Clinical and morphological aspects of metastatic spinal cord compression.

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To my parents and my family
Abstract

Metastatic spinal cord compression (MSCC) is a serious complication of cancer leading to demyelination and axonal damage of the spinal cord with loss of normal function. The Spinal Instability Neoplastic Score (SINS) has been proposed as a tool in order to identify patients with potential unstable bone metastases. The primary aim of this work was to analyse the prognostic value of SINS regarding postoperative survival and neurological outcome in patients with MSCC. In studies I and II, we prospectively evaluated the outcomes after surgery in 69 patients with haematological malignancies and 110 patients with prostate cancer. In study I, we retrospectively evaluated the outcomes after surgery in patients with bone metastases from other primary tumours (n=48). In study III, we retrospectively evaluated the outcomes after surgery in 110 patients with prostate cancer. A total of 106 of 110 patients met the SINS criteria for potential instability or the risk of loss of ambulation one month postoperatively. The median postoperative survival was 3.5 months. The median survival for all patients with MSCC was 20 months. Patients with prostate cancer had the longest median survival (6 years). Patients with prostate cancer and those with myeloma had the shortest median survival (3.5 months). There was no statistically significant difference in the overall risk of death between the tumour and bone in spinal bone metastasis interferes with regenerative bone cell activities between the tumour and bone. The SINS may be helpful in selecting candidates for surgery. The SINS potentially unstable and unstable instability. These patients.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>ADT</td>
<td>Androgen deprivation therapy</td>
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<tr>
<td>AR</td>
<td>Androgen receptor</td>
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<tr>
<td>BMP</td>
<td>Bone morphogenetic protein</td>
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<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>CSF</td>
<td>Cerebrospinal fluid</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>CUP</td>
<td>Cancer of unknown primary</td>
</tr>
<tr>
<td>EBRT</td>
<td>External beam radiation therapy</td>
</tr>
<tr>
<td>ESBT</td>
<td>External stereotactic body radiotherapy</td>
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<tr>
<td>ECOG</td>
<td>Eastern cooperative oncology group</td>
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<tr>
<td>ESCC</td>
<td>Epidural spinal cord compression</td>
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<tr>
<td>ET-1</td>
<td>Endothelin-1</td>
</tr>
<tr>
<td>FGF</td>
<td>Fibroblast growth factor</td>
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<tr>
<td>GSEA</td>
<td>Gene set enrichment analysis</td>
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<tr>
<td>HR</td>
<td>Hazard ratio</td>
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<tr>
<td>IAR</td>
<td>Instantaneous axis of rotation</td>
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<tr>
<td>IGF</td>
<td>Insulin-like growth factor</td>
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<td>IMM</td>
<td>Initial manifestation of malignancy</td>
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<tr>
<td>KPS</td>
<td>Karnofsky performance status</td>
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<tr>
<td>MM</td>
<td>Multiple myeloma</td>
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<tr>
<td>NICE</td>
<td>National Institute for Health and Clinical Excellence</td>
</tr>
<tr>
<td>MISS</td>
<td>Minimal invasive spine surgery</td>
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<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<tr>
<td>MSCC</td>
<td>Metastatic spinal cord compression</td>
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<tr>
<td>NHL</td>
<td>Non-Hodgkin’s lymphoma</td>
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<tr>
<td>PDGF</td>
<td>Platelet-derived growth factor</td>
</tr>
<tr>
<td>PSA</td>
<td>Prostate-specific antigen</td>
</tr>
<tr>
<td>PTEN</td>
<td>Phosphatase and tensin homolog</td>
</tr>
<tr>
<td>PTHrP</td>
<td>Parathyroid hormone-related protein</td>
</tr>
<tr>
<td>RANK-L</td>
<td>Receptor activator of nuclear factor b ligand</td>
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<tr>
<td>SINS</td>
<td>Spinal instability neoplastic score</td>
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<tr>
<td>TGF-β</td>
<td>Transforming growth factor beta</td>
</tr>
<tr>
<td>VCF</td>
<td>Vertebrae compression fracture</td>
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Populärvetenskaplig sammanfattning

Somatic occurrence of spinal metastasis is a serious complication to cancer. When the spine is compressed, circulation is affected and an ischemic damage occurs with risk for paralysis, incontinence, decreased quality of life and worse survival as a consequence if it is not identified and treated in time.

The condition affects approximately 2.5-5% of cancer patients. Spinal compression is most common in patients with known cancer, but it can also be the first manifestation of an earlier unknown malignancy.

Treatment of metastatic spinal compression is palliative and aimed at improving quality of life, function and reducing pain. The primary treatment methods are radiotherapy, chemotherapy or immunotherapy and surgery or a combination of these.

There is a debate about which patients should be selected for surgery. Studies indicate that the neurological function, such as remaining or regained ability to walk, is better with surgery in combination with radiotherapy compared to single radiotherapy.

Spinal metastases can cause instability of the spine and/or a progressive worsening of neurological symptoms or if the tumor is not sensitive to radiotherapy, surgery is often recommended. However, it requires that the patient's survival is estimated to be sufficient for the benefit of the intervention to outweigh the risk.

The concept of tumor-related spinal instability is complex. The tool 'Spinal Instability Neoplastic Score' (SINS) has been developed to facilitate assessment and to classify degrees of instability. SINS has shown high inter- and intra-rater reliability. Studies have shown that patients with increased instability according to SINS have worse results of radiotherapy. There is no evidence that SINS can be used to predict neurological outcome or survival after surgery for metastatic spinal compression.

A part of the dissertation work was to investigate morphological aspects of bone metastases from prostate cancer. Prostate cancer bone metastases are usually categorized as bone-forming (osteosclerotic), but this categorization is simplified since an overlapping with bone-destructive (osteolytic) components is often present. The metastases have shown to be heterogeneous in their morphological and biological structure and can also display a radiological image that resembles hematologic malignancies such as multiple myeloma and lymphoma. This radiologically described subtype is uncommon and no studies have been published about its prognostic value in spine compression.

In Part I, patients with spinal compression as first manifestation of malignancy were studied. In Part II, the predictive value of the selection tool SINS concerning neurological function and survival before surgery in prostate cancer patients with spine compression was investigated. In Part III, the predictive value of SINS for hematologic malignancies with compression of the spine was studied. In Part IV, a subgroup of spinal metastases from prostate cancer with a myeloma-like appearance on magnetic resonance imaging, was studied regarding prognosis compared to other prostate cancer metastases with spine involvement. In connection with surgery, tissue samples from the metastases were taken for analysis using immunohistochemistry and genomics analysis, where the myeloma-like prostate cancer group's gene expression profile, proliferation pattern, bone integration, and androgen receptor expression was compared to the non-myeloma-like prostate cancer group.
Studie II visar att patienter med potentiell instabilitet och instabilitet enligt SINS-klassificeringen har samma nytta av kirurgi avseende neurologisk funktion och överlevnad efter kirurgi vid ryggmärgskompression från prostatacancer. Patienter med tidigare obehandlad (hormonnaiv) prostatacancer hade en signifikant ökad överlevnad.

Studie III visar att SINS inte har ett prognostiskt värde för överlevnad eller neurologisk funktion vid operatio med multipelt myelom och lymfom. Gångfunktion och hemoglobinvärdet innan operation hade prognostisk betydelse för överlevnad.

Studie IV visar att patienter med myelomlika ryggmetastaser från prostatacancer hade sämre överlevnad och neurologisk funktion efter kirurgi jämfört med patienter med övriga ryggmetastaser från prostatacancer. Denna kategorisering är ny och till synes oberoende av tidigare kända biologiska markörer av prognostiskt värde för prostatacancer. Vid genexpressionsanalyser fann vi at PI3-kinas och fettsyremetabolism var uppreglerade hos myelomlika metastaser medan epithelial mesenchymal transition och hedgehog signaling var nedreglerad jämfört med gruppen med icke myelomlika prostatacancer.

Våra resultat (studie I) visar att patienter som debuterar med ryggmärgskompression som första manifestation av deras tumörsjukdom har varierad prognos avseende överlevnad. Genom ett brett diagnostiskt arbete kan majoriteten av primärtumörerna identifieras, vilket möjliggör en selektion till tumörspecifik behandling som kan ha stor betydelse för överlevnad. Vid ryggmärgskompression sker en ischemisk skada av ryggmärgen, ju längre tid som cirkulationsskadan föreligger desto mer ökar risk för bestående förlamning. Detta begränsar möjligheten att driva diagnostiskt arbete innan operation och beslut om kirurgi kan behöva tas även innan slutgiltig diagnos har identifierats.


Myelomlika metastas från prostatacancer är ovanligt med endast ett fåtal fallbeskrivningar presenterade i litteraturen. I studie IV fann vi att denna specifika grupp var relaterad till sämre överlevnad och neurologisk funktion efter kirurgi för ryggmärgskompression. De myelomlika metastaserna skiljde sig inte från den andra gruppen av prostatacancermetastaser med avseende på andra prognostiska biologiska markörer och kan därför tillföra ny oberoende information inför selektion till kirurgi. Med genexpressionsanalys fann vi skillnader rörande fyra tidigare kända signalvägar för prostatacancer, dessa är relaterade till tumöraggressivitet och terapiresistens. Denna nya grupp av prostatacancermetastaser förtjänar vidare uppmärksamhet, och om relationen till dessa signalvägar kan verifierras kan det finnas möjlighet att selektera denna grupp av tumörer till nya behandlingsstrategier.
Thesis at a glance

Study I. Metastatic spinal cord compression as the initial manifestation of malignancy

Patients and methods:
A retrospective analysis of 69 consecutive patients in whom the MSCC was the first sign of previously unknown malignancy.

Conclusion:
Survival after surgery for MSCC was highly dependent on the type of primary tumour. Both pre- and postoperative diagnostic workup is important in order to select patients for surgery and adjuvant treatments.

Study II. The Spinal Instability Neoplastic Score and surgery for MSCC in prostate cancer.

Patients and methods: 110 consecutive patients, retrospective study.

Conclusion:
The SINS was useful for evaluating tumour-related instability in order to select patients for surgery, but it did not predict postoperative survival and neurological outcomes.

<table>
<thead>
<tr>
<th>Overall survival (%)</th>
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<tbody>
<tr>
<td>Time after surgery (months)</td>
</tr>
<tr>
<td>K</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>100</td>
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</table>

Multiple Cox Regression

<table>
<thead>
<tr>
<th>Hazard ratio</th>
<th>P</th>
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<tbody>
<tr>
<td>SINS</td>
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</tr>
<tr>
<td>Hormone status</td>
<td>4.9</td>
</tr>
<tr>
<td>KPS</td>
<td>1.9</td>
</tr>
<tr>
<td>Age</td>
<td>1.1</td>
</tr>
</tbody>
</table>

x
Study III. Surgery for epidural spinal cord compression in haematological malignancies.

Patients and methods: A retrospective analysis of 48 consecutive patients (36 with myeloma and 12 with Non-Hodgkin’s lymphoma).

Conclusion: Surgery maintained and improved walking ability. The SINS was not associated with survival and neurological outcome. Ability to walk before surgery was associated with a superior survival.

