulation of the tumor. The results of this first-in-man study are promising but some limitations should

be considered. Planning both treatments within a 24 hour time frame requires excellent collaboration between spine surgeons and radiation oncologists. This treatment strategy is not suitable for patients requiring emergency surgery (<24 hours) for symptomatic MESCC because of the required time that is necessary to plan and complete the work-up for both treatments. Future studies should investigate if this new treatment strategy not only decreases the treatment burden for the patient but also results in superior clinical and patient reported outcomes compared to the current standard of care.

FUTURE PERSPECTIVES

The increasing incidence of patients with spinal metastases and the expanding treatment options to relieve symptoms and to maintain or improve quality of life, will lead to a further increase in the application of surgery and radiotherapy for spinal metastases in the near future. In light of the advances in treatment strategies of the last two decades, a further shift towards less extensive open surgical procedures and minimal invasive surgical procedures can be expected. Historically, resection of a spinal metastasis was considered if the pertaining spinal metastasis was the only (visible) metastatic site. Currently, we consider a solitary spinal metastasis as not truly being a solitary metastasis. Even though the solitary spinal metastasis is the only visible metastatic site, it is very likely that other sites harbour undetectable (micro-)metastases. Extensive tumor resections with curative intents, accompanied with high risks of peri-operative and post-operative adverse events, and post-operative morbidity are not desirable when the procedure is not curative. Instead, conventional open procedures or minimal invasive approaches may be limited to procedures to decompress the neurological structures and to stabilize the spine. Pre-operative or post-operative SBRT is an important adjuvant treatment to both open and minimal invasive surgical procedures to achieve durable local tumor control *[4]*. Limiting the surgical invasiveness, while still achieving the goals of decompression of the spinal cord, stabilization of the spinal column and achievement of durable local tumor control may improve patient quality of life and disease control. Furthermore, we predict a shift towards more patient-centered care, with different medical specialists collaborating for and together with the patient to optimize treatment.

With the increased attention for patient reported outcomes to evaluate treatment, there is also a trend towards evaluating patient satisfaction with treatment using patient reported experience measures (PREMS) *[39*, *40]*. Patient satisfaction is a complex multidimensional construct and an interplay between pre-treatment expectations, severity of pre-treatment symptoms and post-treatment outcomes *[41]*. It is important to gain insight in both perceived satisfaction with treatment for spinal metastases, and factors that are related with satisfaction to improve patient counselling and outcomes.

Recently Versteeg et al. [unpublished results] conducted a study to assess satisfaction with the outcomes of treatment for spinal metastases using the separate set of post-therapy questions of the SOSGOQ2.0. At 12 weeks post-treatment, 83% of the surgically treated patients and 77% of the patients who underwent radiotherapy reported to be satisfied with the outcomes of their treatment. A distinct difference in changes in HRQOL (pre-treatment vs. post-treatment) was observed between satisfied and dissatisfied patients, with dissatisfied patients experiencing only slight improvements in HRQOL. An important aspect of patient satisfaction and HRQOL is the relation with pre-treatment expectations *[42, 43]*. Quality of life has therefore previously been considered as the appraisal of the current level of functioning compared to what is perceived to be ideal or possible (expectations) *[42, 43]*. In order to optimize post-treatment quality of life, we also need to optimize patient counselling towards realistic expectations *[42]*.

It is imperative that patients understand the goals and limitations of treatments in order to make an informed treatment decision. Previous studies have shown that both physicians and patients are overly optimistic about life expectancy and patients having unrealistic beliefs about the effectiveness of treatments *[44]*. Two recent studies demonstrated that the majority of patients with final stage lung or rectal cancer receiving palliative radiotherapy or chemotherapy reported that their treatment was likely to cure them *[45, 46]*. Patients are willing to accept invasive and toxic treatments if there is a chance of cure, even if this chance is as small as 1% *[45]*. When the treatment goal is palliative, however, the willingness to accept the same treatment decreases *[46]*.

A study by Mitera et al. [47] explored the expectations of patients with spinal metastases regarding palliative radiotherapy and demonstrated that 35% of the patients were unaware of the severity of their disease. Furthermore, 20% of the patients expected that radiotherapy targeting the spinal metastases would have a systemic effect and be able to cure their cancer *[47]*. To improve treatment counselling of patients with spinal metastases, it is imperative to understand patients' expectations and perceptions of received treatment. Yet, to the best of our knowledge, the expectations and level of understanding of patients facing surgical treatment for spinal metastases are currently unknown. A study evaluating patients' expectations regarding surgical and/or radiotherapy for treatment is currently being designed to develop a new questionnaire to assess pre-treatment expectations. In the future, evaluation of patient's expectations may aid in improved patient counselling and patient selection.

