

MRI and clinical assessment of patients with symptomatic spinal metastases

Marta Switlyk, MD
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Department of Radiology and Nuclear Medicine
Oslo University Hospital
Radiumhospitalet
Norway



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ABBREVIATIONS

ADC – apparent diffusion coefficient
ASA – American Society of Anesthesiologists
BPI – brief pain inventory
CRF – case report form
CT – computed tomography
DCE – dynamic contrast enhanced
DWI – diffusion weighted imaging
EPI – echo planar imaging
FOV – field of view
FSE – fast spin echo
GE – gradient echo
IG-IMRT – image-guided intensity-modulated radiotherapy
IR – inversion recovery
IT – inversion time,
KPS – Karnofsky performance score
Ktrans – time-dependent leakage
MRI – magnetic resonance imaging
MSCC – metastatic spinal cord compression
NICE – National Institute of Health and Clinical Excellence
OMED – oral morphine equivalent dose
RECIST – Response Evaluation Criteria in Solid Tumors
RT – radiotherapy
SCS – spinal canal stenosis
SE – spin echo
SI – signal intensity
SRE – skeletal related event
STIR – short tau inversion recovery
T – tesla
TE – echo time
TSE – turbo spin echo
TR – repetition time
UICC – International Union Against Cancer
V_p – plasma volume
WHO – World Health Organization

ABSTRACT

Spinal metastases are frequent manifestations of systemic neoplasia, and the vertebral column is one of the most common sites of skeletal metastases. Bone metastases often cause severe pain and may cause pathological fractures and metastatic spinal cord compression (MSCC). External beam radiotherapy (RT) is frequently used as the primary treatment modality for patients with spinal metastatic disease. Magnetic resonance imaging (MRI) is considered the most specific and sensitive method for imaging spinal metastases and is the primary investigation for suspected MSCC.

In two different studies, the association between pretreatment neurological status and MRI findings, and the association between post treatment pain response and MRI findings was explored. In the third study, we assessed whether clinical, laboratory and MRI parameters were predictive factors for survival in patients with spinal metastases.

The studies showed that the pretreatment degree of MSCC at MRI was significantly associated with the severity of neurological symptoms. We also identified a considerable number of patients with subclinical MSCC, which is important because identifying MSCC early is critical to prevent irreversible neurological deterioration. Furthermore, RT was shown to provide an effective local control of spinal metastases. The pain response rate to treatment did not differ in patients with and without pathological fractures, MSCC or any other recorded MRI findings. Lastly, our results confirmed that primary tumor histology and performance status were the major prognostic factors for survival in patients with spinal metastases and normal neurological function. Importantly, MRI-based extent of spinal metastatic disease had no impact on survival. The pretreatment albumin level was an important predictive factor that should be considered when analyzing survival in these patients.

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1 LIST OF PUBLICATIONS INCLUDED

PAPER I

Switlyk MD, Hole KH, Skjeldal S, Hald JK, Knutstad K, Seierstad T, and Zaikova O. MRI and neurological findings in patients with spinal metastases. *Acta Radiol* 2012;53:1164-72.

PAPER II

Switlyk MD, Bruland OS, Hald JK, Skjeldal S, Seierstad T, and Zaikova O. Radiotherapy for spinal metastases from breast cancer with emphasis on local disease control and pain response using repeated MRI. *J Bone Oncol* 2014;3:5-9.

PAPER III

Switlyk MD, Kongsgaard U, Skjeldal S, Hald JK, Knutstad K, Hole KH and Zaikova O. Prognostic factors in patients with symptomatic spinal metastases and normal neurological function. *Clin Oncol (R Coll Radiol)* 2015 Jan 23. pii: S0936-6555(15)00003-5. doi: 10.1016/j.clon.2015.01.002. [Epub ahead of print].

2 GENERAL INTRODUCTION AND REVIEW OF THE LITERATURE.

2.1 Spinal anatomy

The vertebra is composed of a body that contains cancellous bone with marrow and fat, covered by cortical bone; and the vertebral arch or posterior elements, which include pedicles, laminae, superior and inferior facets, transverse processes, and a spinous process (Yousem and Grossman, 2010).

The intervertebral canal contains the nerve root and its sleeve, the dorsal ganglion, fat and blood vessels (Jindal et al., 2011; Drake et al., 2007). The spinal cord contains 8 cervical, 12 thoracic, 5 lumbar, 5 sacral, and 1 coccygeal pairs of spinal nerves. The spinal canal contains the thecal sac surrounded by the epidural space, which contains epidural fat and large venous plexus. Within the thecal sac are the spinal cord, conus medullaris, and cauda equina, surrounded by cerebrospinal fluid (Jindal et al. 2011; Drake et al., 2007). The spinal cord extends from the medulla oblongata at the upper border of the atlas down to T12-L2 where it terminates in the conus medullaris. The cauda equina emanates from the conus medullaris and contains the nerve roots of the lumbar and sacral nerves.

The blood supply to the spinal cord depends on the location. In the cervical region the anterior and posterior spinal arteries are formed by branches that originate from the vertebral arteries. The midthoracic region (T3-T7) is supplied by intercostal branches from the aorta, subclavian arteries, and lumbar arteries. The lower thoracolumbar region is supplied by the artery of Adamkiewicz (Yousem and Grossman, 2010).

2.2 Pathomechanism of bone metastases

Skeletal metastases are common complications of malignancy. Several mechanisms of bone metastasis have been suggested: escape of cancer cells from a primary tumor, systemic embolization, adherence to bone marrow vascular endothelium, extravasation into the bone microenvironment, propagation within a hospitable environment and interaction with osteoblasts and/or osteoclasts (Paget, 1889; Mundy, 2002; Kozlow et al., 2005; Fili et al., 2009; Clines, 2013). Breast and prostate carcinomas have a high affinity for bone due to the molecular interactions between these cancer cells and host cells. Other cancers also metastasize to bone, but with lower incidence because these cell types do not possess the

properties necessary for the invasion and residence in the bone microenvironment (Fili et al., 2009; Mundy, 2002).

Traditionally, bone metastases are divided into two major categories: osteolytic and osteoblastic. Osteolytic metastases are thought to be caused by factors secreted by the tumor cells that activate osteoclasts. Osteoblastic metastases are thought to be caused by production of factors that stimulate osteoblast proliferation. At present, we know that osteolytic and osteoblastic metastases represent the two extremes and there is substantial evidence that both resorption and formation are activated in most bone metastases. Breast cancer metastases are mostly osteolytic whereas the prostate cancer metastases are mostly osteoblastic (Fili et al., 2009; Mundy, 2002).

Skeletal metastases have a tendency to develop in the axial skeleton in a distribution that correlates with the location of red bone marrow (Algra et al., 1992; Kricun ME, 1985). Within the skeleton, the vertebral column is the most commonly affected region. Historically, haematogenous dissemination to bone was believed to occur primarily through the valveless venous system in the spine - Batson's plexus (Batson, 1940). However, more recent work in animals has supported arterial embolization as the most common and important route of metastasis (Arguello et al., 1990; Cole and Patchell, 2008). The hematopoietic bone marrow of the vertebrae was found to be the target tissue for the cancer cells (Arguello et al., 1990). In the vertebral bodies, the tumor extends toward the posterior elements and centrally to the basivertebral veins. Cancer cells invade the basivertebral veins with secondary thromboses of venous plexuses. Tumor cells enter into the spinal canal through the foramina of the thrombosed basivertebral veins rather than destroying and invading through the cortical bone. Similarly, invasion from the vertebral body into the paravertebral soft tissue occurs through bone foramina of the external venous plexus (Arguello et al., 1990).

2.3 Radiological investigation - MRI

Since its introduction in the early 1980s, MRI has evolved to become the gold standard for evaluating the bone marrow of the spine and the soft tissues within and adjacent to the spinal canal. The magnetic field strengths that are commonly used for clinical MRI of the spine are 1.5 T and 3 T.

2.3.1 Basic principles of MRI

Human MR studies are almost always based on imaging of the hydrogen nucleus because it is highly abundant within human tissues. The hydrogen nucleus contains a single proton (atomic and mass number 1). Placed in an external magnetic field, the hydrogen nucleus precesses at its own resonant frequency known as the **Larmor frequency**. The Larmor frequency of the hydrogen nucleus is linearly related to magnetic field strength by the following equation:

$$\text{Larmor Frequency } (\omega_0) = \text{Magnetic Field Strength } (\mathbf{B}_0) \times \text{Gyromagnetic Ratio } (\gamma)$$

The gyromagnetic ratio of a nucleus is unique and does not vary in different magnetic field strengths. The gyromagnetic ratio for hydrogen nuclei is equal to $2.7 \times 10^8 \text{ rad s}^{-1} \text{ T}^{-1}$. At 1.5 T the Larmor frequency is $\approx 63.86 \text{ MHz}$. To stimulate the hydrogen nuclei, a radiofrequency (RF) pulse must be tuned to the Larmor frequency of the hydrogen nucleus. The frequency varies slightly, depending on the location of nuclei within the magnetic field. The ability to localize protons by variation in their Larmor frequency as response to graded magnetic field allows the spatial characterization in MRI (McRobbie et al., 2010; Yousem and Grossman, 2010).

2.3.2 Relaxation times

After exposing the hydrogen nucleus by a 90° RF excitation pulse with the same frequency as the Larmor frequency of the nucleus, the net magnetization vector is tilted from the z-axis (the axis of the external magnetic field) to the transverse x-y plane. The hydrogen nuclei then return to equilibrium by two simultaneous mechanisms: **T1 and T2 relaxation**.

T1 or spin-lattice relaxation. As the nucleus relaxes back to equilibrium after being excited by an RF pulse, there is an exponential increase in the amplitude of the z-direction magnetization until there is a complete return of the magnetization toward its baseline position. T1 relaxation time is defined as the time it takes for the hydrogen nucleus to recover 63% of its longitudinal (z-axis) magnetization.

T2 or spin-spin relaxation. In the same time the nucleus relaxes back to the equilibrium, there is an exponential decrease in the amplitude of the transversal magnetization in the x-y plane. T2 relaxation time is defined as the time for 63% of the transverse magnetization to be lost owing to its natural dephasing process. In general, phase dispersion is thought to be summation of three factors: T2 from spin-spin relaxation (true T2), T2' caused by main field inhomogeneities and T2'' caused by local susceptibility effects (iron, blood) (Yousem and Grossman, 2010).

2.3.3 Pulse sequences

MRIs are produced using pulse sequences. The two principle types of pulse sequences are **spin echo (SE)** and **gradient echo (GE)**. SE sequences use two RF pulses to create the echo, whereas GE sequences use a single RF pulse followed by a gradient pulse to create the echo. For both types sequences the echo is sampled and used to generate the MRIs.