Study IV. A novel radiological pattern of prostate cancer spinal metastasis.

Patients and methods: 110 consecutive patients, retrospective study. MRI appearance similar to haematological malignancies was used to categorize spinal metastases as myeloma-like (n=20) and nonmyeloma-like (n=90).

Conclusion: The myeloma-like radiological pattern was associated with particularly poor survival and neurological outcomes after surgery for MSCC.
This thesis is based on the following studies, which are referred to in the text by their Roman numerals:


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Introduction

Process of metastasis to bone

Bone metastasis is the third most common site of metastasis, after the lungs and liver (Coleman et al. 2001). Bone metastasis is most common in prostate, breast, lung, thyroid, and kidney cancer (Macedo et al. 2017). Some tumours are osteotropic, with a high tendency to metastasize to bone, while others rarely metastasize to bone. The reason why tumours behave differently in their affinity to bone is not completely understood. In 1889, Stephen Paget published the “seed and soil” hypothesis (Paget et al. 1889), which is still the most accepted explanation for why some tumours metastasize to specific locations. The specific affinity of the tumour cells (“the seed”) for a certain milieu/metastatic site (“the soil”) involves the existence of specific favourable interactions. Another theory known as the “haemodynamic hypothesis” was proposed by James Ewing in 1928. The haemodynamic theory suggests that the distribution of metastases is simply determined by the vascular and lymphatic drainage. The tumour cells follow the anatomical structure of the drainage pathways and develop into metastases in the first organ they encounter (Ewing et al. 1928).

Normal bone undergoes constant remodelling to maintain its structural and supportive functions. Bone remodelling mechanisms are tightly controlled by the bone-forming osteoblasts and bone-resorbing osteoclasts. When a tumour metastasizes to bone, it interferes with and disrupts this balance. This results in a complex interaction between the cancer cells and the microenvironment of the bone. The interaction between osteoblasts and osteoclasts leads to an osteolytic, osteoblastic or mixed bone response (Westendorf et al. 2004). An osteolytic response is characterized by excessive osteoclast recruitment that causes destruction of normal bone. In contrast, an osteoblastic response is characterized by the deposition of new bone (Wong et al. 2019). Bone metastases can be categorized as osteoblastic, osteolytic or mixed based on plain radiography, computed tomography (CT) or magnetic resonance imaging (MRI). Osteolytic metastases are typically associated with lung, breast, thyroid, colorectal and renal cancer, whereas osteoblastic metastases are predominantly encountered in breast and prostate cancer (Böcker et al. 2019). The categorization of osteoblastic or osteolytic metastases is probably a simplification since there are overlapping bone cell activities between these types of metastases. The interaction between the tumour and the mechanism of bone regulation renders the bone more prone to fractures. Pathological fractures are a major cause of morbidity and mortality and occur in 10-30% of all cancer patients (Selvaggi et al. 2005).
Interaction between prostate cancer cells and bone microenvironment has been described by the “vicious cycle” hypothesis (Mundy et al. 1997) (Figure 1). After attachment to the bone surface, the prostate cancer cells start to secrete osteogenic growth factors such as ET-1, PDGF, BMPs, TGF-β and IGF. These activate osteoblasts to start forming bone, but also to produce and release growth factors including IGFs, FGF, and TGF-β, which stimulate prostate cancer cell growth and proliferation. Metastatic colonization is enhanced if osteoclasts become activated by the secretion of the nuclear factor κB (RANKL), and bone resorption facilitates tumour growth (Kuchimaru et al. 2014). Parathyroid hormone (PTH) indirectly stimulates bone resorption by binding to receptors on osteoblasts, leading to the upregulation of RANKL (Huang et al. 2004). Furthermore, it has been suggested that the parathyroid hormone related peptide (PTHrP) plays a crucial role in skeletal metastasis of prostate carcinoma. Bone resorption creates more space for tumour growth and stimulates cancer cells by releasing cytokines (Wong et al. 2019).
It is generally accepted that prostate cancer forms osteoblastic (sclerotic) bone metastases. However, osteolytic activity may play an important role in the development of prostate cancer bone metastases. Markers for bone resorption are, for example, elevated in bone metastases from prostate cancer to a higher extent than in bone metastases from any other malignancy (Maeda et al. 1997, Costa et al. 2002). A hypothesis is that prostate cancer initially induces bone resorption at the time of spreading to bone, which is then followed by the release of diverse growth factors from the bone matrix, which in turn stimulates osteoblastic activities (Roodman et al. 2004). The bone-related parameters of bone metastases from prostate cancer have been shown to be a major prognostic factor of overall survival (Fizazi et al. 2014).

Prostate cancer bone metastases show molecular heterogeneity. In a large set of clinical bone metastases, gene expression profiles in relation to clinical and morphological parameters were analysed, and three different subtypes of prostate cancer metastases, named MetA, MetB and MetC, were identified (Thysell et al. 2019). The MetA-C subtypes showed clear differences in relation to patient prognosis and tumor biology. MetA patients had the best and MetB patients the worst outcome after androgen deprivation therapy. Furthermore, the MetA metastases showed high androgen response, protein secretion and adipogenesis, while MetB metastases were described by high levels of cell cycle activity and DNA repair, and MetC metastases can be described by the epithelial-to-mesenchymal transition and inflammation. The MetA-C subtypes and their prognostic and biological relevance were recently verified in additional patient cohorts (Thysell et al. 2022).

Spinal metastases

The spine is the most frequent site of skeletal metastasis and accounts for approximately 70% of all bone metastases (Delank et al. 2011). The spine has a high vascular supply and extensive lymphatic drainage. These tumours are spread by the arterial system, Batson’s venous plexus, which is responsible for drainage of the abdominal and pelvic organs, cerebrospinal fluid (CSF) or directly by paraspinal disease (Harel et al. 2010). The most common route for metastasis to the spinal column is haematogenous, in which tumour cells find a hospitable environment in the bone marrow. Sites of metastases in the vertebrae are most commonly thoracic (60-80%) followed by lumbar (15-30%) and cervical (<10%) (Sutcliffe et al. 2013). Spinal metastases are most commonly diagnosed in individuals between 40 and 70 years of age but can occur at any age (Harel et al. 2010). The posterior wall of the vertebral body is the most common initial site of involvement. The vertebral body becomes prone to pathological fractures due to destruction of its integral anatomic structure when a critical threshold is reached. Vertebral collapse can further compromise...
the integrity of the spinal channel and cause compression of the spinal cord, leading to paralysis and paraplegia (Cole and Patchell, 2008) (Figure 2). This is the most feared complication of spinal metastases (Coleman et al., 2001). Spinal instability and the risk of neurological deficit together with the patient’s performance status and prognosis for survival of the malignancy based on tumour histology are the most important variables regarding surgical treatment decisions (Fisher et al., 2010). The concept of spinal instability is perhaps the most difficult component to judge. To evaluate tumour-related spinal instability, it is essential to understand the complexity of spinal stability and instability.

Figure 2. Tumour-induced spinal instability with pathological fracture and metastatic spinal cord compression. Spinal stability is based on 3 subsystems: the spinal column, the muscle and tendons and the CNS. The bone becomes more prone to fractures as a tumour metastasizes to the vertebral body and interacts with the bone regulatory mechanisms. The vertebrae may collapse and compress the spinal cord leading to oedema, venous stasis, infarction and paraplegia as a consequence. (Redrawn according to Panjabi et al., 1992 and Cole and Patchell, 2008)
Spinal stability

From an anatomical and clinical point of view, the spine is a biomechanical wonder. The spine can be described as a pillar of bones connected by ligaments and discs that contains the spinal cord and nerves within its anatomical structure and connects them with corresponding muscles. It supports the whole body even under significant mechanical loading while being extremely flexible and enabling a significant range of motion. Hence, the definition of spinal stability is still a subject of extensive research among biomechanical engineers and clinicians. The simplest definition can be summarized as the ability to limit patterns of displacement with damage or irritation of the spinal cord or nerve roots and to prevent incapacitating deformity or pain caused by structural changes under physiological loading (Panjabi and White 1980). Spinal stability is based on three subsystems: the spinal column or passive subsystem, the muscles and tendons and the unit of central nervous control (Panjabi et al. 1992). These systems are integrated with each other both physiologically and biomechanically. A continuous stream of neuroelectric signals regarding load, motion and position in space are transmitted from mechanoreceptors and proprioceptors within the passive subsystems to the CNS, which responds with coordinated muscular actions (Panjabi et al. 1992). The passive stabilization of the spine depends on the architecture of the spinal column, bone mineral density, discs, intervertebral facet joints and ligaments. The vertebral body consists mainly of trabecular (cancellous) bone encapsulated in a “box” of outer shell of hard cortical bone. The load-bearing ability depends on the bone size, density and integrity of the trabecular system. The vertebral bodies increase in size from the cervical to the sacral spine as a result of increasing load due to body weight. The trabecular system within the cancellous bone in the vertebral bodies includes a vertical system, horizontal system and two curved oblique systems. This combination of two types of bone within each vertebra translates into maintenance of the load-bearing capability of the spinal column as an anatomical structure. Moreover, the mineral density is strongly related to the resistance of cancellous bone. Therefore, decreasing mineralization results in an exponential reduction of the mechanical resistance of bone to an applied load (Izzo et al. 2013). Each disc, located between two connecting vertebrae has both tension- and compression-resisting properties. The discs also act as main shock absorbers of mechanical stresses traversing along the spinal column. The facet joints serve two main functions: controlling the direction and amplitude of spinal motions and load sharing. The ligaments are important stabilizers of the integrity of the spinal column. The intrinsic power and the length of the lever arm through which the force is applied on the spinal column are the two most important factors of the impact of ligaments on the stability of the spine. The anatomical silhouette of the spinal column consists of three curves, cervical...
lordosis, thoracic kyphosis and lumbar lordosis, which together have an impact on the sagittal balance and thus the load resistance under physiological loading.

The active stabilization system of the spine consists of muscles and tendons under the control of the nervous system. Muscles can be categorized by their localization as superficial or deep. The main role of the muscles is to support and stabilize the spinal column during standing and load-bearing activities.

Spinal instability

The presumption that the spinal column cannot withstand the applied load is termed instability and originates in traumatology. This concept was eventually extended to several nontraumatic conditions of the spine such as tumors, infections, deformities and even degenerative spine diseases. It is, however, controversial and not well understood. Furthermore, there is no generally accepted definition of instability. White and Panjabi (1980) defined instability as abnormal movement in a motion segment, leading to damage or irritation of the spinal cord or nerve roots. The complexity of the spine and its biomechanics makes this definition very vague, since there are ample numbers of clinical examples that defy this definition. Moreover, this definition makes the quantification of the instability difficult. In general, mechanical instability is referred to as the inability to carry physiological loads, with its clinical implications resulting in neurological deficits and/or pain (Panjabi 2003).