CONCLUSION

In conclusion, the decision for surgery, radiotherapy or a combination of both for the treatment of spinal metastases is complex. The introduction of the SINS has assisted to standardize the assessment of neoplastic spinal instability and to improve communication among physicians. Yet the predictive value of the SINS for treatment outcome requires further research. The main goal of treatment for patients with spinal metastases is to improve their quality of life; use of the spine oncology specific SOSGOQ2.0 HRQOL measure will aid in the accurate evaluation of the impact of different treatment strategies on HRQOL. The results of the studies presented in this thesis showed that surgery with or without additional radiotherapy is associated with clinically meaningful improvements in quality of life in carefully selected patients with (potentially) unstable spinal metastases. The benefits of surgery should however be weighed against the risks of adverse events. In terms of optimizing treatment strategies, we demonstrated that the combination of SBRT and surgical stabilization within 24 hours for spinal metastases is safe and feasible. Whether this new combined treatment strategy results in superior outcomes compared to current standard of care remains to be determined.

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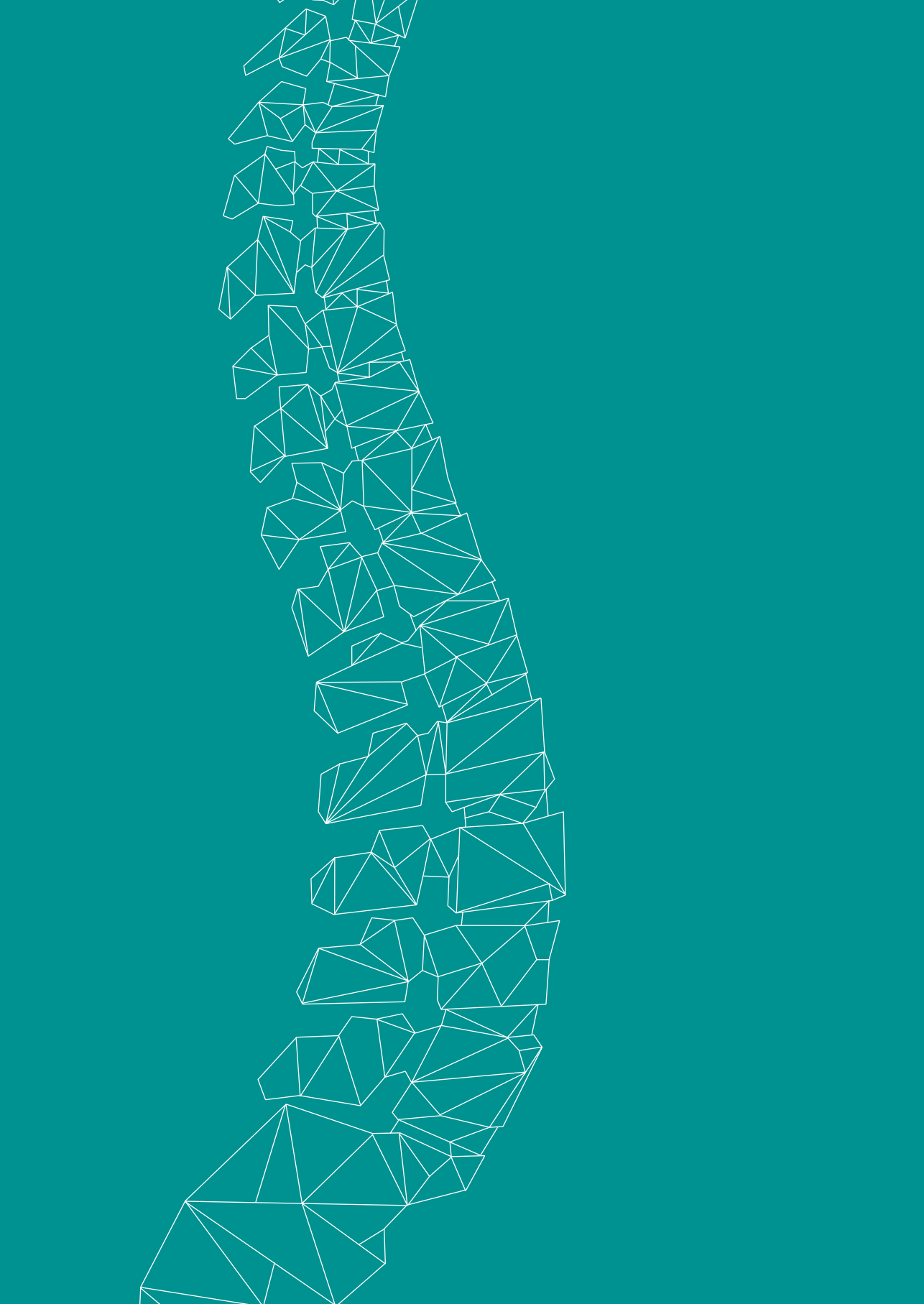