2.3.3.1 Spin echo sequences

In **SE** sequences, a 90-degree pulse flips the longitudinal magnetization from the z axis into the transversal x-y plane. The following 180-degree pulse rephases the protons that are dephased due to magnetic field inhomogeneity. By varying the repetition time (TR, the time between consecutive 90-degree pulses), and the echo time (TE, the time between a 90 degree pulse and sampling of the echo), MR images with different degrees of T1- and T2-contrast can be obtained. **Fast spin echo (FSE) / turbo spin echo (TSE)** sequences are commonly used in spine MRI to speed up the acquisition of images (Yousem and Grossman, 2010; Kaplan et al., 2001).

T1-weighted MR images (TR <800 msec; TE <30 msec). A T1-weighted image is one where the contrast depends predominantly on the differences in the T1 times between tissues (Westbrook et al., 2005; McRobbie et al., 2010). Fat, proteinaceous fluid and subacute hemorrhage appear bright on these images. Most other soft tissues have an

intermediate to low SI and fluid has especially low SI. T1-weighted images are used to assess the marrow architecture, the fat content within masses, subacute hemorrhage and in conjunction with gadolinium contrast agents as the gadolinium shortens the T1 relaxation of tissue causing enhancing lesions to become bright on T1.

T2 weighted MR images (TR >2000 msec; TE >60 msec). A T2-weighted image is one where the contrast predominantly depends on the differences in the T2 times between tissues (Westbrook et al., 2005; McRobbie et al., 2010). Fluid appears bright on T2-weighted images. T2-weighted images are sensitive to the presence of increased water and can effectively visualize edema. Most pathological processes (tumor, infection, injury) are highlighted on T2-weighted images due to their increased water content, especially when the sequence is combined with fat suppression.

2.3.3.2 Gradient echo sequences

In **GE** pulse sequences, the magnetization vector of the protons is tipped off the z axis to the x-y plane, usually less than 90 degrees. As opposed to the 180-degree SE pulse, the rephasing gradient pulse follows the initial flip-angle magnetization. Due to the lack of 180° refocusing pulse, the GE sequences are more susceptible to magnetic field inhomogeneities than SE sequences.

On GE sequences, the selection of appropriate TE enables the creation of images where the contribution from fat and water protons is either additive (**in-phase images**) or subtractive (**out-phase images**). In tissues with an equal amount of water and fat, such as normal bone marrow, the SI will drop between in-phase and out-phase images. Dixon suggested in 1984 that in-phase and out-phase images could be combined to create images of just fat or water, known as **fat/water separation** (McRobbie et al., 2010). **Water-only** images provide excellent fat suppression and can be acquired with either T1- or T2-weighting.

2.3.3.3 Inversion recovery

The **inversion time (IT)** is the time between a 180° inversion pulse and 90° excitation pulse. IT can be set to various values to generate contrast or to null the signal of a specific tissue (Yousem and Grossman; Kaplan et al., 2001).

Short tau inversion recovery (STIR) (TR >2000 msec; TE >30 msec; IT =120 – 150 msec) is a fat saturation technique that results in markedly decreased SI from fat and increased SI from fluid and edema. As a result, this method is a sensitive tool for detecting most types of soft tissue and marrow pathology (Kaplan et al., 2001).

2.3.3.4 Diffusion-weighted imaging

Diffusion-weighted imaging (DWI) is a technique that allows noninvasive characterization of biological tissues based on measurements of the random microscopic motion of water protons (Brownian motion). The basis for the use of diffusion is that malignant tissues usually are more cellular than benign or normal tissue. Thus, this feature will result in higher SI of malignant disease on high b-value images with a corresponding low SI on ADC maps (Schmidt and Baur-Melnyk, 2013; Padhani and Gogbashian, 2011; Baur et al., 2001).

2.3.3.5 MRI perfusion

Dynamic contrast enhanced (DCE) MRI is an imaging technique that provides functional information on tumor vascularity and hemodynamics. This technique involves rapid intravenous injection of gadolinium and repeated acquisition of T1-weighted sequences to track the accumulation of contrast medium in the tissue. Pharmacokinetic modeling of contrast agent uptake can be applied to the measured SI changes (ΔSI) over time, allowing for the quantitative estimation of vascular characteristics. In a two-compartment kinetic model based on the exchange of contrast between the vascular and interstitial spaces, the contrast agent is initially assumed to be distributed in the blood plasma volume (V_p), with a time-dependent leakage (K_{trans}) into the interstitial space (Chu et al., 2013).

2.4 MRI of spinal metastases

MRI provides detailed information of the bone marrow and is highly sensitive to the presence and extraosseous growth of spinal metastases. Fat and water distribution in bone marrow, assessment of bone trabeculae, evaluation of bone edema and cell density and the study of vascularization can be combined to enable good detection and characterization of lesions (Vanel, 2009, Schmidt and Baur-Melnyk, 2013; Guillevin et al., 2007; Ollivier et al., 2007; Hanna et al., 1991; Husband et al., 2001; Li et al., 1988).

For bone metastasis screening, a combination of an unenhanced T1-weighted and STIR sequences has proven to be highly sensitive (Schmidt and Baur-Melnyk, 2013). Figure 2.1 shows an example of routine MRI protocol for assessment of spinal metastases. On T1-weighted images, tumor spread is identified by replacement of normal fat containing marrow, resulting in a hypointense focal signal. In infiltrative disorders, fat disappears in a diffuse, disseminated or solitary way. Fat-suppressed sequences such as STIR depict neoplastic lesions by virtue of the hyperintense signal due to increased water content within the tumor cells. Osteoblastic metastases can be depicted in STIR-sequences with variable SIs ranging from hypointense in dense sclerotic lesions to hyperintense when more cellular components are present (Schmidt and Baur-Melnyk, 2013; Vanel et al. 2009). In cases of suspected infiltration into surrounding tissue such as the spinal canal, the T2-weighted images are useful to improve lesion delineation further (Schmidt and Baur-Melnyk, 2013).

Additional sequences relevant for the evaluation of bone metastases include T2-weighted sequences with fat suppression, Dixon imaging and susceptibility weighted sequences. Susceptibility weighted sequences are sensitive to susceptibility dephasing induced by normal trabecular bone. If the bone trabeculae have been destroyed, the SI will be higher than in preserved parts of the bone (Padhani and Gogbashian, 2011; Schmidt et al., 2009; Messiou and deSouza, 2010; Vanel et al., 2009).

DWI is increasingly being used in the context of bone marrow therapy monitoring. Therapy assessment using DWI is made by observing changes in the extent, symmetry and SI on high *b*-value images and ADC maps, seeking correlations on morphological sequences. When bone marrow disease is treated successfully, tumor cell death usually results in increased water diffusivity manifested as increased ADC (Padhani and Gogbashian, 2011; Biffar et al., 2010). DCE MRI is another imaging technique that shows promising results for the assessment of therapy response. A recent study by Chu et al. showed that changes in blood perfusion, particularly the vascular parameter *V_p*, reflected tumor responses to RT in bone marrow (Chu et al., 2013). The decrease in *V_p* observed after RT most likely represents the diminished vascularity of successfully treated spinal metastases. The increase in *V_p* observed in cases of treatment-failure supports the observation that progressing spinal metastases secrete angiogenesis-inducing factors (Chu et al., 2013).

A summary of MRI sequences for detection and follow-up of spinal metastases is listed in Table 2.1.

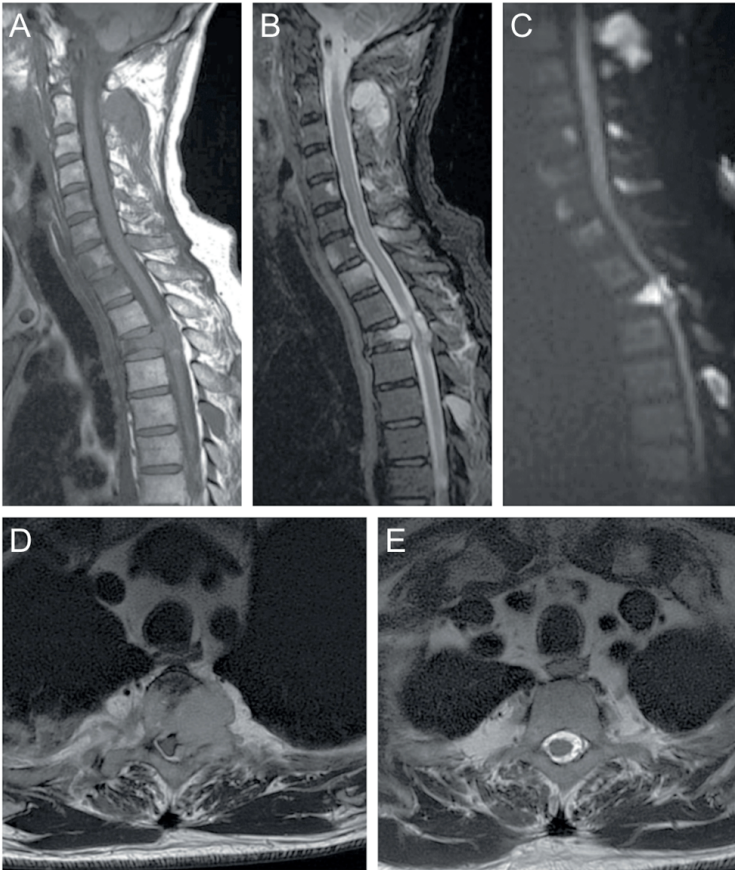


Fig 2.1. Routine MRI protocol for evaluation of spinal metastases and MSCC comprised of unenhanced sagittal T1-weighted (A), STIR (B), DWI (C) and axial T2-weighted sequences (D, E).

Table 2.1. Summary of MRI sequences used for detection and follow-up of vertebral metastases.

MRI sequences for routine detection and follow-up of spinal metastases.
<ul style="list-style-type: none">• Unenhanced sagittal T1-weighted images of the whole spine (or similar contrast e.g. Dixon).• Sagittal STIR of the whole spine (or similar contrast).• Sagittal DWI (whole spine, detection / baseline scan and follow-up). • Optionally, axial T2-weighted images over the region of interest (spinal stenosis, epidural or paraspinal tumor growth).• Optionally, DCE perfusion (whole spine, detection/ baseline scan and follow-up).• Optionally, contrast enhanced sagittal T1-weighted images of the whole spine or Ax T1-weighted images over the lesion in case of intramedullary or leptomeningeal metastases.