The most commonly recognized model for traumatic spinal instability is known as the "three-columns" concept, described by Denis (1983). The model is designed to describe the instability following traumatic fractures in the thoracolumbar spine. Denis divided the spinal column into three vertical parallel columns:

- The anterior column [anterior longitudinal ligament (ALL), anterior two-thirds of the vertebral body and the anterior two-thirds of the intervertebral disc (annulus)]
- The middle column [posterior one-third of the vertebral body, posterior one-third of the intervertebral disc (annulus) and the posterior longitudinal ligament (PLL)]
- The posterior column [all structures posterior to the PLL, including the pedicles, facet joints and articular processes, and the posterior ligament complex (ligamentum flavum, capsule, interspinous ligament and supraspinous ligament)].

According to this model, instability occurs if an injury affects at least two of the three connected columns. This classification has been widely used for decision-making in the context of traumatic injury but is not useful for predicting the risk of instability in neoplastic spine disease.

Neoplasms infiltrate the vertebrae and cause bone destruction gradually over a period of time that successively reduces the load-bearing capability of the affected vertebrae, increasing the risk of pathological fracture. The ligaments and discs are rarely affected by neoplastic disease, and the mechanism of...
Pathological fractures of the spine

The two major patterns of pathological fractures are wedge fractures (the anterior column of the vertebra collapses and the posterior wall of the vertebral body remains intact) and burst fractures (failure of both the anterior and middle columns). The position in relation to the instantaneous axis of rotation (IAR) determines the fracture pattern. Wedge fractures occur due to a compressive force ventral to the IAR, which takes place under forced flexion. The thoracic spine is anatomically kyphotic, and therefore, wedge compression fractures are most common there. Burst fractures are the result of intensive axial loading in line with the IAR. The subaxial cervical spine and lumbar spine have intrinsic lordosis where the point of force is in line with the IAR, and burst fractures occur more commonly in these areas (Leone et al. 2019).

Impending instability

When a critical threshold is reached, the vertebral body becomes prone to fracture (insufficiency of 51-91% of the cross-sectional area, depending on bone density). Biomechanical studies have shown that the risk of burst fracture increases with tumour size, but no clear threshold has been identified (Whyne et al. 2003, Weber et al. 2011). The most important risk factors for pathological fracture are axial rigidity, which is based on the bone material composition and geometry of the vertebrae, location of the metastasis within the vertebrae (anterior third on the sagittal plane, middle third on the axial plane, or dorsal), tumour size and bone density. Furthermore, posterior destruction, especially of the thoracolumbar and lumbar spine, contributes to an increased risk of instability (Leone et al. 2019).

Lytic lesions carry a greater risk of pathological fractures due to their demineralization process (Mirels et al. 1989).

Spinal Instability Neoplastic Score (SINS)

Spinal instability as a result of a neoplastic process is significantly different from traumatic instability. The Spine Oncology Study Group (SOSG) defined
neoplastic spinal instability as “loss of spinal integrity as a result of a neoplastic
progressive deformity, and/or neural compromise under physiological loads”. It
is a challenging and important task to evaluate spinal instability in the
management of metastatic lesions. In 2010, the SOSG published the
score known as the Spinal Instability Neoplastic Score (SINS) (Fischer et al.
2010). The goal was to provide physicians with a score characterized by high
validity, reproducibility and reliability, with the intention of facilitating the decision-making process in regard to the spinal instability caused by metastases. The SINS has gained wide acceptance among practitioners. It consists of the sum of 5 radiographic parameters and 1 clinical parameter, resulting in a mathematical score between 0 and 18 points (Table 1). The SINS is meant to be evaluated for each individual metastatic lesion and does not account for “overall spinal instability”. Hence, it cannot be used to predict interactions of multiple lesions within the spine. The location of the lesion is the first parameter in the SINS. Junctional regions have the highest scores, and rigid regions have the lowest scores. It is known that junctional regions in the spine are at a higher risk of instability that may lead to deformity due to transitional forces (Mazel et al. 2004). These regions may also be at an increased risk of neurological deterioration due to both the biomechanical forces and blood supply characteristics (An et al. 1994). The more rigid vertebrae, supported by the ribs (thoracic spine) or the sacrum, have an extra biomechanical support and are therefore more stable. The presence of mechanical (activity-related) pain is considered to be related to structural abnormalities in the spine and is present in the majority of patients with spinal metastases (Fischer et al. 2010). Bone quality is another important factor regarding the risk of pathological fractures. The cross-sectional area of the defect combined with the bone mineral density have been shown to be excellent predictors of the risk of pathological fracture in biomechanical studies (Tschirhart et al. 2008). The spinal alignment with deformity has also been previously described as an indicator of instability. Moreover, the loss of integrity of posterolateral vertebral structures is considered an independent indicator of instability (Tomita et al. 2001). The sum of the parameters above contributes to the SINS score, which is divided into three different categories; stable (0-6 points); potentially unstable (7-12 points); and unstable (13-18 points). The score has high inter- and intraobserver reliability and predictability in identifying neoplastic spinal instability (Fourney et al. 2011, Fox et al. 2017). Although the SINS has facilitated improvement in the search for a definition for spinal neoplastic instability, its clinical prognostic value remains controversial (Versteeg et al. 2016). The SINS may be helpful in quantifying spinal instability in relation to malignancy, but it is important to emphasize that stability is only one component in the decision process regarding surgical treatment. Other parameters that need to be taken into consideration in the process of selecting treatment options for spinal metastases are the general health of the patient, the neurological status, the histopathology of the tumour,
the general oncological prognosis regarding survival and the patient’s own preferences.

<table>
<thead>
<tr>
<th>Component</th>
<th>Points</th>
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</thead>
<tbody>
<tr>
<td>Junctional region (C0-C2, C7-T2, T11-L1, L5-S1)</td>
<td>3</td>
</tr>
<tr>
<td>Mobile spine (C3-C6, L2-L4)</td>
<td>2</td>
</tr>
<tr>
<td>Semirigid region (T3-T10)</td>
<td>1</td>
</tr>
<tr>
<td>Rigid region (S2-S5)</td>
<td>0</td>
</tr>
<tr>
<td>Mechanical or postural pain</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3</td>
</tr>
<tr>
<td>No</td>
<td>1</td>
</tr>
<tr>
<td>Pain-free lesion</td>
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<tr>
<td>Bone lesion quality</td>
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<td>Lytic</td>
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</tr>
<tr>
<td>Mixed lytic/blastic</td>
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<td>Blastic</td>
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<tr>
<td>Spinal alignment</td>
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</tr>
<tr>
<td>Subluxation/translation</td>
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<tr>
<td>De novo deformity (kyphosis/scoliosis)</td>
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</tr>
<tr>
<td>Normal alignment</td>
<td>0</td>
</tr>
<tr>
<td>Vertebral body involvement</td>
<td></td>
</tr>
<tr>
<td>&gt;50% collapse</td>
<td>3</td>
</tr>
<tr>
<td>&lt;50% collapse</td>
<td>2</td>
</tr>
<tr>
<td>No collapse with &gt;50% body involved</td>
<td>1</td>
</tr>
<tr>
<td>None of the above</td>
<td>0</td>
</tr>
<tr>
<td>Posterior involvement</td>
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<tr>
<td>Bilateral</td>
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</tr>
<tr>
<td>Unilateral</td>
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</tr>
<tr>
<td>None of the above</td>
<td>0</td>
</tr>
<tr>
<td>Total SINS</td>
<td></td>
</tr>
<tr>
<td>Stable</td>
<td>0-6</td>
</tr>
<tr>
<td>Potentially unstable</td>
<td>7-12</td>
</tr>
<tr>
<td>Unstable</td>
<td>13-18</td>
</tr>
</tbody>
</table>
Metastatic spinal cord compression

Definition and incidence
Metastatic spinal cord compression (MSCC) is defined as compression of the spinal cord or cauda equina by a metastatic tumour mass inside the spinal canal or direct spread from the vertebrae, which may collapse and cause neurological deficits (Drudge-Coates et al. 2008). The true incidence of MSCC is unknown and varies with regard to primary tumour and age. Loblaw et al. (2003) reported an incidence of 2.5% of MSCC in the last 5 years of life among in-hospital patients in a population-based study from Canada. The estimated incidence of MSCC was 3.4% in patients who died from cancer in the U.S (Mak et al. 2011). The incidence rate reported in a hospitalised palliative care unit in Spain was 1.6% (Campillo-Recio et al. 2019). Because the detection rate in these studies depends on presentation to a hospital, the true incidence is most likely underestimated. Postmortem evidence indicates that MSCC affects 5-14% of patients with solid tumours (Boussios et al. 2018). Approximately 20% of patients with spinal metastases will develop MSCC (Sutcliffe et al. 2013).

MSCC is most common in the late stage of the disease but may be the initial manifestation of the malignancy (IMM) in 8-34% of patients (Schiff et al. 1997, Prasad et al. 2005). MSCC is both an oncological and surgical emergency that requires urgent evaluation and intervention. The tumour causes damage to the spinal cord by direct compression and secondary vascular compromise, leading to demyelination and axonal damage that presents clinically as paralysis and paraplegia (Cole and Patchell. 2008). Neurological deficits can be prevented or even reversed with early diagnosis and treatment in most patients with MSCC (Abram et al. 2008). A gradual and slow onset of compression permits a degree of cord adaptation, which predicts a better outcome than a sudden onset and loss of neurological functions. Primary tumours differ in their tendency to metastasize to the spine and cause MSCC. The primary tumours that most frequently cause MSCC are prostate, breast and lung tumours, each accounting for 15-20% of all cases. Approximately 5-10% of cases involve non-Hodgkin’s lymphoma, renal cell cancer and myeloma. The majority of the remainder are accounted for colorectal cancer, sarcoma, and cancer of unknown primary (CUP) (Cole and Patchell. 2008).
Symptoms

Back pain is the earliest and most common symptom of MSCC and is present in 83-95% of patients at the time of diagnosis (Prasad et al. 2005, Cole and Patchell. 2008). Pain is a nonspecific symptom, but pain characteristics that better predict MSCC include locations in the upper or middle spine, worsening after a period of lying down due to distension of the epidural venous plexus, and aggravation with activity (Prasad et al. 2005). Three different pain syndromes have been associated with tumours: biological pain, mechanical pain and radiculopathy. Biological pain arises from a reaction to inflammatory mediators released by the tumour and is usually worse during the night due to the nocturnal decrease in steroid secretion. Mechanical pain is related to movement and may be caused by destruction of the vertebral body, with increased pain under axial loading. Both biological and mechanical pain may progress to radiculopathy or myelopathy, which reflects direct injury of the spinal cord or nerve roots.

The second most common symptom of MSCC is limb weakness. In a study by Levack et al. (2002), 85% of patients with MSCC had weakness and only 18% were ambulatory without assistance. A higher frequency (63%) of ambulatory patients was found by Rades et al. (2010) at the time of diagnosis.

Sensory symptoms, including paraesthesia and numbness, are less common but are detectable in 50-70% of patients and are usually present in later stages of the disease. Sensory deficits are commonly presented distally with an ascending progression as the cord compression advances. Autonomic dysfunctions, including bladder and bowel incontinence, are also late consequences of MSCC and are present in 67% of patients (Levack et al. 2002). Sphincter dysfunction, tested by digital rectal examination, is associated with poor neurological recovery (Ganesh et al. 2020).