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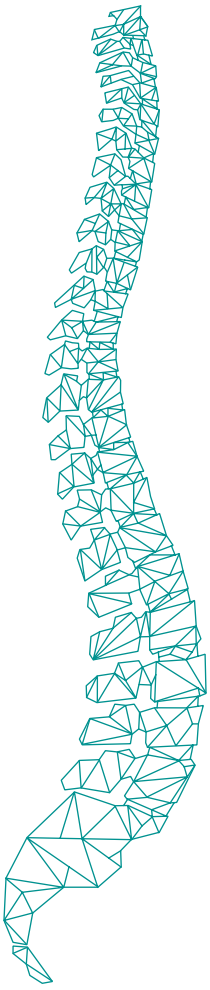


SUMMARY IN DUTCH (NEDERLANDSE SAMENVATTING)

INTRODUCTIE

Na de longen en de lever is het skelet, en dan met name de wervelkolom, het vaakst aangedaan door metastasen van kanker. Wervelmetastasen veroorzaken vaak pijnklachten die leiden tot een vermindering van de kwaliteit van leven van patiënten. Verschillende mechanismen liggen ten grondslag aan de pijn van wervelmetastasen. Veelal wordt onderscheid gemaakt tussen twee soorten pijn, lokale tumorpijn en mechanische pijn. Lokale tumorpijn wordt veroorzaakt door directe infiltratie van de tumorcellen in het bot, rek van het periostium door tumorgroei en/of het afgifte van van pro-inflammatoire cytokinen. Tegelijkertijd leidt een verstoorde homeostase tussen osteoclasten en osteoblasten tot een verlies van de sterkte van het bot wat op den duur leidt tot verlies van de integriteit van het bot. Het is aannemelijk dat beide mechanismen bijdragen aan de pijn bij wervelmetastasen, waarbij de relatieve bijdrage van beide mechanismen varieert. Daarnaast kunnen wervelmetastasen leiden tot neurologische uitval door compressie van neurologische structuren en/of instabiliteit van de wervelkolom.

Het belangrijkste doel van de behandeling van patiënten met wervelmetastasen is het verbeteren van de kwaliteit van leven door verlichting van pijn en het behoud of herstel van neurologische functie en stabiliteit van de wervelkolom. Conventionele radiotherapie is de standaard behandeling voor patiënten met symptomatische wervelmetastasen. Echter, een substantieel deel van de patiënten ervaart geen verlichting van de pijnklachten na radiotherapie. Onze hypothese is dat pijn die hoofdzakelijk veroorzaakt wordt door mechanische instabiliteit een inferieure respons heeft op radiotherapie in vergelijking met pijn met een overwegend lokale tumor pijn karakter. Mechanische instabiliteit is echter waarschijnlijk slechts een van de factoren die de respons op radiotherapie beïnvloedt, daarnaast wordt een dosis-respons relatie verondersteld. Ontwikkelingen in radiotherapeutische technieken hebben geleid tot een toename van stereotactische bestraling (SBRT) voor de behandeling van wervelmetastasen. Middels SBRT kan een ablatieve dosis op de tumor worden gegeven terwijl de dosis op het myelum en andere omliggende organen wordt beperkt.

Het concept van mechanische instabiliteit van de wervelkolom is essentieel in de evaluatie en behandeling van patiënten met wervelmetastasen. Mechanische instabiliteit van de wervelkolom ten gevolge van metastasen is als volgt gedefinieerd: “het verlies van de integriteit van de wervelkolom ten gevolge van een neoplastisch proces dat geassocieerd is met bewegingsgerelateerde pijnklachten, symptomatische of progressieve deformiteit van de wervelkolom en/of neurologische uitval onder fysiologische omstandigheden”. Deze definitie geeft echter geen handvaten om instabiliteit van de wervelkolom te evalueren. Vanwege het gebrek aan objectieve criteria om instabiliteit van de wervelkolom ten gevolge van metastasen vast te stellen werd de Spinale Instabiliteit Neoplastische Score (SINS)

ontwikkeld. De SINS score bestaat uit de som van zes factoren waarmee de stabiliteit van de wervelkolom wordt onderverdeeld in stabiel, potentieel instabiel en instabiel **(Tabel 1)**. Het advies is om alle patiënten met een (potentieel) instabiele wervelkolom te verwijzen naar een wervelkolomchirurg voor evaluatie voor chirurgische behandeling.