2.5 Skeletal-related events

Patients with bone metastases have a high risk for potentially debilitating skeletal-related events (SREs) that can substantially reduce their quality of life (Lipton, 2012). The SREs associated with bone metastases include bone pain requiring palliative RT, pathological fracture, the need for bone surgery to treat or prevent an impending pathological fracture, spinal cord compression, and hypercalcaemia of malignancy (Fig. 2.2) (Lipton, 2012).

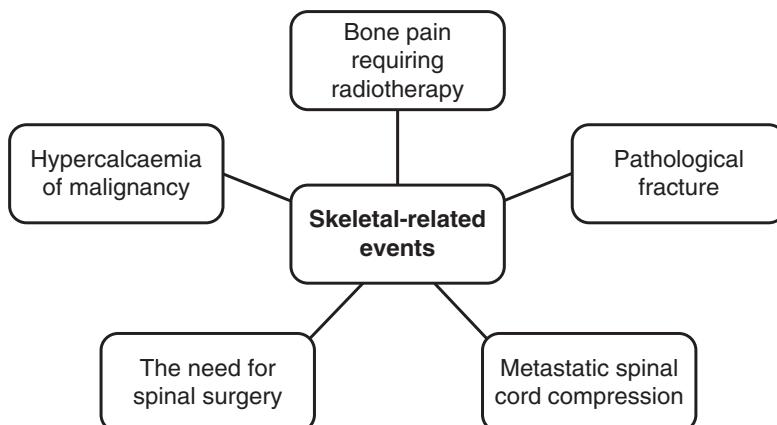


Fig. 2.2. Skeletal-related events.

2.5.1 Metastatic spinal cord compression

2.5.1.1 Definition

Metastatic spinal cord compression (MSCC) is usually defined as a compression of the dural sac and its contents (spinal cord and/or cauda equina) by the epidural tumor mass (Loblaw et al., 2005; Cole and Patchell, 2008). The term MSCC is widely used in the literature and frequently contains both radiological and clinical criteria.

Definitions of MSCC differ in various publications and may include the following: radiological criteria alone sufficient for the diagnosis of MSCC (Husband et al., 2001; Levack et al., 2002), including compression of nerve roots running within the spinal canal (Helweg-Larsen et al., 2000); radiological findings with neurological symptoms or pain (Loblaw and Laperriere, 1998; Patchell et al., 2005); and radiological findings with diminished motor function (Rades et al., 2005). The variety of MSCC definitions causes an inconsistency in reporting outcomes of radiological, surgical and radiotherapeutic studies.

In general, the presence of radiological features at the level of clinical features is defined as a **manifest MSCC** whereas the presence of radiological features in the absence of clinical features is defined as a **subclinical (occult) MSCC**.

2.5.1.2 Pathomechanism of MSCC

There are two ways metastatic tumors can reach the epidural space and compress the spinal cord. The less common way is growth of paravertebral tumor directly into the spinal canal through an intervertebral foramen. This process causes approximately 15% of MSCC and is commonly associated with lymphomas and neuroblastomas. However, in more than 85% of patients the tumor reaches the spinal cord by the hematogenous route. The metastasis grows in the bone and subsequently spreads to the epidural space causing compression of the spinal cord. The compression can be gradual; however, acute compression can occur, often when there is destruction of the vertebral cortical bone, vertebral body collapse and displacement of bone fragments into the epidural space (Cole and Patchell, 2008; Gilbert et al., 1978).

MSCC damages the cord by direct compression causing demyelination and axonal damage and by secondary vascular compromise. Vascular damage is the most important mechanism. At an early stage of compression, the edema and associated neurological dysfunction can be partially or completely reversed by giving corticosteroids. In the terminal stages arterial blood flow to the spinal cord is impaired and causes cord ischemia and irreversible damage (Cole and Patchell, 2008; Kato et al., 1985).

The frequency of the location of compression site in the spinal column is proportional to the relative bone mass and blood flow. Thus, approximately 15% of MSCC occur in the cervical spine, 60% occur in the thoracic spine and 25% are found in the lumbosacral spine (Cole and Patchell, 2008; Bach et al., 1990; Constans et al., 1983; Helweg-Larsen, 1996). Multiple sites of spinal cord compression are observed in 20-35% of patients with MSCC (Cole and Patchell, 2008; Van der Sande and Boogerd, 1990; Schiff et al., 1997).

2.5.1.3 Clinical presentation and management of MSCC.

Back pain is the earliest and most common symptom of MSCC. A prospective cohort study by Helweg-Larsen and Sorenson showed that 88% of the patients with MSCC reported back pain (Helweg-Larsen and Sorenson, 1994). MSCC-associated back pain can take several forms. Localized pain is confined to the region of the spine affected by metastases and is frequently present when the bone metastases stretch the periosteum or invade soft tissues. Radicular pain is caused by the compression or invasion of the nerve roots. Mechanical back pain is caused by vertebral body collapse or other pathological fractures.

Motor deficit is the second most common symptom and is present in 37-87% of the patients (Cole and Patchell, 2008; Bach et al., 1990; Constans et al., 1983; Gilbert et al., 1987; Helweg-Larsen and Sorenson, 1994). The magnitude of motor deficits depends on the location of the spinal cord compression. Sensory deficits rarely occur before motor deficits or pain, although approximately 70% of the patients can have some type of sensory deficits at the time of diagnosis (Cole and Patchell, 2008; Gilbert et al., 1987; Helweg-Larsen and Sorenson, 1994). Autonomic symptoms occur late in the progression of MSCC and isolated bowel or bladder dysfunction is rarely the presenting symptom (Cole and Patchell, 2008; Bach et al., 1990; Gilbert et al., 1987).

The role of the National Institute of Health and Clinical Excellence (NICE) is to produce evidence-based guidance and advice for health and social care practitioners in the United Kingdom and internationally (<http://guidance.nice.org.uk/CG75/Guidance/pdf/English>; <https://www.nice.org.uk/Guidance/QS56>). Patients at high risk of developing bone metastases (known cancer of the lung, breast, prostate or myeloma), with diagnosed bone metastases, or patients with cancer who present with spinal pain should be informed about the symptoms of MSCC.

According to the NICE guidelines pain suggestive of spinal metastases includes progressive spinal pain, severe unremitting spinal pain, localized spinal tenderness or nocturnal spinal pain preventing sleep. Furthermore, symptoms suggestive of MSCC includes progressive spinal pain, severe unremitting spinal pain, localized spinal tenderness or nocturnal spinal pain preventing sleep, spinal pain aggravated by straining, pain described as “band like”, neurological symptoms (radicular symptoms, any limb weakness, difficulty in walking, sensory loss, and bladder or bowel dysfunction) and neurological signs of spinal cord or cauda equina compression (<http://guidance.nice.org.uk/CG75/Guidance/pdf/English>; <https://www.nice.org.uk/Guidance/QS56>).

The NICE guidelines recommend MRI as the primary investigation in MSCC. MRI of the whole spine should be performed within 1 week in patients with spinal pain suggestive of spinal metastases and within 24 hours or immediately in the case of spinal pain and neurological symptoms suggestive of MSCC. Definitive treatment should be started ideally within 24 hours of the MSCC diagnosis.

2.5.1.4 MRI-based grading of MSCC

A validated, uniform MSCC grading system provides consistent reporting in the radiation, surgery, and radiology literature (Bilsky et al., 2010; Gerszten et al., 2007). Different grading systems have been proposed in the current literature (Bilsky et al., 2010; Lurie et al., 2008).

A 4-grade, MRI-based grading system based on the degree of impingement of the thecal sac and spinal cord compression has previously been developed. In this system, grade 0 indicates bone involvement only; grade 1, epidural impingement; grade 2, spinal cord compression, but cerebrospinal fluid visible and grade 3, spinal cord compression, but no cerebrospinal fluid observed (Bilsky et al., 2010; Bilsky et al., 2001).

A more recent study proposed a qualitative, 6-point grading system to standardize MSCC reporting (Bilsky et al., 2010). This grading system is based on the axial T2-weighted images and was validated and found to be a sensitive, reliable grading device that provided important consistency when describing MSCC. On this new scale, the original grade 1 was subclassified into grades 1a, 1b, and 1c to reflect different degrees of epidural impingement. The subclassification of grade 1 impingement improved the original grading system particularly for stereotactic radiosurgery requirements.

A quantitative grading system for assessing the severity of spinal stenosis has previously been reported in the literature. Lurie *et al.* proposed a 4-grade scale for evaluating lumbar spinal stenosis (Lurie et al., 2008). Mild stenosis represented a compromise of the area $< 1/3$ of its normal size. A moderate stenosis was a compromise between $1/3$ and $2/3$ of its normal size and severe stenosis was defined as a compromise $> 2/3$ of its normal size. This quantitative grading system was primarily suggested for the evaluation of degenerative spinal canal stenosis; however, this scale can also be useful in the assessment of epidural tumor extent.

2.5.1.5 Subclinical MSCC

The term subclinical MSCC is used in the literature to describe the discrepancy between radiographic findings and neurological status. Some studies have included any degree of epidural space invasion in the definition of subclinical MSCC (Venkitaraman et al., 2007; Venkitaraman et al., 2010). Others have used separate terms for thecal impingement and compression of the spinal cord and the cauda equina (Bayley et al., 2001).

The early diagnosis and treatment of patients with MSCC is important for the preservation of neurological function. The detection of occult MSCC before clinical manifestations such as neurological deficits may provide important lead-time for early treatment and could reduce irreversible neurological deterioration (Venkitaraman et al., 2007; Husband et al., 2001). Several studies support the irradiation of subclinical cord compression as a method of preserving neurological function. There are predictive risk models emerging that may help to define a population of patients at higher risk of developing spinal cord compression. However, the optimal screening strategy, population, and intervention have not been elucidated (Loblaw et al., 2005; Bayley et al., 2001; Talcott et al., 1999). Previous studies have examined factors that can predict MSCC (Bayley et al., 2001). The findings of Bayley et al. were consistent with those of Talcott et al., which demonstrates that back pain was not predictive of MSCC (Loblaw et al., 2005; Bayley et al., 2001; Talcott et al., 1999).

2.5.1.6 Neurological status and prognosis

The most important prognostic indicator of ambulatory outcome is the pretreatment motor function (Cole and Patchell, 2008; Rades et al., 2006; Rades et al., 2008, Klimo et al., 2005; Sioutos et al., 1995; Maranzano and Latini, 1995; Helweg-Larsen et al., 2000). Husband et al. examined 301 patients with MSCC and found that approximately 70% of the patients had loss of neurological function between the onset of symptoms and the start of treatment. The majority of delays were caused by lack of symptom recognition by the patient and diagnostic delay at the general practitioner or general hospital (Loblaw et al., 2005; Husband et al., 1998).