Diagnosis of MSCC

MRI is regarded as the golden standard imaging modality for the diagnosis of MSCC due to its high sensitivity (93%) and specificity (97%) (Mossa-Basha et al. 2019). MRI of the whole spinal column should be performed to identify other potential levels of MSCC and to identify asymptomatic metastases in the vertebrae, as multiple lesions are found in up to 30% of patients with MSCC (Lawton et al. 2019). More than two-thirds of the MSCC lesions occur in the thoracic spine, while 4-7% occur in the cervical spine (Levack et al. 2002). CT is less sensitive than MRI for detecting metastases, but in patients with contraindications to MRI, such as a pacemaker or metallic foreign bodies, CT myelography is recommended. CT is recommended to assess bone characteristics and to evaluate spinal instability (Fischer et al. 2010).
Bilsky et al. (2010) proposed a tool known as the Epidural Spinal Cord Compression (ESCC) scale in order to evaluate the severity of the MSCC (Figure 3). It is a six-point grading system based on T2-weighted MRI findings at the most severe compression site, with good inter- and intraexaminer reliability (Quraishi et al. 2015, Uei et al. 2018). The degree of spinal cord compression is not always correlated with neurological function. Uei et al. (2018) found no relation between the severity of paralysis and the ESCC scale. Neurological symptoms may appear even with low grades of spinal cord compression, and MRI alone cannot be used to predict paralysis (Uei et al. 2018). In a study by Venkitaraman et al. (2007), 27% of patients with metastatic prostate cancer showed a symptomatic MSCC on MRI. MRI can be used to evaluate the lesion type as lytic, sclerotic or mixed, but it is not specific for identification of the primary tumour, which is best determined by biopsy (Böcker et al. 2019).

Figure 3. The ESCC-scale consists of 6 grades: grade 0, only bone involvement; grade 1 (a-c), epidural impingement; grade 2, spinal cord displacement with visible CSF; and grade 3, spinal cord displacement with no visible CSF. (T = tumour). (Redrawn according to Bilsky et al. 2010 and Uei et al. 2018).

Treatment

In general, MSCC represent a stage when the original tumour has started to spread by seeding metastases to the spine. Therefore, it has to be regarded as a surgically incurable disease. However, surgery, although palliative, can play an essential role in the treatment of patients with spinal metastases. In general, the objective is improving quality of life by pain control, regaining and/or
preserving ambulatory function and sphincter control, and achieving spinal stability. Apart from surgery, other treatment options include spinal radiotherapy and medical treatment that involves the administration of corticosteroids, bisphosphonate therapy, chemotherapy and immunotherapy. The Spine Oncology Consortium proposed several factors to consider before initiating treatment (Spratt et al. 2017). The functional status of the patient prior to initiation of treatment has an important impact on the outcome. The most commonly used scales for evaluating the functional status are the Karnofsky Performance Status (KPS) scale (Karnofsky et al. 1948) and the Eastern Cooperative Oncology Group (ECOG) scale (Oken et al. 1982). Survival is dependent on the type of primary tumour and the response to antineoplastic treatment. Subtypes of primary tumours may have specific favourable prognostic profiles due to the development of new oncological treatments; these profiles require constant updating to be able to predict survival. The overall burden of the disease and the prognosis for survival are of high importance for the selection of the optimal treatment. Surgery for MSCC is generally only recommended if the expected survival time is at least 3 months because of surgery-related morbidity and the risk of complications (George et al. 2015). Some tumours are sensitive to radiotherapy, whereas others are deemed radio-resistant. In the case of hematological malignancies, generally there are systemic treatment protocols that may be superior to surgery and local radiotherapy even when spinal cord compression is present (Ganesh et al. 2020). The ambulatory function prior to treatment is the most important factor in determining the treatment response (Cole and Patchell 2008). Furthermore, spinal instability, most commonly evaluated by the SINS, is an important indication for surgical treatment in order to reduce mechanical pain and prevent deformity and further neurological deterioration. The complexity of MSCC and selection of the optimal treatment for each individual patient is best addressed by integrated multidisciplinary management. However, the timing for the treatment of MSCC is crucial, as prolonged loss of motor function cannot be restored by surgery or radiotherapy. Surgical treatment within 48 hours has been shown to yield superior results (Quraishi et al. 2013). Thus, it is a challenge for clinicians to propose and initiate a treatment within a limited time period. MSCC as the IMM pose an additional challenge because it might limit the opportunities for preoperative diagnostic workup due to the risk of persistent paraplegia.
coagulopathies, poor nutritional status and medical comorbidities (Hill et al. 1977). The complication rate is significantly higher in patients who undergo radiotherapy before surgery because it impede wound healing and increases the risk of deep infection (Ghogawala et al. 2001). Finkelstein et al. (2003) reported a 27% rate of major complications in patients who underwent surgery for spinal metastases in a large study of 987 patients. Williams et al. (2020) reported a complication rate of 18% and a 30-day mortality rate of 12% in their multicentre study with 4576 patients. Potential complications included among others respiratory complications, CSF leak age, wound infection, thromboembolism and deterioration of neurological function (Raj et al. 2013). The most common reasons for reoperations are primary-site infection, neurological deterioration and instrumentation failure (Tarawneh et al. 2020).

On the other hand, several studies have demonstrated that surgery can improve neurological function and quality of life (Patchell et al. 2005, Ibrahim et al. 2008, Quan et al 2011, Fehlings et al. 2016, Morgen et al. 2016, Dea et al. 2020, Quraishi et al 2020). A meta-analysis reported by Klimo et al. (2005) showed improved pain control and regained ambulatory function in 41% of patients treated by surgery followed by radiotherapy (n=999) versus 24% of patients treated by radiotherapy alone (n=543). These results were later supported by Lee et al. (2014) in their meta-analysis. They found better clinical improvement in the ambulation status and survival with the combination of surgery and radiotherapy than with radiotherapy alone. A paradigm shift with a surgery as a cornerstone in the treatment of patients with MSCC occurred after a randomized nonblinded multicentre study in which patients treated with surgical decompression followed by radiotherapy showed more favourable outcomes regarding preserved or improved ambulatory function and pain control than patients treated with radiotherapy alone (Patchell et al. 2005). However, it is important to emphasize that the median postoperative survival was only 4.2 months. Moreover, a later study on the same data revealed that patients 65 years old and older gained no significant benefits from surgery (Chi et al. 2009).

Surgery is associated with superior outcomes regarding ambulation when compared with radiotherapy alone but is not appropriate for patients with a limited life expectancy. Therefore, proper patient selection before surgery is crucial. Fortunately, several advancements in surgical techniques have been developed (Boussios et al. 2018). The surgical approach is determined by the location of the tumour within the vertebral body. Laminectomy is effective only in cases with posterior cord compression; it was historically the standard method, but several studies have supported the superiority of decompression and stabilization over decompression alone (L’Espérance et al. 2012). Decompression and stabilization can be performed with a variety of methods: by conventionally “open” surgery or minimal invasive spinal surgery (MISS) and with a posterior approach, an anterior approach or a combined approach (360 degrees).
More aggressive resection of the vertebral body (corpectomy) enables direct removal of ventral compression of the spinal cord caused by tumors (Wang et al. 2004). Corpectomy performed by either a posterolateral or anterior approach has been shown to be more effective regarding postoperative ambulatory function and pain control than laminectomy (L'Esperance et al. 2012). MISS techniques minimize the exposure and injury to the soft tissues (skin, muscles and ligaments) as well as small blood supply vessels and hence reduce surgical morbidities, with a positive effect on quality of life similar to that of traditional open surgery (Kim et al. 2013). Percutaneous procedures such as vertebroplasty and kyphoplasty have shown significant improvement in mobility and pain control and may be used as MISS alternatives in some cases for patients without spinal cord compression (Fourney et al. 2003, Mendel et al. 2009). Another surgical innovation that facilitates postoperative radiotherapy is separation surgery. During this surgery, the spinal cord is extensively and circumferentially decompressed to improve neurological function but most importantly to create space for an ablation target in stereotactic radiosurgery (SRS) (Perna et al. 2020). The gap between the tumor mass and the spinal cord allows radiation without damage due to exposure of the spinal cord.

Radiotherapy

Radiotherapy is the principal treatment for patients with spinal metastases and almost all patients undergo radiotherapy either alone or in combination with surgical treatment (Spratt et al. 2017). Most patients with MSCC do not meet the criteria for surgery and therefore undergo only radiotherapy (Morgan et al. 2013). Palliative radiotherapy alone is a reasonable treatment for patients with MSCC when the expected survival time is less than 6 months. The management of patients undergoing radiotherapy is complex; the principle is to control pain and local tumor growth to improve or prevent neurological dysfunction. These goals need to be carefully balanced due to the risk of adverse effects after radiation. The planned dose fraction should be weighed against the performance status and expected survival.

Radiotherapy can have several adverse effects, including gastrointestinal toxicity, mucositis, bone marrow suppression and radiation-induced myelopathy (Boussios et al. 2018). External beam radiation therapy (EBRT) and stereotactic body radiotherapy (SBRT) are the two most common forms of radiation therapy for spinal metastases. EBRT is the most common treatment, and approximately 60-70% of patients achieve a complete or partial response to EBRT. The most common doses of conventional EBRT are 8 Gy in one fraction, 20 Gy in five fractions or 30 Gy in ten fractions. The different radiation treatment regimens have demonstrated similar results (Sze et al. 2004), but single-fraction regimes have a 3-fold greater risk of retreatment than multifraction regimes (Howell et al. 2013). It has been shown that the results of a split course of 30 Gy over 2 weeks in terms of pain control, ambulation maintenance and bladder function preservation are similar to those of a short course of radiotherapy in patients with MSCC and a poor prognosis.
In general, higher doses of radiation in abbreviated courses are offered to patients with shorter expected survival times, whereas lower doses over a prolonged period of time are given to patients with better prognosis (Cole and Patchell, 2008). Radiation-induced toxicity is an important adverse effect that depends on the cumulative radiation, dose per fraction, the amount of tissue irradiated and the irradiated organ. Radiotherapy for MSCC should both provide efficient tumour control and have a low risk of complications, including a low risk of radiation-induced myelopathy. In conventional radiotherapy, the whole vertebra and surrounding tissue including the spinal cord, are exposed to radiation beams, which limits the opportunity for the safe delivery of radiation doses (Boussios et al., 2018). In contrast, confocal beams of radiation are used in SBRT for a more specific targeting. The technique enables the delivery of a higher biologically equivalent dose, which may improve the response rates in terms of pain and local control. Spinal SBRT is a safe and efficient method for the treatment of spinal metastases, enabling local control in up to 98% of cases (Yamada et al., 2017) and a low risk of high-grade toxicity risk, with generally only mild complications (Moussazadeh et al., 2015). The use of SBRT is the treatment of high-grade epidural disease is limited due to currently accepted doses, which has increased the interest in using the ESCC scale to select appropriate candidates (Mossa-Basha et al., 2019). The introduction of SBRT has revolutionized treatment paradigms and induced change in surgical indications. Vertebral compression fracture (VCF) is an important complication that has been reported in up to 40% of SBRT-treated patients compared to less than 5% of EBRT-treated patients (Sahgal et al., 2013, Jawad et al., 2016). It has been proposed that the SINS might be used to identify lesions at a greater risk of post-SBRT VCF (Sahgal et al., 2013, Faruqi et al., 2018). The related literature for the SBRT is limited, but nevertheless, it is recommended for patients with an expected survival exceeding 3 months, for tumours with a radio-resistant histology, in cases of limited disease (no more than 3 separate spinal sites), for bone-only metastases and in cases of low-grade epidural disease (Husain et al., 2017).