Instabiliteit van de wervelkolom is een belangrijke indicatie voor chirurgische behandeling van patiënten met wervelmetastasen. Veelal wordt chirurgische stabilisatie van de wervelkolom gevolgd door adjuvante behandeling met radiotherapie voor lokale tumor controle en additionele pijnverlichting. Een tijdsinterval van tenminste 1 tot 2 weken tussen chirurgische stabilisatie en radiotherapeutische behandeling wordt momenteel geadviseerd ter preventie van een gestoorde wondgenezing door radiotherapie. Gezien het palliatieve karakter is het verkorten van het tijdsinterval tussen de twee behandelingen wenselijk. Verschillende studies hebben de positieve impact van chirurgische behandeling op de kwaliteit van leven aangetoond. Echter, een chirurgische interventie gaat gepaard met risico op complicaties. Gezien het palliatieve karakter van de behandeling moeten de potentiële voordelen van chirurgische behandeling zorgvuldig worden afgewogen tegen de risico's.

Het doel van dit proefschrift is verbetering van de zorg voor patiënten met wervelmetastasen door middel van het verbeteren van de selectie van patiënten en behandelstrategieën.

PROEFSCHRIFT

Dit proefschrift bestaat uit drie delen. Deel I beschrijft de waarde van de SINS in de voor wetenschappelijk onderzoek, de klinische praktijk en de mogelijke prognostische waarde voor de pijnrespons na radiotherapie. Sinds de publicatie van de SINS wordt deze in toenemende mate in de literatuur over wervelmetastasen gebruikt als instrument om de stabiliteit van de wervelkolom te beschrijven. Daarnaast heeft de SINS impact gehad op de dagelijkse klinische praktijk rondom de zorg voor patiënten met wervelmetastasen. De SINS heeft geleid tot een toegenomen bewustwording voor het concept van instabiliteit van de wervelkolom ten gevolge van metastasen. Dit heeft er waarschijnlijk toe geleid dat patiënten met wervelmetastasen eerder worden verwezen voor evaluatie voor chirurgische behandeling. Door vroegere verwijzing van patiënten met potentieel instabiele wervelmetastasen naar een wervelkolom chirurg kunnen patiënten in een vroeger stadium chirurgische behandeling ondergaan voordat progressie tot volledige instabiliteit optreedt met het risico op neurologische uitval. Een SINS score duidend op een stabiele wervelkolom is geassocieerd met een grotere kans op een complete pijnrespons na conventionele radiotherapie in vergelijking met SINS scores duidend op een (potentieel) instabiele wervelkolom.

TABLE 1. DE SPINALE INSTABILITEIT NEOPLASTISCHE SCORE (SINS)

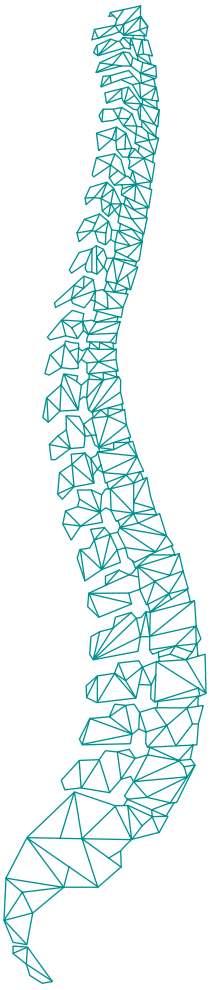
	Score
Lokalisatie metastase	
overgangsgebieden (occiput-C2, C7-T2, T11-L1, L5-S1)	3
mobiele wervelkolom (C3-C6, L2-L4)	2
semi-rigide wervelkolom (T3-T10)	1
rigide wervelkolom (S2-S5)	0
Pijn *	
Ja	3
Pijn, niet mechanisch van karakter	1
geen pijn	0
Aard van de bot laesie	
lytisch	2
gemengd (lytisch / blastisch)	1
blastisch	0
Radiologische stand	
subluxatie/translatie aanwezig	4
de novo deformiteit (kyfose/scoliose)	2
normale anatomische stand	0
Vertebral body collapse	
> 50% inzakking	3
< 50% inzakking	2
Geen inzakking, wel >50% van het corpus aangedaan	1
geen van bovenstaande	0
Betrokkenheid van de posterolaterale elementen†	
bilateraal	3
unilateraal	1
geen van bovenstaande	0