Another important predictive factor is the time to developing motor deficit. The prospective study of Rades et al. found that the patients with the slowest development of neurological dysfunction before RT had better functional outcome compared to patients with faster development of motor deficits (Loblaw et al., 2005; Rades et al., 2002). Poor prognosis after rapid development of motor dysfunction can be explained by disruption of the arterial blood flow, which may lead to spinal infarction. A slower development of motor deficits is thought to be a result of venous congestion, which is more likely to be reversible (Rades et al., 2007). The dynamics of the development of motor deficits may also reflect the velocity of tumor growth (Rades et al., 2006).

Previous studies have shown that a longer time interval between cancer diagnosis and cord compression independently predicts improved survival (Loblaw et al., 2005; Rades et al.,

2006). The negative prognostic impact of a shorter interval between tumor diagnosis and MSCC likely reflects the faster growth of more aggressive tumors.

2.5.2 Vertebral fractures

Vertebral fractures in the oncological population frequently result from tumor growth in the bone marrow and/or treatment. Metastatic vertebral body collapse is one of the major causes of severe back pain and neurological compromise (Ebihara et al., 2004). Depending on the force applied and the vertebral body strength, fracture severity varies from a small peripheral fracture to a complete vertebral body collapse. Most vertebral fractures occur in the mid-thoracic and thoracolumbar regions (Griffith et al., 2013). Several biomechanical and clinical studies have attempted to estimate fracture risk due to metastatic spinal disease (Asdourian et al., 1990; Dimar et al., 1998; Ebihara et al., 2004; Rose et al., 2009). Bone mineral density, tumor size in the vertebral body, endplate involvement, tumor location in the lower thoracic and lumbar spine and destruction of the costovertebral joints have been shown to be important predictors of impending vertebral fracture (Ebihara et al., 2004; Asdourian et al., 1990; Rose et al., 2009; Oda et al., 2002).

RT is the standard treatment for bone metastases and MSCC. Fractures that occur at irradiated skeletal sites remain a major source of morbidity, can reduce the clinical response rate to treatment, and can have fatal consequences (Willey et al., 2013).

Osteoporosis and osteopenia are common among women receiving adjuvant therapy for breast cancer, also without skeletal involvement (Lipton, 2012; Brufsky, 2008). These conditions can predispose patients to fragility fractures and SREs. Similar to the situation with hormone therapy for breast cancer, androgen-deprivation therapy for prostate cancer can undermine skeletal reserves and increase the risk of fractures (Lipton, 2012).

2.5.3 Bone pain

Pain is the most common presenting symptom in patients with spinal metastases. Local mechanisms that can cause bone pain include release of chemical mediators, increased pressure within the bone, microfractures, stretching of the periosteum, reactive muscle spasm, and compression of nerves due to epidural tumor or fracture (Vakaet et al., 2004; Saarto et al., 2002).

RT effectively relieves pain from localized sites of skeletal metastases (Chow et al., 2013; Chow et al., 2001; Sze et al., 2003). The mechanism by which RT alleviates pain is not completely understood. The rapid onset of pain relief within days is most likely attributed to the decrease of chemical pain mediators, whereas tumor shrinkage and recalcification of osteolytic lesions can contribute to the longer-lasting effect (Saarto et al., 2002).

Numerous studies have evaluated the benefits of RT and different RT regimens (Chow et al., 2012; Chow et al., 2007; Cole, 1989; Gaze et al., 1997; Nielsen et al., 1998; Roos et al., 2005; Sze et al., 2003; Wu et al., 2003; Steenland et al., 1999; Sande et al., 2009; McQuay et al., 1997). However, because of the varying endpoints used, different results can be obtained from different trials, making comparisons of pain response after RT difficult (Chow et al., 2012). In 2002, the International Bone Metastases Consensus Working Party published its first consensus on palliative RT in an attempt to encourage investigators to adopt a set of endpoints for future clinical trials in bone metastases (Chow et al., 2002). The consensus was updated in 2012 (Chow et al., 2012).

2.6 Treatment of spinal metastatic disease

2.6.1 Corticosteroids

Corticosteroids are the first line of treatment for most patients with MSSC (Cole and Patchell, 2008). An improvement in neurological status is often documented after steroid administration (Sorensen et al., 1994). The mechanism of action of corticosteroids in this setting is not completely understood, but a reduction in peritumoral spinal cord edema is at least partially responsible (Jacobs et al., 2001). The optimum dose of corticosteroids administered is also debated. It is standard practice in Norway to administer 16 mg of methylprednisolone or 4 mg of dexamethasone every 6 hours. Medical complications such as exacerbation of diabetes mellitus, hypertension, immune suppression, gastric ulceration, acute delirium and wound infection must be carefully monitored (Jacobs et al., 2001). Although it is common practice to administer steroids prior to RT, Maranzano et al. reported that corticosteroids might not be necessary for patients with good motor function (Maranzano et al., 1996; Loblaw et al., 2005; Cole and Patchell, 2008).

2.6.2 Radiotherapy

RT is considered to be the mainstay of therapeutic intervention in patients with spinal metastases (Jacobs et al., 2001; Katagiri et al., 1998; Maranzano et al., 1995). Despite general acknowledgement of the effectiveness of RT, the optimal dose and the selection of treatment regimens are controversial. The main question is whether a protracted schedule of moderate or low daily doses is better than high daily doses with a shorter course of treatment (Cole and Patchell, 2008). The factors to consider when prescribing palliative RT for bone metastases are presented in Table 2.2 (Chow et al., 2013). The common RT doses usually extend from 8-20 Gy given in 1-5 fractions to 30-40 Gy given in 10-20 fractions.

Table 2.2. The factors to consider when prescribing palliative radiotherapy for bone metastases (Chow et al., 2013).

Single-fraction radiotherapy	Multifraction radiotherapy
<ul style="list-style-type: none">• Indication: "pain relief"• Short life expectancy• Concomitant visceral metastases• Poor performance status• Inflammatory pain• Aspects of cost and inconvenience	<ul style="list-style-type: none">• Indication: "local tumor control"• Expected long term survival• Predominantly bone metastases• Good performance status• Neuropathic pain and MSCC• Postoperative radiotherapy

The response to RT reflects the parameters of pain relief (1) and functional status (2).

(1) RT is effective in providing relief from painful bone metastases (all locations in the skeleton); 50-80% of the patients experience reduced pain, and 20-50% of the patients report complete pain relief (Hartsell et al. 2005). Several randomized controlled trials have compared different RT doses for the treatment of uncomplicated metastatic bone pain. These have consistently shown that short course treatment or single doses are as effective in producing pain relief as longer fractionated courses (Chow et al., 2007; Cole, 1989; Gaze et al., 1997, Nielsen et al., 1998; Roos et al., 2005; Sze et al., 2003; Wu et al., 2003; Steenland et al., 1999; Sande et al., 2009; McQuay et al., 1997; Hoskin, 2012). Single-fraction RT should be considered in patients with limited survival prognosis.

(2) A functional response to RT alone (full recovery or preservation of walking ability) has been reported in 66-88% of the patients (Jacobs et al., 2001; Maranzano et al., 1995; Katagiri et al., 1998). In general, the patient's pretreatment functional status is known as the most important prognostic indicator. Gilbert et al. reported that only 5% of the patients that initially were paralyzed regained gait function (Gilbert et al, 1978). However, Helweg-Larsen showed that 21-28% of the initially paralyzed or paraplegic patients recovered gait function (Helweg-Larsen, 1996). In some of the patients, recovery can be delayed for a long period after RT, so the observed rate of recovery depends upon the length of follow-up (Helweg-Larsen, 1996). Different trials have been conducted to evaluate dose fractionation schedules in patients with complicated bone metastases, such as those presenting with neuropathic pain, at risk of fracture, and MSCC. In these circumstances, multiple fractions may have increased efficacy, especially in those with better prognosis (McDonald et al., 2014; Roos et al., 2005; Loblaw et al., 2012).

Numerous reports have evaluated predictive factors for survival after RT in patients with spinal metastases. An accurate prediction of survival can guide health care professionals in choosing optimal treatment for patients with symptomatic spinal metastases (Chow et al., 2006). For patients with a short expected survival, a RT schedule with a short overall treatment time is preferable, if it will provide equivalent functional outcomes and pain relief as the more protracted schedules. For patients with a longer expected survival, the RT schedule associated with the best functional outcomes and local control of spinal metastases will be the most appropriate (Rades et al., 2006).

Several independent predictors of survival have been identified for patients with spinal metastases treated by RT (Table 2.3). In most studies, performance status and visceral metastases were significant predictive factors for survival (van der Linden et al., 2005; Rades et al., 2012; Douglas et al., 2012; Rades et al., 2013; Rades et al., 2006; Mizumoto et al. 2008). In studies that included patients with a variety of cancers, the anatomic site of the primary tumor was an important predictor for survival (van der Linden et al., 2005; Rades et al., 2006; Kataoka et al., 2012; Mizumoto et al., 2008; Rades et al., 2013). In reports that included patients with neurological dysfunction, the pretreatment ambulatory status and time to the development of motor deficits were statistically significant (Rades et al., 2006; Rades et al., 2012; Douglas et al., 2012; Rades et al., 2013; Weber et al., 2013; Rades et al., 2007).

Table 2.3. Prognostic factors for survival after radiotherapy for spinal metastases - review of the literature.