Medical therapy MSCC requires urgent treatment in order to improve and restore neurological function. The role of chemotherapy in treating MSCC is limited due to the slow response in the majority of patients (Boussios et al., 2018). Bisphosphonates are effective in reducing the risk of pathological fracture, but their effect on reducing the risk of MSCC remains uncertain (Cole and Patchell, 2008, Farii et al., 2020). Other important effects of bisphosphonates are pain relief and a reduced risk of malignancy-associated hypercalcæmia (Sciubba et al., 2010).
Corticosteroids act by reducing the spinal cord vasogenic oedema. Oedema is one of the most important factors of progressive neurological deficit in MSCC. Oedema develops due to either direct mechanical pressure from the tumour or from occlusion of the epidural venous plexus (L’Esperance et al. 2012). Corticosteroids can improve or stabilize the neurological function. The improvement can be seen as a prognostic sign for further amelioration of neurological function after treatment. Sørensen et al. (1994) performed a single-blinded randomized study on the administration of high-dose steroids (96 mg intravenous bolus followed by 24 mg orally every 6 hours) combined with radiotherapy vs. radiotherapy alone in patients with MSCC. They found improved ambulatory function at 6 months post-radiotherapy in the group treated with steroids. A similar outcome with an improved safety profile was obtained when therapy was initiated with a lower dose bolus (10-16 mg/day) (Vecht et al. 1989, Heimdal et al. 1992). The optimal dose and duration of treatment with steroids remain controversial because of several serious potential side effects, including hyperglycaemia, increased risk of infection, steroid-induced myelopathy, hypomania, psychosis and gastrointestinal haemorrhage.

Prognosis

Postoperative survival

The median survival rate of patients with MSCC ranges between 6 and 9 months (Ganesh et al. 2020) but the prognosis varies widely. The estimation of survival is probably the most important component of providing appropriate treatment for patients with MSCC. The estimation is complex and needs to be discussed in a multidisciplinary context. A high-quality, prospective multicentre study of 142 patients with surgically treated MSCC identified the primary tumour type (breast, prostate and thyroid), the absence of organ metastasis and a high functional status score as three independent factors associated with longer postoperative survival (Nater et al. 2018). There is also a strong correlation between preoperative ambulatory function and survival rate (Lei et al. 2016 and Wan-Yo et al. 2017). Several prognostic scoring systems have been developed to guide and predict the overall survival of patients with spinal metastases. The most commonly used in clinical practice for postoperative survival are the Tokuhashi score (TS), the modified Bauer score and the Tomita score. The TS was published in 1990 (Tokuhashi et al. 1990) and revised in 2005 (Tokuhashi et al. 2005). The Bauer score was introduced in 1995 (Bauer et al. 1995) and was originally designed to address metastases to both the spine and extremities. The score was later modified by Leithner et al. (2008). The Tomita score was published in 2001 (Tomita et al. 2001).
The TS was the first reported system for scoring the prognosis of patients with spinal metastases and is probably the most recognized and most commonly used by spine surgeons. It comprises 6 variables: general condition, number of extraspinal bone metastases, number of other visceral metastases, primary site of cancer and the presence of paralysis according to the Frankel grade. The TS has been evaluated in several studies, with a reported predictive accuracy ranging from 51 to 88% (Cassidy et al. 2018). Zoccali et al. (2016) concluded in their review that TS is useful in patients with good prognosis but not in patients with a predicted survival of less than 1 year. Furthermore, the TS has been shown to be inaccurate in specific types of cancer, such as lung cancer (Ogihara et al. 2006, Hessler et al. 2011, Wang et al. 2012 and Tan et al. 2016), myeloma (Amelot et al. 2017) and kidney cancer (Wang et al. 2012).

The modified Bauer score comprises 4 parameters: absence of visceral metastasis, solitary skeletal metastasis, not primary lung cancer and if the primary tumour is breast, kidney, lymphoma or myeloma. It has been reported to have the best correlation with the survival rate (Leithner et al. 2008, Wibmer et al. 2011, Dardic et al. 2015).

The Tomita score is composed of only 3 parameters: tumour growth, visceral metastases and number of bone metastatic lesions. The score shows a significant association with survival but unfortunately can be inaccurate for specific tumour subtypes. A comparison of the Tomita and TS scores, demonstrated superior accuracy for the TS (Cassidy et al. 2018).

However, these scoring systems were developed for more than 20 years ago and do not account for the oncological advancements and new treatment options that have significantly improved patient survival for several cancer diagnosis. A systematic review of the literature regarding prognostic factors of survival after surgical treatment for MSCC concluded that evidence of predictors is low (Nater et al. 2017). Tokuhashi et al. (2017) described in their review that scoring systems in general have been useful but due to improved survival, increased diversity among tumours and advancements in treatments, it is important to emphasize multidisciplinary development and revision of classifications and scoring methods in order to adapt to the future. Recently, Carrwik et al. (2019) reported that these scores in general underestimate rather than overestimate survival. They proposed that the systems need to adapt more quickly to advancements in treatment regimens and speculated about the future development of a decision algorithm with the capability of real-time data analysis through artificial intelligence. Furthermore, the scores make it difficult to draw conclusions for specific tumours.

To specifically address the prognosis of prostate cancer patients after surgery for MSCC, Crnalic et al. (2012) presented a score based on the hormone status, KPS, presence of visceral metastasis and prostate-specific antigen (PSA) level. This scoring system...
showed good discrimination compared with the revised TS but still lacks external validation. Neurological function after surgery can be considered a key component of treatment modality selection in patients with MSCC. The functional status of cancer patients correlates with both the duration of survival and quality of life (Patchell et al. 2005). The best prognostic factor regarding posttreatment neurological function is the ambulatory function at the time of diagnosis. Pretreatment ambulation is associated with better outcomes and reduced rates of morbidity and mortality (Ganash et al. 2021). Several independent factors for regained ambulatory function were evaluated in a systematic review (Lauffer et al. 2016) in order to determine the likelihood of neurological improvement in patients with MSCC and neurological deficits prior to surgery. The duration of neurological deficits between onset and surgical intervention correlated significantly with improved postoperative outcomes, and patients who underwent surgery within 48 hours after presenting with neurological symptoms were more likely to regain ambulation after surgery (Chaichana et al. 2009, Fürlstenberg et al. 2009, Crnalic et al. 2013, Quraishi et al. 2013, Wan-Yo et al. 2017). Ohashi et al. (2017) found in their cohort of 82 nonambulatory patients before surgery that the speed of motor deficit progression independently predicted postoperative ambulation recovery. Rapid motor deficit progression is associated with a negative prognosis regarding the recovery of ambulation (Easterly et al. 2012). Furthermore, the severity of neurological deficits is related to postoperative neurological recovery, and bladder dysfunction is associated with poor neurological recovery (Fürlstenberg et al. 2009). Preserved muscle strength against gravity is a positive predictor for ambulation recovery (Park et al. 2013). Additionally, radiographic parameters, including the presence of a VCF and thoracic spinal cord compression, as well as grades of the ESCC scale, were associated with a negative prognosis of neurological recovery, but the association did not reach statistical significance (Quraishi et al. 2015, Laufer et al. 2016, Uei et al. 2018).

Algorithms and clinical perspectives

Early detection and awareness of MSCC among clinicians are crucial. Patients with MSCC often suffer from severe delays, with a major impact on the possibility of preventing paralysis as a consequence. The National Institute for Health and Clinical Excellence (NICE) guidelines were presented in 2008 to address the topic of MSCC (White et al. 2008). The key priorities include information about early symptoms of MSCC for all patients who have a risk of bone metastases. Patients with known cancer and the onset of spinal pain should be considered to have spinal metastases until proven otherwise. MRI should be performed within a week in these patients or within 24 hours if neurological
symptoms are present, and even sooner if there is the need for emergency surgery.

The guidelines suggest that all hospitals that are responsible for the treatment of MSCC patients should have the capability for MRI all 24 hours and that an MSCC coordinator should be available at all times. Definitive treatment should be started within 24 hours after confirmed diagnosis to prevent further neurological deterioration (White et al. 2008).

The complexity of the patient selection process to tailor the most appropriate treatment for spinal metastases has attracted interest over the past decade. Previously treatment algorithms involved either decompression surgery or cEBRT. However, technological advancement including development of SRS and MISS techniques, in combination with increasing survival of several oncological malignancies necessitate a multimodal assessment. A new decision framework for metastatic spine disease that consists of four parts was developed in 2012 and has gained popularity. It is called NOMS and consists of the assessment of four fundamental components: neurologic factors, oncologic factors, mechanical instability, and systemic disease (Laufer et al. 2013). The advantage of NOMS can be attributed to the fact that it incorporates advancements in both techniques and evidence-based medicine as they become available instead of algorithms that are fixed in terms of time and technology. The neurologic assessment is related to the grade of compression on the ESCC scale (Bilsky et al. 2010) and the clinical features of myelopathy or radiculopathy. The oncologic consideration focuses on the expected tumor response to currently available treatments, including cEBRT, SRS, surgery, chemotherapy, hormone therapy and immunotherapy.

Mechanical instability, addressed by the SINS, is an independent indication for surgical stabilization, regardless grades of the ESCC scale or radiosensitivity of the tumor. The evaluation of systemic disease aims to estimate the expected survival and the ability of the patient to tolerate a proposed treatment (Laufer et al. 2013). NOMS is a promising tool to address the complexity of assessment and decision-making processes in the treatment of spinal metastases (Sciubba et al. 2021). Other further directions might include implant selection, multicentre databases and adaptation to tumour specific treatments based on morphological analyses. The development of machine-learning algorithms and a combination of classification-based systems are other promising steps toward more tailored therapeutic models created specifically to fulfill the patient’s needs (Chang et al. 2020).
General aim

To study the clinical and morphological aspects of metastatic spinal cord compression (MSCC) in patients with prostate cancer and other tumours.

Specific aims

Study I

To evaluate the results of surgery including complications, survival, and neurological outcome, in patients with MSCC as the initial manifestation of a previously unknown malignancy.

Study II

To investigate the association between tumour-related spinal instability and clinical outcomes after surgery for MSCC in patients with prostate cancer.

Study III

To investigate the association between tumour-related spinal instability and clinical outcomes after surgery for MSCC in patients with haematological malignancies.