* Pijn verbeterd in rust en/of toename van pijn bij beweging/belasting van de wervelkolom.
† Facet, pedikel of costovertebrale overgang
0-6 stabiel, 7-12 potentieel instabiel, 13-18 instabiel

Deel II beschrijft de validatie van een nieuw instrument voor de evaluatie van kwaliteit van leven en de klinische uitkomsten na chirurgie en/of radiotherapie voor patiënten met wervelmetastasen. Voor een nauwkeurige evaluatie van uitkomsten van behandelingen voor patiënten met wervelmetastasen is het van belang om een instrument te gebruiken dat niet alleen specifiek maar ook sensitief is voor veranderingen in de kwaliteit van leven van deze patiëntenpopulatie. Na kleine aanpassingen in de structuur van de "Spine Oncology Study Group Outcomes Questionnaire" (SOSGOQ), is de SOSGOQ2.0 een valide en sensitief instrument gebleken om kwaliteit van leven bij patiënten met wervelmetastasen te meten. Een verbeterd inzicht in het effect van verschillende behandelstrategieën op de kwaliteit van leven kan in de toekomst bijdragen aan de besluitvorming voor radiotherapeutische en/of chirurgische behandeling. Patiënten met potentieel instabiele wervelmetastasen vormen de grootste groep symptomatische patiënten maar tegelijkertijd ook de groep waarbij de optimale behandelstrategie vaak niet duidelijk is. Wij lieten zien dat patiënten die een chirurgische behandeling ondergingen, al dan niet gevolgd door adjuvante radiotherapie, klinische relevante verbeteringen in kwaliteit van leven toonden in vergelijking met patiënten die alleen met radiotherapie werden behandeld voor potentieel instabiele metastasen. Het is hierbij van belang om te vermelden dat de chirurgisch behandelde patiënten binnen het spectrum van potentieel instabiele wervelmetastasen (SINS 7 – 12) meer karakteristieken hadden die duiden op de aanwezigheid van mechanische instabiliteit. Inherent aan chirurgische behandeling is het risico op complicaties. Patiënten met wervelmetastasen vormen een kwetsbare patiëntengroep en het risico op complicaties is dan ook groot. Bij de conventionele open chirurgische benadering trad er bij 76% van de patiënten een complicatie op, variërend van zeer milde complicaties zonder enige klinisch consequenties tot overlijden. Percutane schroeffixatie is een minimaal invasieve chirurgische benadering met diverse voordelen ten opzichte van de conventionele open chirurgisch benadering waaronder verminderd bloedverlies, vroegere mobilisatie door minder pijnklachten en een lagere kans op complicaties.

In het derde deel van dit proefschrift beschrijven we een nieuwe behandelstrategie voor patiënten met wervelmetastasen die zowel een chirurgische als radiotherapeutische behandeling moeten ondergaan. Door gebruik te maken van stereotactische radiotherapie in plaats van conventionele radiotherapie is het mogelijk om de dosis in het operatiegebied significant te verlagen, waardoor het risico op wondcomplicaties potentieel verlaagd en het tijdsinterval tussen de twee behandelingen beperkt kan worden. In een first-in-man studie lieten wij zien dat met behulp van stereotactische radiotherapie, waarbij het operatiegebied actief wordt gespaard, het mogelijk is om radiotherapie gevolgd door chirurgische stabilisatie op een veilige manier binnen 24 uur te combineren.

Dit proefschrift heeft geleid tot een verbeterd inzicht in de klinische uitkomsten en het effect van chirurgische en/of radiotherapeutische behandeling op de kwaliteit van leven van patiënten met wervelmetastasen. Daarnaast is een nieuwe behandelstrategie ontwikkeld, waarbij stereotactische radiotherapie binnen 24 uur wordt gevolgd door chirurgische stabilisatie. Vervolg onderzoek zal moeten uitwijzen of deze nieuwe behandelstrategie ook leidt tot verbeterde uitkomsten.