Study	Primary diagnosis	Prognostic factors for survival (multivariate analysis)	Number of patients
Van der Linden <i>et al.</i> ; 2005	All diagnoses	Performance status, histology, visceral metastases.	342
Rades <i>et al.</i> ; 2006	All diagnoses	Histology, visceral metastases, other bone metastases, pretreatment ambulatory status, time to developing motor deficits, interval between tumor diagnosis and MSCC.	1852
Rades <i>et al.</i> ; 2012	Non-small cell lung cancer	Performance status, pretreatment ambulatory status, visceral metastases, time to developing motor deficits.	356
Douglas <i>et al.</i> ; 2012	Myeloma	Performance status, pretreatment ambulatory status.	216
Douglas <i>et al.</i> ; 2012	Unknown primary	Performance status, pretreatment ambulatory status, visceral metastases, time to developing motor deficits.	182
Rades <i>et al.</i> ; 2012	Colorectal cancer	Performance status, pretreatment ambulatory status, visceral metastases, time to developing motor deficits.	121
Rades <i>et al.</i> ; 2012	Prostate cancer	Performance status, ambulatory status, other bone metastases, visceral metastases, interval from tumor diagnosis to RT.	436
Kataoka <i>et al.</i> ; 2012 ¹	All diagnoses	Histology, visceral metastases, disease-free interval before spinal metastasis, other bone metastases.	143
Rades <i>et al.</i> ; 2013	Breast cancer	Performance status, pretreatment ambulatory status, other bone metastases, visceral metastases, interval from cancer diagnosis to RT, time to developing motor deficits.	510
Weber <i>et al.</i> ; 2013	Prostate cancer	Number of involved extra-spinal organs, performance status, interval from cancer diagnosis to RT, pretreatment ambulatory status.	95
Rades <i>et al.</i> ; 2006	Breast cancer	Performance status, visceral metastases, deterioration of motor function after RT, rapid development of motor deficits.	335
Mizumoto <i>et al.</i> ; 2008	All diagnoses	Age, performance status, histology, previous chemotherapy, visceral metastases, multiple bone metastases, serum calcium level.	544
Weber <i>et al.</i> ; 2013	Breast cancer	Number of involved extra-spinal organs, performance status, pretreatment ambulatory status, time to developing motor deficits.	145
Rades <i>et al.</i> ; 2013	All diagnoses	Performance status, histology, bone metastases, visceral metastases, interval from cancer diagnosis to development of MSCC, time to developing motor deficits, pretreatment ambulatory status.	2029
Rades <i>et al.</i> , 2012	Breast cancer	Involvement of 1-2 vertebrae, pretreatment ambulatory status, other bone metastases, visceral metastases, time to developing motor deficits.	504
Rades <i>et al.</i> , 2007	Unknown primary	Visceral metastases, other bone metastases, pretreatment ambulatory status, slower development of motor deficits.	143
Rades <i>et al.</i> , 2014	All diagnoses	Number of involved extra-spinal organs, gender, primary tumor type, interval from cancer diagnosis to RT, pretreatment ambulatory status, time to developing motor deficits.	552
Rades <i>et al.</i> , 2014	Renal cell carcinoma	Number of involved extra-spinal organs, the interval from cancer diagnosis to RT, pretreatment ambulatory status.	69
Pointillart <i>et al.</i> , 2011 ¹	All diagnoses	Primary tumor type, performance status, ASA score, pain	142
Rades <i>et al.</i> , 2014	All diagnoses, elderly patients	Age, performance status, primary tumor type, pretreatment ambulatory status, other bone metastases, visceral metastases, the interval from cancer diagnosis to RT, time to developing motor deficits.	1128
Bollen <i>et al.</i> , 2014 ¹	All diagnoses	Performance status, visceral metastases, brain metastases	1043

¹both surgical treatment and radiotherapy

2.6.3 Surgery

Hematogenously disseminated disease to the spine is by definition not curable and represents stage IV disease. Thus, the goal of surgical therapy of metastatic spinal tumors is related primarily to symptom palliation and improvement of quality of life. The indications to surgery in spinal metastatic disease are controversial (Bauer, 2005), but surgery may preserve neurological function in selected patients (Patchell et al., 2005). Of the non-ambulatory surgical patients, 70-75% regained ambulatory status and half of the patients with severe paraparesis became completely ambulatory (Abrahm, 2004). Pain relief after surgery was reported in 85-94% of patients (Abrahm, 2004; Harrington, 1988). Recently, there has been a shift in international orthopedic oncology towards operative management of spinal metastases. The concept of surgical stabilization to provide pain relief and to treat progressive deformity has been introduced, and the clinical results favor these interventions (Kurth, 2012). However, surgery is not an appropriate treatment for many patients with spinal metastases (Zaikova et al., 2011).

3 AIMS OF THE STUDY

In the broader perspective, this thesis will investigate the performance of MRI in patients with symptomatic spinal metastases and the clinical assessment of these patients.

The specific objectives were:

- To assess utility of MRI in evaluating patients with symptomatic spinal metastases with emphasis on the association between pretreatment neurological status and MRI features (Paper I).
- To evaluate treatment response after RT for spinal metastases in breast cancer with emphasis on the association between pain response and MRI findings (Paper II).
- To evaluate clinical, laboratory and MRI parameters as potentially predictive factors for survival after RT for painful spinal metastases (Paper III).

4 STUDY DESIGN AND PATIENTS

Papers I-III are based on the evaluation of a dataset from a clinical prospective single-institution cohort study that included patients with symptomatic spinal metastases admitted for RT or surgery to our institution from February 2007 to December 2008. All patients underwent MRI examinations of the whole spine prior to the treatment. The patients included in Paper II underwent additional post-treatment MRI of the spine. The MRI studies were evaluated retrospectively. The information obtained from the medical records included age, gender, primary cancer histology, RT regimens, and ongoing systemic treatment (high-dose corticosteroids, chemotherapy, bisphosphonates and hormone therapy). In Paper III, laboratory parameters (albumin and hemoglobin) and the number of extra-spinal bone metastases and visceral metastases were also recorded.

The Regional Ethics Committee approved the study and written informed consent was obtained from all patients.

All patients were interviewed before the treatment. Two months after starting treatment, the research nurse contacted patients and completed the CRF.

The inclusion criteria for Paper I were first-time admittance for palliative RT or surgery for symptomatic spinal metastases, available pretreatment MRI of the entire spine and age above 18 years. A total of 284 patients were included in the study. We excluded patients who received RT after surgery, in-field re-irradiation, patients with other metastases that could affect neurological or ambulatory status, patients with prevertebral tumors with direct ingrowth to the vertebral bodies, and patients with meningeal and intramedullary metastases.

The inclusion criteria for Paper II were first-time admittance for RT for spinal metastases from breast cancer, no motor deficit prior to RT, survival for more than 6 months after RT, available pre- and post-treatment MRI of the vertebral column, and age above 18 years. The pretreatment MRIs were performed within 2 months prior to RT. The post-treatment MRIs were performed within 2 to 6 months of the RT. A total of 32 patients were included in the study. The exclusion criteria were the same as for Paper I.

The inclusion criteria for Paper III were first-time admittance for palliative RT for painful spinal metastases, no motor deficit prior to RT, available pretreatment MRI of the entire spine, and age above 18 years. A total of 173 patients were included in the study. The exclusion criteria

were the same as for Paper I. All patients with primary hematological malignancies were also excluded.

The flow of the study cohort is presented in Figure 4.1.

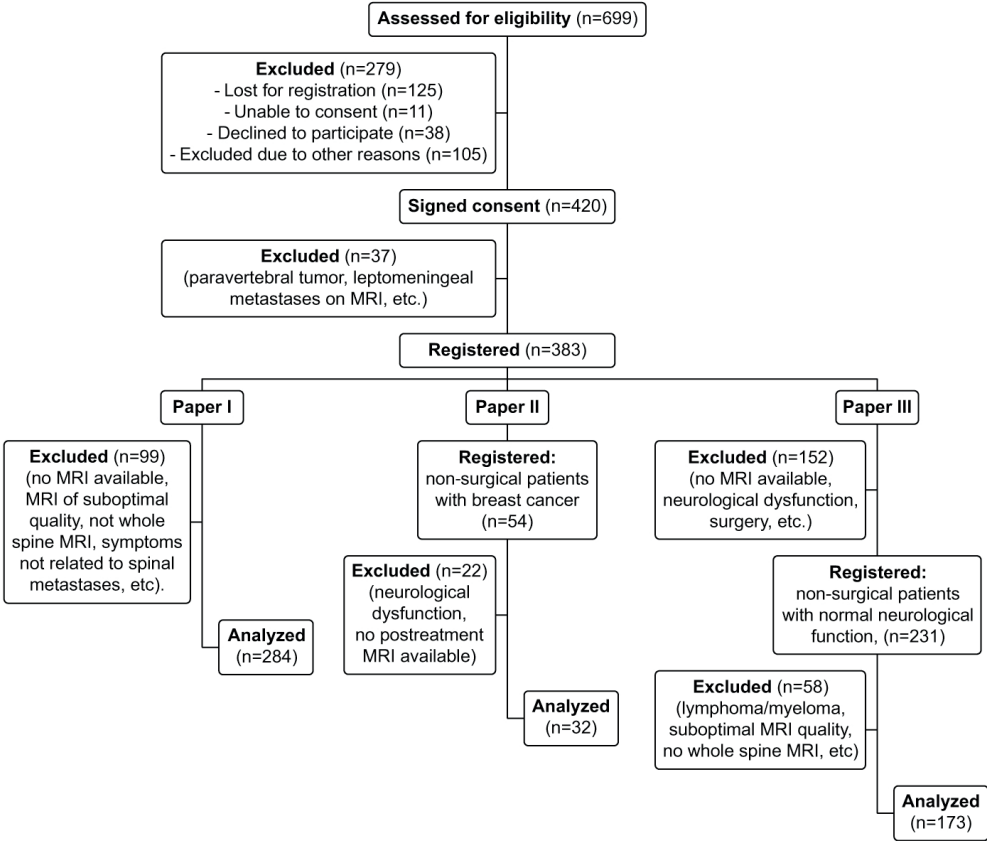


Fig. 4.1. The flow of the study cohort.

5 METHODS

5.1 MRI-based grading of MSCC

The extent of epidural tumor was graded both qualitatively and quantitatively using two MRI-based scales; a 6-point MSCC-scale (Bilsky et al., 2010) and a 4-point scale to define spinal canal narrowing (Lurie et al., 2008). The 6-point MSCC scale was an anatomy-based qualitative grading system, as shown in Fig. 5.1. This scale was used to evaluate patients with lesions at the level of the spinal cord.

The 4-point spinal canal narrowing scale was an area-based, semi-quantitative scoring system. Narrowing of the central spinal canal was classified using the following categories: “none” indicated bone-only disease, “slight” indicated a reduction of 1/3 or less in the cross-sectional area of the spinal canal, “moderate” indicated a 1/3 to 2/3 decrease in the cross-sectional area of the spinal canal, and “severe” indicated a reduction of 2/3 or more in the cross-sectional area of the spinal canal. To evaluate spinal canal narrowing, the cross-sectional area of the spinal canal at the affected level (measured on the axial images) was compared with the cross-sectional area of the spinal canal at the level immediately above or below the compression. This grading system was used to evaluate patients with lesions at or below the level of the spinal cord.