Study IV

To analyse the presence, prognostic value, and biological features of prostate cancer spinal bone metastases with myeloma-like radiological patterns.
Patients and methods

Study I

The study enrolled 69 consecutive surgically treated patients with MSCC as the IMM at Umeå University Hospital, Umeå, Sweden, between 2003 and 2015. None of the enrolled patients had a previous history of cancer and the primary tumour was unknown at the time they presented with the symptoms of MSCC. The indication for surgery was pain (n=2) and/or neurological deficit (n=67). A combination of laboratory analyses, clinical examinations, bone biopsies and radiographic examinations including CT, bone scintigraphy, ultrasound, positron emission tomography and MRI, was used in order to identify the location of the primary tumour. Pre- and postoperative neurological function was evaluated according to the Frankel scale (Table 2). The general functional status before presentation with MSCC was estimated retrospectively according to the KPS scale (Table 3). The postoperative follow-up period was defined as the interval between surgery and the latest examination or death. Complications that occurred within 30 days after surgery were registered.
### Table 2. Frankel scale.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Neurological Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Complete paraplegia (no motor or sensory function)</td>
</tr>
<tr>
<td>B</td>
<td>No motor function, only sensory function</td>
</tr>
<tr>
<td>C</td>
<td>Motor function present, but not of practical use (non-ambulatory)</td>
</tr>
<tr>
<td>D</td>
<td>Motor function present, sufficient to allow walking (ambulatory)</td>
</tr>
<tr>
<td>E</td>
<td>No neurological symptoms</td>
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### Table 3. Karnofsky performance status scale.

<table>
<thead>
<tr>
<th>Definition</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Able to carry on normal activity and to work.</td>
<td>100</td>
</tr>
<tr>
<td>Normal; no complaints; no evidence of disease.</td>
<td>90</td>
</tr>
<tr>
<td>Able to carry on normal activity; minor signs or symptoms of disease.</td>
<td>80</td>
</tr>
<tr>
<td>Normal activity with effort; some signs or symptoms of disease.</td>
<td>70</td>
</tr>
<tr>
<td>Unable to work; able to live at home.</td>
<td>60</td>
</tr>
<tr>
<td>Cares for self. Unable to carry on normal activity or to do active work.</td>
<td>50</td>
</tr>
<tr>
<td>Requires occasional assistance, but is able to care for most personal needs.</td>
<td>40</td>
</tr>
<tr>
<td>A varying amount of assistance is needed.</td>
<td>30</td>
</tr>
<tr>
<td>Requires considerable assistance and frequent medical care.</td>
<td>20</td>
</tr>
<tr>
<td>Unable to care for self.</td>
<td>10</td>
</tr>
<tr>
<td>Disabled, requires special care and assistance</td>
<td>0</td>
</tr>
<tr>
<td>Requires equivalent of institutional or hospital care.</td>
<td></td>
</tr>
</tbody>
</table>
Study II

A retrospective analysis of 110 consecutive patients with prostate cancer who underwent surgery for MSCC at the Department of Orthopaedics, Umeå University Hospital, between 2003 and 2017 was performed. Neurological function was graded with the Frankel scale before and 4 weeks after the surgery. The KPS scale was used to retrospectively estimate the functional status of the patients before the onset of neurological symptoms. The postoperative follow-up period was defined as the time between surgery and the latest follow-up date or death. Complications within 30 days after surgery were registered. SINS Preoperative MRI or CT was used to calculate the radiological component of the SINS. This analysis was blinded to the preoperative clinical data and postoperative outcomes. The mechanical or postural pain element of the SINS was determined from medical records.

Treatment before surgery for MSCC

The majority of the patients received high dose steroids shortly after the onset of neurological symptoms (n=106). Patients with hormone-naïve prostate cancer underwent treatment with androgen deprivation therapy short time before (n=8) or after (n=18) surgery for MSCC. Twenty-two of these 26 patients underwent orchidectomy, two patients received a gonadotropin-releasing hormone agonist (GnRH-a), one patient received a GnRH-a with the addition of antiandrogen, and one patient received only an antiandrogen. Castration-resistant prostate cancer (CRPC) patients underwent different treatments for their primary tumour. Four patients underwent radical prostatectomy, and in 10 patients, the primary tumour was treated with curative radiation therapy. The most common was androgen deprivation therapy with a GnRH (n=70) or orchidectomy (n=14). Two patients were treated with both orchidectomy and a GnRH. Some patients (n=53) received an antiandrogen as an additional treatment, and chemotherapy was given to 25 patients due to the dissemination of cancer or failure of hormone treatment.
Study III

A retrospective analysis of 48 consecutive patients (36 patients with myeloma and 12 with non-Hodgkin’s lymphoma) who underwent surgery for ESCC at the Department of Orthopaedics, Umeå University Hospital, Sweden, between 2003 and 2019 was performed.

The indication for surgery was neurological deficit (n=40) and/or pain (n=8). The KPS scale was used to estimate the functional status before presentation with neurological symptoms and the Frankel scale was applied to evaluate neurological function before surgery and at 1 and 6 months after surgery. The time between the date of surgery and the latest follow-up examination or death was defined as the follow-up period. Histopathology together with blood samples and/or bone marrow biopsy analysis was used to confirm the diagnosis of myeloma and lymphoma. In 24 patients with myeloma and in 10 patients with lymphoma, ESCC was the first sign of a previously unknown malignancy.

Complications within 30 days after surgery were registered.

SINS Preoperative MRI and CT were used to calculate the radiological component of the SINS. This analysis was blinded to the preoperative clinical data and postoperative outcomes. The mechanical or postural pain component of the SINS was determined from medical records.

Treatment before surgery for ESCC
Chemotherapy was administered to 8 of the 12 myeloma patients with a previously known malignancy at an earlier stage of the disease, and 6 of them had also undergone stem cell transplantation. Chemotherapy was administrated to the 2 patients with previously diagnosed lymphoma. A high dose of steroids was prescribed prior to surgery to 29 of the 36 patients with myeloma and to 11 of the 12 patients with lymphoma.
Study IV

Patients

We evaluated 110 patients with metastatic prostate cancer who underwent surgery for MSCC at the Department of Orthopaedics, Umeå University Hospital, between 2003 and 2017. The follow-up period was defined as the time between the initial diagnosis of prostate cancer, the start of androgen deprivation therapy, or surgery for MSCC and the latest follow-up date or death.

Radiological classification

Preoperative MRI and CT were used to identify the radiological features of spinal bone metastases and determine the SINS and ESCC scale scores. The analyses were performed by a neuroradiologist who was blinded to the patients’ clinical characteristics before surgery and postoperative outcomes.

Morphological analysis

Tissue samples were collected during surgery and stored as freshly frozen or formalin fixed, paraffin-embedded samples. Immunohistochemical analysis of Ki67, PSA and androgen receptor (AR) expression was performed as previously described (Crnalic et al. 2010). PSA and AR immunoreactivity was assessed by a scoring system that includes the percentage and intensity of staining of tumour epithelial cells and the tumour cell proliferation index was determined as the percentage of Ki67-stained tumour epithelial cells (Crnalic et al. 2010).

Transcriptomic profiling

Whole-genome expression profiling was previously performed on frozen metastatic tissue samples from 69 of the 110 patients by using the Illumina BeadArray technology (Illumina, San Diego, CA, USA). The MetAC subtypes were classified according to the method described by Thysell et al. (2019).

Differential expression and gene set enrichment analysis

The samples of bone metastases were stratified based on their radiological pattern as myeloma-like (n=13) or nonmyeloma-like (n=56). The R (v4.0.5) limma (v3.46.0) package was used for differential expression analysis (DEA). Gene set enrichment analysis (GSEA) was performed based on a T statistic preranked list, and the built-in GSEA software (v4.1.0) preranked function was used to quantify the enrichment of hallmark gene sets (n=50) (v7.5), acquired...
from the Molecular Signature database (MSigDB). Gene sets with a false discovery rate (FDR) of \( \leq 0.1 \) are reported.
Statistical analysis

Descriptive statistics of continuous variables are expressed as medians (ranges), whereas categorical data are expressed as numbers and percentages. Independent samples were compared using the Mann-Whitney U test for continuous variables and the chi-square test or Fisher’s exact test for categorical variables. Paired observations of categorical variables were compared with the McNemar’s test (study II). Logistic regression analysis was used to evaluate the risk of loss of ambulation (study II), and the results are expressed as odds ratios with corresponding 95% confidence intervals. In all studies, survival was estimated by Kaplan-Meier analysis, and the survival curves were compared with the log-rank test. In studies II, III, and IV, a Cox proportional hazards model was used to assess the effects of the prognostic variables. The results are expressed as hazard ratios with corresponding 95% confidence intervals. In studies II and III, the assumption of proportional hazards was investigated by the introduction of an interaction term of the covariate of interest with time and by finding that the interaction term was not statistically significant. A P-value of < 0.05 was considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics version 25 and GraphPad Prism version 6.0.

Ethics

These studies were part of a larger prospective study on skeletal metastasis that had been approved by the local ethics review board (No. 223/03, dnr 03-185, dnr 04-26M (2007-08-24), dnr 03-158, dnr 2010-240-32).
Results

Study I

 Patients

Sixty-nine patients (18 women and 51 men) were enrolled in the study. The median age was 72 years (55–88). The site of MSCC was most commonly located in the thoracic spine (n=54), followed by the lumbar (n=10), cervical (n=4) and sacral (n=1) spine.

Diagnostic workup

Identification of the primary tumour was possible in 59 patients. Eleven different types of malignancies were diagnosed (Table 4). No specific tumour diagnosis could be established in the remaining 10 patients, and they were defined as having CUP. All patients with CUP had a negative chest and abdominal CT scan, and the histopathological analysis of metastatic tissue samples showed adenocarcinoma (n=5), poorly differentiated cancer (n=2), undifferentiated cancer (n=1), squamous cell carcinoma (n=1) and clear cell carcinoma (n=1).

Surgery

Twenty-three patients underwent posterior decompression and 43 patients underwent posterior decompression and posterior stabilization. Three patients underwent surgery with an anterior approach with corpectomy and anterior stabilization with plate.

Survival

The median overall survival time was 20 (1.2–118) months. The survival varied depending on the primary tumour type (Table 4). Patients with prostate cancer showed the longest survival, with a median postoperative survival time of 6 years and patients who were classified as having CUP showed the shortest survival, with a median postoperative survival of 3.5 months. Sixteen patients were still alive at the end of the study with a median follow-up time of 30 (1.4–76) months.
Thirty of the 69 patients had preserved ambulatory function (Frankel grade D–E) prior to surgery, and 29 of these retained the ability to walk one month after surgery. Regained ambulatory function one month after surgery was observed in 20 of the 39 patients who had lost the ability to walk before surgery.

Table 4. Postoperative survival and neurological outcome in relation to final diagnosis:

<table>
<thead>
<tr>
<th>Tumour type</th>
<th>Median postoperative survival (mo)</th>
<th>Ambulatory prior to surgery</th>
<th>Ambulatory 1 month after surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate cancer (n=24)</td>
<td>72 (1.4–118)</td>
<td>5</td>
<td>18</td>
</tr>
<tr>
<td>Myeloma (n=11)</td>
<td>63 (4.8–94)</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Lymphoma (n=6)</td>
<td>16 (12.9–59)</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Lung cancer (n=7)</td>
<td>10 (1.2–19)</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Other a (n=4)</td>
<td>9 (4.1–13)</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Colon cancer (n=3)</td>
<td>7 (5–34)</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Kidney cancer (n=4)</td>
<td>5 (1.2–8)</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>CUP b (10)</td>
<td>4 (1.3–11)</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Total (69)</td>
<td>20 (1.2–118)</td>
<td>30</td>
<td>49</td>
</tr>
</tbody>
</table>

Complications and recurrence of MSCC

A total of 20 complications were registered in 15 of the 69 patients within one month after surgery. Five patients had systemic complications, 7 patients had local complications, and 3 patients suffered from both systemic and local complications. Superficial wound infection (n=4) and wound dehiscence (n=4) were the 2 most common complications.