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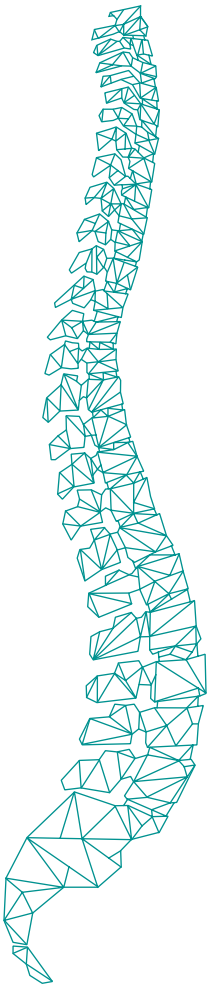

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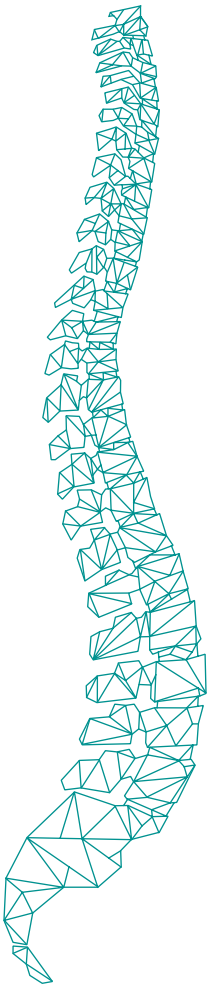

LIST OF PUBLICATIONS

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Peer reviewed publications

JG Steverink, SM Willems, MEP Philippens, N Kasperts, WSC Eppinga, **AL Versteeg**, JM van der Velden, M Faruqi, A Sahgal, JJ Verlaan. Early tissue effects of stereotactic body radiotherapy in spinal metastases.
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* authors contributed equally

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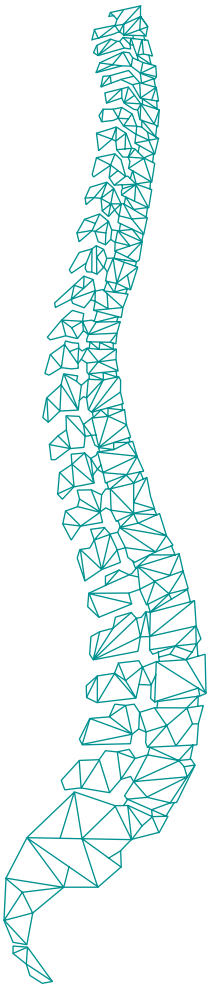

CURRICULUM VITAE

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Annemarie Leontine Versteeg was born on April 17th, 1989, in Utrecht, the Netherlands to Leo Versteeg and Joke Versteeg-Uppelschoten. She grew up in De Meern with her two older brothers Jasper and Joost. After obtaining her high-school degree (Atheneum) at the Sint Bonifatius College in Utrecht, she started medical school at the Utrecht University School of Medicine in 2007. During her studies she participated in the bachelor and master honors program of medicine at the department of Orthopaedic Surgery under supervision of René Castelein, MD, PhD and Cumhur Öner, MD, PhD. Prior to completing her final year of medical school, Anne visited the Vancouver Spine Surgery Institute (Vancouver, BC, Canada) for six months as a clinical research fellow. Under the supervision of Charles Fisher, MD, MHSc, FRCSC she conduced clinical research involving patients with spinal metastases. In the last year of medical school she received the prestigious MD-PhD Alexandre Suermann grant from the University Medical Center Utrecht to continue her research in the form of a PhD project at the department of Orthopaedic Surgery in collaboration with the department of Radiation Oncology under supervision of Jorrit-Jan Verlaan MD, PhD, Cumhur Öner, MD, PhD, and Helena Verkooijen, MD, PhD. The overall aim of her research is to optimize care for patients with spinal metastases, through improvements in patient screening and treatment strategies using a multidisciplinary approach, as described in this thesis.

In August 2016, she moved to Vancouver (BC, Canada) for a one-year research fellowship at the Vancouver Spine Surgery Institute under supervision of Charles Fisher, MD, MHSc, FRCSC. During this year she completed the Postgraduate Master of Health Science in clinical epidemiology and biostatistics at the University of British Columbia and started several spine oncology related research projects. Since 2016, she is also involved with the AOSpine Knowledge Forum Tumour, a group of renowned spine oncology surgeons and radiation oncologists who perform international multicenter research. Anne is currently pursuing a career in Orthopaedic Surgery.