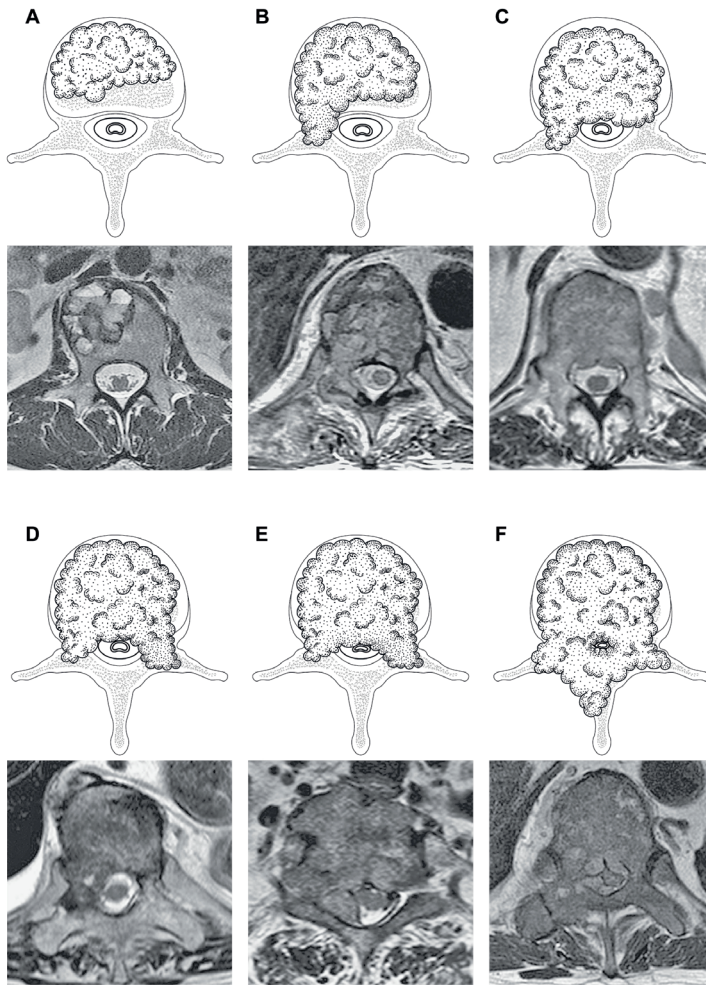


Fig. 5.1. The 6-point MSCC scale. Grade 0, bone-only disease (A); grade 1a, minor infiltration to the epidural space (B); grade 1b, tumor compressing the dural sac (C); grade 1c, contact with the spinal cord (D); grade 2, spinal cord compression, visible cerebrospinal fluid in the dural sac (E); grade 3, spinal cord compression, cerebrospinal fluid not visible (F).

5.2 Assessment of neurological function

The severity of neurological compromise was recorded using the Frankel scale (Frankel et al., 1969). The Frankel scale classifies patients using the following grades: *grade A*, no motor or sensory function; *grade B*, preserved sensation only, no motor function; *grade C*, non-ambulatory, wheelchair-bound but with some motor function; *grade D*, ambulatory, but with some motor deficit; and *grade E*, normal motor function. The patients with normal motor function were assigned a Frankel score of E. The patients with neurological dysfunction in the upper extremities due to metastases in the cervical spine were assigned a Frankel score of D. The ambulatory patients with known minor neurological impairment due to causes other than spinal metastases (e.g. sequelae of trauma, poliomyelitis, and cerebral stroke) were assigned a Frankel score of E.

5.3 Assessment of pain

The validated Norwegian version of the BPI was used for the evaluation of pain intensity (Klepstad et al., 2002) by assessing the worst pain, average pain and least pain experienced during the previous 24 hours in addition to “pain right now”. A numerical rating scale was used where “0” was “no pain” and “10” was “worst imaginable pain”. The worst pain experience was used as the principal outcome measure. The details on opioid consumption during the previous 24 hours including the drug name, daily dose, and administration route were recorded. All opioids were converted into the OMED. In addition, the following 4 levels of analgesic-drugs use were recorded in all patients: no analgesic use, non-opioid analgesics (e.g., a nonsteroidal anti-inflammatory drug or paracetamol), weak opioids (e.g., codeine) and strong opioids (e.g., morphine, oxycodone) (Cleeland et al., 1994).

5.4 Assessment of radiological response to radiotherapy

Modified RECIST criteria were used to evaluate radiological response to RT in the bone lesions (Eisenhauer et al., 2009). The appearance of new lesions, changes in the metastatic pattern from focal to diffuse, or at least a 20% increase in the largest diameters of the target lesions after RT were defined as progression. The disappearance of lesions or reduction of more than a 30% reduction in the target lesion diameters was defined as a response. The radiological response of spinal lesions was evaluated both inside and outside the RT portals.

5.5 Assessment of pain response after radiotherapy

The clinical response to treatment was defined according to the updated International Bone Metastases Consensus Working Party palliative RT endpoints (Chow et al., 2012) (Table 5.1). Patients with either complete response or partial response were defined as responders and patients with indeterminate response or pain progression were defined as non-responders.

Table 5.1. Pain response after radiotherapy for spinal metastases (Chow et al., 2012).

Term	Definition
Complete response	A pain score of 0 at treated site with no concomitant increase in analgesics intake (stable or reducing analgesics in daily oral morphine equivalent (OMED))
Partial response	Pain reduction of 2 or more at the treated site on scale of 0-10 without analgesics increase, or Analgesics reduction of 25% or more from baseline without an increase in pain.
Pain progression	Increase in pain score of 2 or more above baseline at the treated site with stable OMED, or An increase of 25% or more in OMED compared with baseline with the pain score stable or 1 point above baseline.
Indeterminate response	Any response that is not captured by the complete response, partial response, or pain progression definitions.

5.6 Prediction of survival

The scoring system for predicting survival was estimated based on factors found to be significant in the univariate and multivariate analysis. The points for each variable were based on 6-month survival rates and the variables associated with the longest survival were assigned the highest scores. Adding together all of the points for individual factors produced the prognostic score. The predictive value of the following factors was assessed: primary tumor site (breast: score 2, prostate: score 1, other: score 0), visceral metastases (0-1 location: score 1, 2 locations or more: score 0), albumin level (>30 g/L: score 1, <30 g/L: score 0), and KPS (good: score 2, moderate: score 1, poor: score 0). The patients were

divided into the following 3 groups: group 1 (score 0-2), group 2 (score 3-4), and group 3 (score 5-6). The patients allocated to group 1 had the lowest survival rates and patients allocated to group 3 had the highest survival probabilities.

5.7 MRI protocols

A MRI of the whole spine was performed at our institution or at local hospitals using similar protocols. At our institution the MRIs were acquired with a 1.5 T GE Signa Horizon LX whole body scanner (GE Medical Systems, Milwaukee, Wisconsin, USA) or a 1.5 T Siemens Espree (Siemens, Erlangen, Germany) whole body scanner. The protocol consisted of sagittal T1-weighted SE (TR/TE 400/14 msec) and STIR (TR/TE/TI 3000/34/150 msec) imaging of the whole spine. The image matrix was 512 x 512 and the FOV was 400 mm. The slice thickness was 4 mm and the slice gap was 0.5 mm. The echo train length was 4 and 10 for T1-weighted and STIR images, respectively. In regions of suspected epidural space invasion or spinal cord compression axial T2-weighted FSE/TSE (TR/TE 3000/84) images were obtained. The image matrix was 256 x 256 and the FOV was 180 mm. The slice thickness was 4 mm and the slice gap was 1 mm. The echo train length was 16. The sagittal T1-weighted and STIR images were obtained to detect osseous lesions and delineate the extent of bony disease. The axial T2-weighted images were used to detect and chart epidural disease and to assess the degree of spinal cord compression.

6 RESULTS

6.1 Paper I

MRI and neurological findings in patients with spinal metastases

The purpose of this paper was to analyze the association between motor and sensory function and the MRI-assessed extent of spinal metastases.

A total of 284 patients were included. There were no patients assigned a Frankel score of A. There were 28 non-ambulatory patients (Frankel B or C) and 49 patients were ambulatory with minor motor deficits (Frankel D). Two hundred and seven patients had normal motor function (Frankel E). Sensory deficits were identified in 49 patients.

All patients with radiological MSCC and Frankel E score were defined as having occult (subclinical) MSCC. The patients with radiological MSCC and Frankel score A-D were defined as having manifest (overt) MSCC. MSCC was present in 32% of the patients with normal neurological function (occult MSCC).

The extent of the epidural tumor was graded using two different, MRI-based scales: a 4-point scale to define spinal canal narrowing and a 6-point MSCC scale. Both grading systems were associated with the Frankel score. The percentage of patients with radiological evidence of spinal cord compression increased with increasing Frankel grade. All of the non-ambulatory patients had radiological spinal cord compression (MSCC scale grade 2-3). Spinal cord compression was present in 100% of the patients with Frankel scores B or C and in 66% of patients with Frankel score D and 32% of patients with a Frankel score E (occult MSCC). All patients with bone-only disease were ambulatory. The percentage of patients with occult MSCC was lower when the 4-point spinal canal narrowing scale was used (5%) as compared to the 6-point MSCC grading system (19%). Both scoring systems were significantly associated with the sensory deficits (at the level of the spinal cord).

6.2 Paper II

Radiotherapy for spinal metastases from breast cancer with emphasis on local disease control and pain response using repeated MRI

The aim of this study was to evaluate the irradiated metastatic lesions and the rate of local tumor control using repeated MRIs. The study compared imaging findings with pain response after fractionated RT in 32 patients with spinal metastases from breast cancer.

The pain intensity was evaluated using a validated Norwegian version of BPI. The pain experience during the last 24 hours and the current pain level was recorded using a 10-point scale. The pain response to treatment was defined according to the updated International Bone Metastases Consensus Working Party palliative RT endpoints. The recorded MRI findings were presence and extent of spinal metastases, tumor-conditioned spinal canal stenosis (SCS), compression of the spinal cord, cauda equina and nerve roots, and the presence and severity of vertebral fractures.

The mean pain scores were 4.3, 3.9 and 3.7 at baseline, 2 months and 6 months after RT, respectively. At 2 and 6 months after RT, 38% and 44% of the patients were classified as responders. None of the patients developed neurological symptoms. Age, ongoing chemotherapy, hormone therapy and use of bisphosphonates were not associated with the pain response. Patients younger than 65 years of age tended to be responders more often than older patients; however these data did not reach statistical significance.

On the pretreatment MRIs, 21 patients had tumor-conditioned spinal canal stenosis and 8 patients presented with compression of the spinal cord or cauda equina. Fractures were noted in 22 patients (38 lesions). All fractures were pathological, tumor-induced fractures.

On the post-treatment MRIs, a decrease in the intraspinal tumor volume was reported in all patients. Only 6% of the patients showed progression of bone metastases within the radiation field, whereas 60% of the patients showed disease progression outside the RT portals. Fracture progression was observed in 55% of lesions and 5 patients developed new fractures. The pain response did not correlate with any recorded MRI features of metastatic lesions. Patients with advanced disease (large metastases or diffuse bone marrow infiltration) and patients with compression of the spinal cord/cauda equina tended to be non-responders more frequently. However, the difference was not statistically significant.