Recurrence of MSCC occurred in 12 patients at a median of 4.5 (2–14) months after surgery. The site of recurrence was in the same location in 6 patients and in a new spinal location in 6 patients.
Study II

Twenty-six patients were categorized as having a hormone-naïve prostate cancer, with a median age at the time of surgery of 75 (55-88) years, and 84 patients had CRPC, with a median age at the time of surgery of 71.5 (54-88) years. The patients with CRPC had a median post-operative survival of 5.5 (0.25-80.3) months compared to 60 (1.4-117.6) months in patients with hormone-naïve disease (P<0.001).

In the CRPC group, 4 patients met the SINS criteria for stability (score: 0-6), while the SINS was classified as potentially unstable (score: 7-12) in 70 patients and unstable (score: 13-18) in 10 patients, with a median SINS of 10 (6-15).

The median survival for the patients in the potentially unstable group was 6.5 (1-80.3) months vs. 4.8 (0.4-15) months for those in the unstable group (P=0.114).

In the hormone-naïve group, the SINS was classified as potentially unstable in 22 patients and as unstable in 4 patients, with a median SINS of 9 (7-16).

Patients in the potentially unstable group had a median survival of 60 (1.4-117.6) months.

The multivariate Cox proportional hazards model showed no statistically significant difference in the risk of mortality between the potentially unstable and unstable SINS categories (adjusted hazard ratio: 1.3, P=0.4).

The hormone status (adjusted hazard ratio: 4.9, P<0.001) and KPS (adjusted hazard ratio: 1.9, P=0.003) showed a strong ability to predict postoperative survival.

Sixty-four out of the 84 patients in the CRPC group were nonambulatory before surgery. One month after surgery, 28 of these patients had regained their ability to walk, 26 patients remained nonambulatory, and 10 patients had died.

Seventeen of the 20 patients who were ambulatory before surgery, maintained their ability to walk at one month after surgery, one patient lost the ability to walk, one patient was lost to follow-up and one patient had died. There was no statistically significant difference in the ambulatory status between the potentially unstable and the unstable SINS groups either before surgery (P=0.11) or after the surgery (P=0.39).

In the hormone-naïve group, 21 out of the 26 patients were nonambulatory before surgery. Thirteen of these patients regained the ability to walk one month after surgery, 7 patients remained nonambulatory, and one patient had missing data. The 5 patients who were ambulatory before surgery maintained their ability to walk one month after surgery. There was no significant difference in
the ability to walk between the potentially unstable and unstable SINS categories before surgery (P=1.0) or after surgery (P=1.0).

Multivariate logistic regression analysis of the risk of loss of ambulation one month after surgery showed no statistically significant difference between the potentially unstable and unstable SINS categories (adjusted odds ratio 1.4, P=0.6). The ability to walk before surgery was a strong predictor for ambulation at one month after surgery (adjusted odds ratio 19.8, P=0.005).

Complications within 30 days after surgery occurred in 39 (35%) of the 110 patients. Systemic complications occurred in 18 patients, and local complications occurred in 17 patients. Three patients had both systemic and local complications.
Study III

In the myeloma group, posterior decompression and stabilization was the most common surgical procedure and was applied in 26 of the patients. Three patients underwent only posterior decompression, and two underwent posterior decompression with corpectomy and stabilization with pedicle screws. An anterior approach with plate fixation was used in one patient, and 4 patients underwent treatment with a combination of anterior and posterior approaches.

In the lymphoma group, 8 patients underwent surgery with posterior decompression and stabilization with pedicle screws, 3 underwent only posterior decompression, and one patient underwent surgery with anterior corpectomy and stabilization with plate and screws.

The median SINS was 10 (4-16). Four patients met the SINS criteria for stability (score: 0-6), while the SINS was classified as potentially unstable (score: 7-12) in 33 patients and as unstable (score: 13-18) in 11 patients.

Neurological function

Twenty-three of the 36 myeloma and 3 of the 12 lymphoma patients were ambulatory before surgery, and they also maintained the ability to walk one month after surgery. In total, 28 of the 36 patients with myeloma and 6 of the 12 patients with lymphoma were ambulatory at the one-month follow-up. Four patients who were nonambulatory at one month further improved and were ambulatory 6 months after surgery. There were no statistically significant differences between the potentially unstable and unstable SINS categories regarding the ambulatory status before surgery (P=0.3) or at one month after surgery (P=0.24).

Survival

The median postoperative survival was 71.5 (1.9-150.8) months in myeloma patients and 58.7 (1.6-100.2) months in lymphoma patients (P=0.58). In total, the median survival of the 48 patients was 58.7 (1.6-150.8) months. The ambulatory function before surgery (hazard ratio: 3.4, P=0.012) and preoperative blood hemoglobin level (hazard ratio: 2.9, P=0.04) were independent predictors of survival in the multivariate Cox regression model.
Complications
Thirteen patients (27%) suffered from 16 complications within 30 days after surgery.

Recurrence of ESCC
Recurrence of ESCC occurred in 4 of the 36 patients with myeloma at 1, 5, 23, and 36 months, respectively, and in 4 of the 12 patients with lymphoma at 1, 11, 13, and 17 months, respectively.
Study IV

On preoperative MRI, we identified a radiological pattern of spinal bone metastasis that was similar to that of myeloma and other haematological malignancies. These patients had widespread metastatic infiltration of the vertebral column and diffuse metastatic infiltration within the vertebrae that replaced the normal fatty bone marrow. This pattern was used to categorize the metastases as myeloma-like (n=20) or nonmyeloma-like (n=90). The myeloma-like bone metastases were best visualized on the T1-weighted images (Figure 4), where they appeared as low-signal tumours with a infiltration process that suppressed the normal bone marrow: they also had a high signal on T2-weighted images.

Figure 4. MRI T1 sequence. Myeloma-like pattern of prostate cancer bone metastases.

The groups of patients with myeloma-like and nonmyeloma-like prostate cancer bone metastases were similar in terms of the clinical and radiological characteristics but the proportion of patients with a lower performance status (KPS <80) was higher in the myeloma-like group (P=0.026).
Patients with a myeloma-like metastatic pattern had a median survival after surgery for MSCC of 1.7 (0.1-33) months compared to 13 (0-140) months in patients with nonmyeloma-like metastases (P < 0.001). In the multivariate Cox proportional hazards model assessing the risk of mortality after surgery for MSCC, the myeloma-like pattern (hazard ratio: 2.5, P = 0.012), PSA immunoreactivity (hazard ratio: 0.54, P = 0.034), and KPS (hazard ratio: 2.6, P = 0.002) were all identified as independent prognostic factors.

Three of the 20 patients in the myeloma-like group and 22 of the 90 patients in the nonmyeloma-like group could walk prior to surgery. One month after surgery, only 5 of 13 patients in the myeloma-like group had the ability to walk, 6 had died, 1 patient died 6 weeks after surgery but was missed at the one-month follow-up. Fifty-seven of 83 patients in the nonmyeloma-like group had walking ability, six patients had died, and one patient was missed at follow-up. The postoperative ambulatory function was significantly reduced in the myeloma-like group (P = 0.034).

Bone metastasis morphology
Markers previously reported to be associated with the aggressiveness of metastasis in this patient cohort were compared between the group with myeloma-like pattern and the group with nonmyeloma-like pattern. No significant differences were seen with respect to the examined markers: the metastasis subtypes (MetA, MetB and MetC) (P = 0.68), tumour cell proliferation (P = 0.33), PSA (IR score) (P = 0.15), AR (IR score) (P = 0.74) and bone density (P = 0.61) between the two groups.

Transcriptomic profiling
The GSEA identified two hallmarks that were positively associated (PI3K-AKT-TOR signalling and fatty acid metabolism) and two hallmarks that were negatively associated (epithelial-to-mesenchymal transition and hedgehog signaling) with the myeloma-like pattern.
Discussion

The main finding of study I was the heterogeneous prognosis regarding survival for patients after surgery for MSCC as the IMM. This highlights the importance of the diagnostic workup, as the knowledge of a favourable prognosis for certain diagnoses can help clinicians in their decision regarding surgery.

Diagnosing and treating MSCC as the IMM is a challenging task for clinicians, since the onset of the disease is usually rapid, with sudden deterioration of neurological function. Therefore, all the information required for determining the prognosis and planning the most valid management strategy needs to be obtained during a very limited time interval.

MSCC is the IMM in approximately 20% of cases (Shiff et al. 1997), but these patients have rarely been analysed as a clearly distinguished group. Some studies are heterogeneous and include patients with spinal metastases both with MSCC and without MSCC (Aizenberg et al. 2012, Quraishi et al. 2014, Park et al. 2019, Carrwik et al. 2021). Most studies have focused on metastases from unknown primary tumours and do not distinguish these from cases in which the primary tumour was found later. An unknown primary tumour is defined as a biopsy-proven histological malignancy demonstrating a cancer that is not originating from the biopsy site and for which no identifiable primary tumour site can be found. Generally, metastases with no identifiable primary tumour after the diagnostic workup are classified as CUP. They share a characteristic aggressive clinical course, with rapid progression to metastasis, usually in an atypical pattern and with a poor response to therapy and consequently poor survival (Bouchtler et al. 2019). MSCC caused by an unknown primary tumour has previously been associated with a poor prognosis, with an average survival of 2-4 months (Enkaoua et al. 1997, Rades. et al. 2007).

Our results indicate that patients with MSCC as the IMM represent a heterogeneous group with a diverse course and prognosis, which highlights the importance of the diagnostic workup in selecting patients for surgical treatment. The median postoperative survival in our study was almost 20 months and was highly dependent on the primary tumour. The median postoperative survival far exceeded the recommended life expectancy of 3-6 months for patients undergoing surgery for spinal metastases (George et al. 2015). Other studies on patients with spinal metastases or MSCC caused by an unknown primary tumour at the time of surgery have reported a postoperative survival times of 5-8 months (Aizenberg et al. 2012, Quraishi et al. 2014, Carrwik et al. 2021) and 16-23 months (Park et al. 2019, Carrwik et al. 2021), respectively.

Differences in the tumour type and the primary tumour detection rate might to some extent
explain the differences between these results and the results of our study. The postoperative survival rate and the high detection rate of 85% in our study are similar to the results of Park et al. (2019), who reported postoperative survival for MSCC as the IMM and Carrwik et al. (2021), who reported postoperative survival for unknown primary tumours. Similar to our study, a relatively high frequency of haematological malignancies were reported in both of these studies, but with a lower proportion of patients with prostate cancer than in our study. The primary tumour detection rate in our study is also comparable with that of studies on bone metastases of an unknown origin in general (Takagi et al. 2015) and spinal metastases in particular (Iizuka et al. 2009). MSCC is most common in patients with known cancer for which further therapeutic opportunities might have already expired and whose general condition is already affected by the tumour itself and the treatments.