6.3 Paper III

Prognostic factors in patients with symptomatic spinal metastases and normal neurological function

The purpose of this work was to evaluate clinical, MRI and laboratory parameters as potential predictive factors for survival in patients with spinal metastases and normal neurological function.

A total of 173 patients were included. The median survival time was 8.2 months. Prostate, breast, and lung cancers were the most common primary diagnoses. A total of 46 patients (27%) reported severe pain and 120 patients (69%) used strong opioids. All patients were treated by RT. RT was given in combination with ongoing chemotherapy (16 patients), hormone treatment (68 patients), bisphosphonates (30 patients), and high-dose corticosteroids (54 patients). Two months after RT, 29 patients died because of their malignant disease; 50 patients (35%) were defined as responders; and 79 patients (55%) were defined as non-responders (missing data in 15 patients).

The extension of bony disease in the spine was assessed using a MRI-based scoring system. Sixty-six and 107 patients were allocated to group A (limited extent of spinal metastases) and B (widespread spinal metastatic disease), respectively. A total of 118 patients had tumor-conditioned SCS and 47 patients had MSCC. Neither the MRI-based extension of bone metastases nor the presence of SCS and MSCC influenced survival.

In the univariate analysis, prolonged survival was associated with the primary cancer diagnosis (favorable diagnoses), albumin level (≥ 30 g/L), KPS (good), number of visceral metastases (0-1 locations), analgesics use (none, non-opioid analgesics or weak opioids) and ongoing hormone treatment. Patients receiving chemotherapy had significantly shorter survival in the univariate analysis. In the multivariate analysis, primary cancer diagnosis (favorable diagnoses), albumin level (≥ 30 g/L), KPS (good), number of visceral metastases (0-1 locations), analgesic drug use (none, non-opioid analgesics or weak opioids) were associated with prolonged survival.

Based on the results of the multivariate analysis, a scoring system for the prediction of survival was developed. Three survival groups were proposed. The median survival times for

groups 1-3 were 2.1, 5.5 and 24.9 months. At 6 months, survival rates for groups 1-3 were 13, 46 and 94%. At 12 months, survival rates for groups 1-3 were 4, 28 and 79%.

7 GENERAL DISCUSSION AND FUTURE PERSPECTIVES

7.1 MRI in the pretreatment assessment of spinal metastases

A variety of imaging methods have been applied to patients with suspected spinal metastatic disease and MSCC. Medical history and a physical examination are the first assessments. However, clinical features are not sensitive or specific enough to make a diagnosis alone (Cole and Patchell, 2008). Over the past two decades, MRI has become the technique of choice for imaging of spinal metastatic disease.

MRI may be used for general disease follow-up in patients without known MSCC or as diagnostic procedure initiated due to symptoms of MSCC.

A wide range of MRI sequences are used to assess malignant bone lesions. The combination of an unenhanced SE T1-weighted and STIR sequences were shown to be highly sensitive for bone metastasis screening (Schmidt and Baur-Melnyk, 2013) and these sequences were also included in the study protocol. The retrospective character of this study did not allow inclusion of functional techniques such as diffusion in the imaging protocol. DWI is an attractive detection technique that immediately draws attention to abnormal skeletal regions and reduces image interpretation times (Padhani et al., 2011). DWI also allows improved tissue characterization that can be beneficial in differentiating benign from malignant skeletal lesions (Padhani et al., 2009). Although lesion differentiation is essential in tumor diagnosis, this issue was less important for the study requirements because all patients had an established diagnosis of spinal metastases prior to study entry.

Previous studies have evaluated the ability of MRI to identify MSCC (Loblaw et al., 2005; Loughrey et al., 2000; Cook et al., 1998). The results of these studies supported the use of whole-spine MRI for patients with known malignancy and suspected MSCC. The importance of imaging the whole spine is well known as MSCC may occur at multiple spinal levels. In our study, multifocal MSCC was present in 5% of the patients and this result supports the policy of whole-spine MRI and not only localized imaging (Husband et al., 2001; Cook et al., 1998). The relatively low frequency of multiple sites of compression in our study compared to previous series (5% in our study vs. 20 to 35% in other studies) (Cole and Patchell, 2008; Van der Sande and Boogerd, 1990; Schiff et al., 1997) may reflect current trends in oncology with MRI being performed early in MSCC progression.

There is a need for a uniform and clearly defined grading system for MSCC. In our series, two MRI-based scales were used to evaluate the extent of epidural tumor. The 6-point scale was recommended by Bilsky et al. as a valid and reliable instrument that may be used to precisely describe the degree of MSCC (Bilsky et al., 2010). Both scoring systems were significantly associated with neurological symptoms. However, both scales exhibited some strengths and limitations, as reported in Paper I. The 6-point scale, developed as a grading system for frank spinal cord compression, could not be used to evaluate patients with metastatic lesions located in the lumbar spine, below the conus. Moreover, the interpretation of subtle differences between subgroups of the 6-point scale was challenging and required high-quality images. A sufficient image quality was occasionally difficult to obtain due to motion artifacts, particularly in patients with pain. In contrast, quantitative measurements (the 4-points scale) were easy to perform and could be provided throughout the whole spine. A limitation of this scale was that moderate grades of spinal canal narrowing included a large and heterogeneous group of patients (one-third to two-thirds reduction of the cross-sectional area of the spinal canal). Despite some shortcomings, both grading systems can be considered for the assessment of MSCC and epidural space compromise.

7.2 Neurological symptoms and MRI findings. Subclinical MSCC


Motor status before treatment is one of the most important prognostic factors for the functional outcome in patients with spinal metastases (Cole and Patchell, 2008). The creation of clinical guidelines for identifying patients who are at risk of developing symptomatic MSCC are important in order to allow initiation of treatment before motor deficits develop.

Several studies have explored the association between radiological findings and symptoms (Helweg-Larsen et al., 2000; Hamamoto et al., 2009; Maranzano et al., 1991; Kim et al., 1990; Husband et al., 2001). In a prospective study of 105 patients with MSCC, Maranzano et al. showed that patients with complete myelographic block had severe motor dysfunction in a higher percentage than those with partial blockage (Maranzano et al., 1991). Kim et al. found that the degree of spinal cord compression correlated well with functional status. Furthermore, they found that the degree of spinal cord block on myelography was directly related to the degree of motor dysfunction and the degree of sphincter dysfunction in their series (Kim et al., 1990). Similarly, a prospective cohort study of Helweg-Larsen and Sorensen reported a correlation between the degree of myelographic blockage and gait function. The diagnosis of MSCC was established by myelographic findings and a

supplementary MRI was performed in one-third of the patients (Helweg-Larsen et al., 2000). These findings are in agreement with our results reporting the presence and severity of neurological deficits primarily associated with high grades of epidural space compromise. The percentage of patients with MRI-assessed spinal cord compression (MSCC scale grades 2-3) increased with increasing Frankel score.


According to our results, a considerable number of the patients had occult/subclinical MSCC. This finding is within the ranges reported by other studies (Bayley et al., 2001; Venkitaraman et al., 2007; Godersky et al., 1987) and suggests that in many patients spinal cord compression may be present for a significant period of time before development of neurological deficits, and that MRI may provide important lead time for the diagnosis and treatment compared to history and physical examination alone (Bayley et al., 2001). Consequently, it may be possible to identify and treat patients before development of neurological dysfunction. However, our results did not directly address how the extent of epidural space compromise could influence the risk of developing motor deficits. The management of patients with spinal metastases should thus be based upon a combination of clinical findings, the duration of symptoms and a radiological evaluation of epidural space invasion using reproducible parameters.

The importance of delays in the diagnosis and treatment of patients with MSCC has been highlighted in previous studies (Husband, 1998; Loblaw et al., 2005). Approximately 90% of the patients in our study were ambulatory at the time of treatment. This finding is in contrast with previous publications reporting that only 25-32% of the patients were ambulatory at the initiation of therapy (Husband, 1998; Findlay, 1984). The low percentage of non-ambulatory patients and relatively high percentage of patients with bone-only disease (26%) in our study may reflect current clinical practice with efforts used on identification of patients with subclinical MSCC. There are several reported methods to increase awareness among health professionals concerning the combination of signs and symptoms of MSCC. These efforts will improve early detection of MSCC, e.g. the use of Red Flag credit cards in combination with specific training programs and guidelines (Turnpenney et al., 2013) (Fig. 7.1).

 **EARLY WARNING SIGNS OF MSCC**
Greenhalgh S, Turnpenney J, Richards L, Selfe J (2010)

R	Referred back pain is multi-segmental or <u>band-like</u>
E	<u>Escalating pain</u> which is poorly responsive to treatment (incl medication)
D	<u>Different</u> character or site to previous symptoms
F	Funny feelings, odd sensations or <u>heavy legs</u> (multi-segmental)
L	<u>Lying flat</u> increases back pain
A	<u>Agonising pain</u> causing anguish and despair
G	<u>Gait disturbance</u> , unsteadiness, especially on stairs (not just a limp)
S	Sleep <u>grossly</u> disturbed due to pain being worse at night

NB - Established motor / sensory / bladder / bowel disturbances → late signs

 **METASTATIC SPINAL CORD COMPRESSION (MSCC)**
KEY RED FLAGS

Past medical history of cancer
(but note 25% of patients do not have a diagnosed primary)

Early diagnosis is essential
as the prognosis is severely impaired once paralysis occurs

A combination of Red Flags increases suspicion
(the more red flags the higher the risk and the greater the urgency)

To access the Greater Manchester and Cheshire MSCC guidelines go to:
www.christie.nhs.uk (search 'spinal cord compression')



 The Christie 
NHS Foundation Trust

Fig. 7.1. The Red Flag card - a credit card sized reminder proposed as a quick and a visually attractive way of raising awareness among health professionals in the United Kingdom (with permission from The Christie NHS Foundation Trust, <http://www.christie.nhs.uk/>).

The clinical course of occult MSCC is not well defined. There have been no studies on how and if, the early treatment of patients with occult MSCC influences the development of neurological deficits (Bayley et al., 2001; Sutcliffe et al., 2013). However, the natural history of progression of skeletal metastasis suggests that patients with occult MSCC on MRI may progress to develop neurological deficit if left untreated (Venkitaraman et al., 2010). In our series, all patients with subclinical MSCC were treated with RT to prevent neurological deterioration. The decision to treat these patients was based on the high efficacy, low toxicity and low cost of RT in the management of spinal cord compression compared with the high potential cost of a missed diagnosis in terms of physical disability, quality-of-life impairment and expense to the health care system (Bayley et al., 2001).