Our patients with MSCC generally had a high KPS, which can be explained by selection bias in that patients with a good performance status were more likely to undergo surgery. However, even within this selected group, some patients might have remarkable therapeutic options and a remarkable prognosis, as the best postoperative survival in our study was almost ten years. In contrast, patients with no specified diagnosis of their cancer, which was defined as CUP, had a short median postoperative survival of only 3.5 months, and thus did not benefit from surgery.

Making decisions on a stable ground
Since the SINS was introduced, the awareness of and consensus on tumour-related instability among physicians has increased (Versteeg et al. 2016). The growing trend in the literature regarding clinical applications of the SINS indicates that it will become an important tool in the evaluation of spinal metastases (Cassidy et al. 2018).

Our results indicate that the SINS may be used for the classification of spinal instability but does not predict postoperative survival or neurological outcomes in patients with MSCC. Spinal instability, as a result of a neoplastic process, is a key component that requires meticulous evaluation to select the optimal treatment for patients. The concept of tumour-related spinal instability is a difficult component to judge. Spinal instability, with the risk of vertebral fracture, carries an intrinsic risk of neurological impairment. Therefore, evaluation with the aid of the SINS may have indirect prognostic value regarding ambulation, quality of life and survival in patients with cancer types that tend to seed to the spine.

The SINS may be reliable for predicting the risk of VCF after radiotherapy (Lee et al. 2021). Few studies have investigated the predictive value of the SINS regarding postoperative survival. Afsar et al. (2017) found no prognostic value...
for survival in a retrospective analysis of 63 patients with mixed tumours. In contrast, Masuda et al. (2018) found a significantly longer postoperative survival for patients with mixed tumours with a SINS <12 compared to those with a SINS ≥13. Donnellan et al. (2020) found a statistically significant difference in survival after vertebrectomy between the potentially unstable SINS and unstable SINS categories. Studies on myeloma (Zadnik et al. 2015, Amelot et al. 2016) and breast cancer (Zadnik et al. 2014) have found no association between postoperative survival and the SINS. We evaluated the prognostic value of the SINS for clinical outcomes after surgery for MSCC in prostate cancer, which is generally classified as osteoblastic (paper II), and in haematological malignancies, which are generally classified as osteolytic (paper III). In both studies, we found no difference between the SINS categories in relation to survival or neurological outcome. The majority of the patients in our studies met the SINS criteria for potential instability or instability, which retrospectively indicates that the SINS is suitable for assessing spinal instability when selecting patients for surgery.

Hormone status of prostate cancer in relation to postoperative survival

The median postoperative survival of 5 years in patients with hormone-naïve prostate cancer in our study II is in agreement with previous studies (Huddart et al. 1997, Crnalic et al. 2012, Ju et al. 2013, Clarke et al. 2017, Miyoshi et al. 2020). However, these studies included fewer patients and had a shorter postoperative follow-up period. Huddart et al. (1997) reported a median postoperative survival of 627 days, and Crnalic et al. (2012) reported a median postoperative follow-up of 26 months during which 8 out of 13 hormone-naïve patients were still alive. In a study by Ju et al. (2013), all 3 hormone naïve patients survived, with a postoperative follow-up periods of 37, 40 and 46 months, respectively. Only 8 patients with hormone-naïve prostate cancer were evaluated by Miyoshi et al. (2020), and the median postoperative survival was not reached. The hormone status was not included in a later meta-analysis of overall survival in patients with spinal metastases from prostate cancer (Gao et al. 2020). Thus, the evidence of the effect of the hormone status on the postoperative survival of prostate cancer patients limited. Crnalic et al. (2012) proposed a new score for prostate cancer with MSCC, in which the hormone status had the maximal weight. Furthermore, the hormone status was the strongest independent prognostic factor for postoperative survival in study II. The long postoperative survival in patients with hormone-naïve prostate cancer might to some extent be explained by selection bias because patients with a high performance status were more likely to undergo surgery. Our results indicate that the hormone status is an important factor in the evaluation of surgical candidates.
Spinal surgery for ESCC in haematological malignancies

In study III, we found a relatively long postoperative survival for patients with haematological malignancies and ESCC. Furthermore, most patients regained or preserved the ability to walk after surgery. We found no statistically significant association between the SINS and preoperative or postoperative neurological function or survival.

ESCC in patients with haematological malignancies is usually treated with radiotherapy (Sang-Il et al. 2017). Few studies have addressed the surgical treatment of ESCC in these patients (Dürr et al. 2002, Rehak et al. 2009, Flouzat-Lachaniette et al. 2013, Fleury et al. 2015, Eeles et al. 1991, Cai et al. 2015). Interestingly, radiosensitive tumours such as myeloma and lymphoma were excluded from the only randomized, multicentre, nonblinded study comparing surgery followed by radiotherapy with radiotherapy alone in the treatment of MSCC (Patchell et al. 2005). Surgery has been proposed to increase overall survival in patients with myeloma and gross instability (Amelot et al. 2016). In contrast, our results indicate that the SINS do not predict survival or neurological outcomes, as also previously suggested by Zadnik et al. (2015). The most important prognostic factor regarding postoperative survival and neurological outcomes in our study was the preoperative ambulatory status, which is in accordance with the results of Liu et al. (2018).

ESCC is more often presented as the first manifestation of a previously unknown malignancy rather than as a late symptom of the disease in patients with haematological malignancies (Jung et al. 2014, Perry et al. 1993). Consequently, patients may be in a good general condition and able to tolerate aggressive treatment. Hence, the majority of the patients in our study had ESCC as the IMM. Despite the high performance status among the patients in our study, the complication rate was high (27%) and in line with previously reported complication rates after surgery for ESCC (Finkelstein et al. 2003).
Identification of a new subtype of prostate cancer spinal bone metastases associated with MSCC

We identified a new radiological pattern of prostate cancer spinal bone metastases that showed a myeloma-like appearance on MRI and was associated with a particularly poor outcome after surgery for MSCC. Furthermore, the myeloma-like radiological pattern was an independent prognostic factor for the risk of mortality after surgery for MSCC on multivariate Cox regression analysis. This subgroup of patients also had significantly reduced ambulatory function after surgery.

There have only been a few case-reports addressing this specific phenotype of prostate cancer bone metastases (Maharaj et al. 1986, Mathur et al. 2018, Idowu et al. 2018). Prostate cancer bone metastases with a myeloma-like radiological appearance have been suggested to be osteolytic (Idowu et al. 2018), and osteolytic activity has previously been linked to a poor prognosis in metastatic prostate cancer (Fizazi et al. 2014). However, the categorization of prostate cancer bone metastases as osteoblastic or osteolytic is probably an oversimplification, as the majority of metastatic lesions in our study were classified as mixed osteoblastic/osteolytic or osteolytic, with no difference between the myeloma-like and nonmyeloma-like groups.

Prostate cancer bone metastases have been demonstrated to be heterogeneous in their genomic, transcriptomic, proteomic, metabolic and morphologic profiles (Crnalic et al. 2010, Thysell et al. 2010, Robinson et al. 2015, Ylitalo et al. 2017, Iglesias-Gato et al. 2018, Quigley et al. 2018). We have previously identified three different molecular subtypes of prostate cancer bone metastases, named MetA-C (Thysell et al. 2019), and these subtypes have shown prognostic value and biological relevance in several separate patient cohorts (Thysell et al. 2022). The myeloma-like subtype was not related to these subtypes or to other known prognostic biological markers in metastatic prostate cancer, such as tumor cell proliferation, PSA immunoreactivity, androgen receptor immunoreactivity, and bone remodelling. Instead, differences were found between two gene sets that were upregulated in the myeloma-like bone metastases, those for the PI3-kinase signalling pathway and fatty acid metabolism, and two gene sets that were significantly downregulated, those for the epithelial-to-mesenchymal transition and hedgehog signalling in the myeloma-like group. These pathways are well-known oncogenic pathways related to metastatic progression and treatment resistance in metastatic prostate cancer that are being explored in order to find new treatments (Gonnissen et al. 2013, Piddock et al. 2017, Shorning et al. 2020, Scaglia et al. 2021 and Papanikolaou et al. 2021). Hence, this subtype of prostate cancer bone metastases may be the subject of new treatments in the future and deserves further investigation.
Limitations
The main limitations of our studies (studies I, II and III) are the retrospective nature, the relatively small sample size and the lack of control groups. The medical and surgical treatments were not randomized but were chosen according to the preference of the surgeon and the oncological teams. Furthermore, the long span of data collection creates another limitation as advances in both diagnostic techniques and adjuvant therapy may influence the primary tumour detection rate and classifications to specific subgroups and thus the treatment opportunities and therefore survival. Additionally, we measured mRNA expression in the morphological studies, which may not necessarily reflect biological activities.
Conclusions

• Patients with MSCC as the initial manifestation of malignancy represent a heterogeneous group with different tumour types and a wide range of expected postoperative survival, which highlights the importance of the diagnostic workup to select patients for surgery and adjuvant therapies.

• The SINS is helpful in assessing spinal instability in prostate cancer patients prior to surgery for MSCC but does not predict postoperative survival or neurological outcome.

• Patients with haematological malignancies and ESCC may have long survival durations after surgery for ESCC. The SINS has no predictive value for postoperative survival or ambulatory function. Ambulation prior to surgery is the most important predictor of postoperative survival and neurological outcome in these patients.

• The myeloma-like radiological pattern of spinal bone metastases in patients with prostate cancer is associated with particularly poor survival and neurological outcome after surgery for MSCC.

• A high KPS score and hormone naïvety are related to longer postoperative survival in prostate cancer patients with MSCC.

• Surgery for MSCC is associated with high morbidity rates. Only carefully selected patients may benefit from surgery.
Clinical implications

Our results highlight the importance of guidelines for the treatment of MSCC as the IMM. Knowledge of the differences in the prognosis regarding survival for these patients is important for clinicians to propose surgery only to patients who can benefit from it and to distinguish the subgroup of patients in whom the primary tumour diagnosis may be obtained after the initial workup from the subgroup of patients with CUP. The next step will be to explore the primary tumour detection rate and clinical outcomes in a multiregistry study on a national level.

Our results show that the SINS may be suitable for the evaluation of tumour-related spinal instability, but cannot be used for the estimation of prognosis regarding survival or neurological outcomes. More studies are needed to evaluate the SINS as an appropriate screening tool for the selection of patients who will benefit from surgery.

The positive effect of hormone naïvety on postoperative survival in prostate cancer patients with MSCC has previously been reported, and our results further confirm the validity of these findings. The clinical and morphological characteristics of this subgroup of patients with metastatic prostate cancer need further evaluation in larger series.

A novel radiological pattern of prostate cancer spinal bone metastases showing a myeloma-like appearance is associated with particularly poor outcomes after surgery for MSCC. Other palliative treatments should be offered to these patients rather than surgery. The tumour biology of this subtype also merits further investigation, with the possibility to aid future therapeutic developments.

Our data implicate the importance of studying the complex molecular mechanisms regulating bone metastases in tumour tissue obtained during surgery as well as the importance of studying clinical outcomes using larger patient materials.
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