7.3 MRI in the assessment of treatment response in spinal metastases

Imaging is an essential part of the clinical management of patients with bone metastases. Unfortunately, there are no universally accepted methods for assessment of tumor response for skeletal metastases. There are overwhelming clinical needs to develop and validate non-invasive response biomarkers for bone metastases.

The two established sets of criteria for assessment of bone metastases, one from UICC and the other from WHO are more than 30 years old and based on the findings from plain radiography or skeletal scintigraphy. These criteria are inadequate because they do not incorporate modern methods (CT, MRI) in assessing the response of bone metastatic lesions to treatment (Hamaoka et al., 2010; Hayward et al., 1977; WHO, 1979). The MD Anderson Cancer Center criteria (Hamaoka et al., 2004; Hamaoka et al., 2010) include both CT and MRI. However, the structural changes in bone metastases after treatment are predominantly evaluated with CT. The role of MRI is mainly confined to evaluation of tumor signal extension and assessment of signal changes after treatment is not included in the response criteria.

Another widely used system, RECIST (v 1.1), allows osteolytic or mixed osteolytic/osteoblastic metastases with soft tissue component > 10 mm to be measured (Eisenhauer et al., 2009). However, diffuse disease and true osteoblastic bone metastases are still considered non-measurable (Padhani and Gogbashian, 2011; Costelloe et al., 2010; Eisenhauer et al., 2009). Researches have transposed the RECIST guidelines to bone metastases and have shown that MRI of the axial skeleton enables precise measurement and follow-up of skeletal lesions similar to soft-tissue metastases (Tombal et al., 2005). In Paper II, modified RECIST criteria were used to assess the treatment responses in spinal

metastases after RT. For all but two patients in our study, the largest diameter of the target lesions remained unchanged. However, all treated metastases exhibited differences in SI. This result is consistent with previous studies that support the qualitative assessment of response in bone metastases rather than size measurements (Bauerle et al., 2009; Hamaoka et al., 2010). Unfortunately, it is difficult to identify residual active malignancy within bone marrow based on changes in SI alone (Brown et al., 1998). When abnormalities persist after RT or chemotherapy, low SI may either reflect residual active tumor or fibrosis (Vanel, 2009), and standard, morphological MRI sequences often do not permit a reliable differential diagnosis. DWI was shown to be more useful in monitoring the response of bone metastases to therapy. In addition, a recent study have reported efficacy of DCE MRI in therapy assessment of spinal metastases (Chu et al., 2013).

7.4 MRI findings and pain response after radiotherapy.

The mechanism of RT-induced bone injury has not been fully defined and may occur secondary to the alterations in the marrow microenvironment including changes to the vasculature, osteoblasts, osteoclasts, and osteocytes (Van Poznak and Taxel, 2013). Fractures that occur at irradiated skeletal sites can remain a major source of morbidity and can reduce the clinical response to treatment (Willey et al., 2013). A recent study reported a significantly increased risk of vertebral fracture after single fraction IG-IMRT to the spinal metastases (Rose et al., 2009). According to their results, patients with fracture progression were more likely to require narcotic pain medicine and also showed a trend towards high pain scores. The patients with fracture progression also showed more than double the reduction in KPS. Fortunately, fracture did not portend worse neurological outcome and after treatment excellent tumor control was achieved (Rose et al., 2009). IG-IMRT is given as a single dose ranging from 18-24 Gy as and is very different radiobiologically from doses used in conventional RT. Consequently, findings presented by Rose et al. are difficult to compare with results of the present study and other studies that used different radiation techniques.

Limited data exist regarding the incidence of fractures after conventional RT to the spine. Previous studies have reported the rate of fractures after single or multifraction RT; however, they did not stratify between spine and other locations in the skeleton (Sande et al., 2009; Chow et al., 2013; Hartsell et al., 2005; Steenland et al., 1999; Sze et al., 2003). In general, more fractures occurred after single-fraction RT than after multifraction therapy, but the absolute percentage was low (Chow et al., 2013; Steenland et al., 1999; Sze et al., 2003). Sze et al. reported that 3% of the patients treated by single-fraction RT developed a

pathological fracture after treatment compared with 1.6% for those treated by multifraction RT (Sze et al., 2003). Our results identified fracture progression in 53% of the patients (55% of lesions) and 16% of the patients presented with new fractures after RT. This percentage is higher than in previous studies including the study by Rose et al. (Rose et al., 2009). This difference could possibly reflect a higher incidence of vertebral fractures in patients with breast cancer (Kanis et al., 1999) and tumor tendency to osteolytic metastases (Kozlow and Guise, 2005). In general, outcomes from previous reports were difficult to compare due to different RT regimens, different definitions used and heterogeneous patient groups in the context of tumor diagnoses, imaging modalities and anatomical locations of metastases.

Mitera et al. reported pathological vertebral fractures in 28% of lesions observed on the pretreatment CT of the spine (Mitera et al., 2010). The pain responses in their study did not differ in patients with and without pathological fracture or any other imaging features related to the extent of tumor involvement (Mitera et al., 2010). Furthermore, Maranzano et al. reported pathological vertebral collapse in 32% of patients with MSCC treated by surgery or RT. A comparison of responses and survival between patients with or without vertebral collapse showed no significant differences (Maranzano et al., 1991). Our results are in agreement with these findings and identified similar pain responses after RT in patients with or without vertebral fracture, fracture progression or new fractures. Because pain response was not associated with any recorded MRI-findings of the metastatic lesions, all patients with painful spinal metastases may similarly benefit from palliative RT. An excellent local tumor control was achieved in the majority of patients and the cross-sectional area of the spinal canal was significantly improved despite increasing vertebral body collapse.

7.5 Survival after radiotherapy for spinal metastases

Personalizing cancer care is one of the most important trends in oncology. To administer the best treatment regimen to the individual patient it is mandatory to consider the patient's prognosis (Douglas et al., 2012). Several prognostic factors have been explored in different studies (Table 2.3). In our series, primary tumor site and KPS were identified as the as major factors predicting survival after RT of spinal metastases. Slow growing tumors such as breast and prostate cancer (Tomita et al., 2001; Kataoka et al., 2012) and good performance status were associated with prolonged survival. These results are in agreement with previous studies shown in Table 2.3. The number of visceral metastases is another known predictor for survival. In our series, survival was negatively affected by the presence of two or more visceral organs involved.

In our study, the patient's pretreatment albumin levels were identified as an independent prognostic factor. Previous reports suggested that low serum albumin is associated with higher mortality from cancer (Gupta et al., 2010). To our knowledge, this factor, although important, has not previously been included in a score predicting survival after RT for spinal metastases.

Optimal hemoglobin levels during RT or concomitant radio-chemotherapy result in optimal tumor oxygenation and may improve outcomes after cancer treatment (Rades et al., 2009). The association between anemia and poor tumor oxygenation has been described previously (Rades et al., 2009; Becker et al., 2000) and hemoglobin levels have been reported as one of the prognostic factors for survival (Rades et al., 2009). In our study, pretreatment hemoglobin levels showed a strong trend toward statistical significance.

Pain was reported as a significant predictive factor for survival after surgical treatment for spinal metastases (Pointillart et al., 2011; Hosono et al., 2005). We assessed pretreatment analgesic drug use, pain intensity and pain control after RT as potential prognostic indicators because these factors were not widely evaluated in patients treated conservatively. Pointillart et al. have reported subjective pain score from 0-10 (<6 vs. >6) as a significant factor predicting survival in a pre-surgical assessment of patients with spinal metastases (Pointillart et al., 2011). In our series, neither self-reported pain intensity nor pain response to RT influenced survival. The non-responders had shorter survival times than responders but the difference was not statistically significant. Our study identified use of non-opioid analgesics as a positive predictive factor both in the univariate and multivariate analyses. This finding is in agreement with previous study (van der Linden et al., 2006). Short survival times in patients using strong opioids may be explained by general advancement of metastatic disease in these patients. Additionally, physicians and patients may also be reluctant to administer opioids in non-terminal situations (van der Linden et al., 2006).

As reported in Paper III, the MRI findings had no impact on survival after RT. Patients with widespread metastatic disease in bone had shorter survival times than patients with more limited disease observed on MRI, but not statistically significant. This result may be influenced by a great avidity for bone in breast and prostate carcinomas; at the same time these patients have a relatively long median survival after diagnosis of bone involvement. Neither the presence of MSCC nor epidural tumor growth was associated with prolonged survival.

The selection of the treatment for each patient must take into account the survival prognosis. Our study proposed 3 survival groups. The patients allocated to group 1 had a very poor survival prognosis and could be considered as candidates for short-term treatment such as single-fraction RT or in some cases best supportive care alone. However, most of these patients were treated by long-course RT, but the longer-course treatment did not appear to improve survival in these patients compared to the short course (Mizumoto et al., 2008). Furthermore, most of these patients will not live long enough to experience local tumor recurrence. Conversely, patients with a favorable survival prognosis are better treated with longer-course RT, which usually consists of 10 fractions of 3 Gy given in 2 weeks or even 20 fractions of 2 Gy delivered over 4 weeks in the context of an extraordinarily good prognosis. The long-course RT leads to better local control rates than single-fraction or short-course RT (Rades et al., 2013; Rades et al., 2006; Rades et al., 2011).

7.6 Limitations

Since the publication of Papers I-III technical evolution and refinement of methods have continued. New imaging techniques have been introduced. In the context of bone marrow assessment in metastatic disease, new contrast mechanisms, in particular diffusion, have emerged in the recent years. The lack of functional sequences in the study protocols can be considered a limitation. However, this deficiency most likely does not influence the final results of the study. The major limitation of Paper II remains the limited number of patients. Precisely predicting treatment response and identifying statistically significant groups may not be feasible in small samples. Additional limitations include relatively broad time variations in the post-treatment MRI studies, which are a consequence of repeated MRIs not being a part of the prospective study design. In Paper III, the retrospective nature of the data included in the survival score must be taken into account when interpreting the results. Retrospective data may have a hidden selection bias (Rades et al., 2013). Furthermore, our study was limited by a lack of a direct control group and the score should be validated in future prospective studies.

7.7 Future investigations

Further investigations are needed to establish MRI response biomarkers for skeletal metastases as there are no universally accepted methods for assessing tumor response in bone. Therapy response criteria that include new contrast techniques (DWI, DCE) need to be established and further tested in prospective clinical studies.

Further research should investigate factors that can predict MSCC. Predictive risk models are emerging that may help to define a population of patients at higher risk of developing spinal cord compression. However, the optimal screening strategy, population, and intervention have not been identified.

Neither the impact of vertebral fractures upon treatment response nor the risk of fracture in different RT regimens are assessed properly and need to be examined. There is evidence that factors related to the tumor extent do not influence the treatment response and all patients with spinal metastases receive similar benefits from RT. These results need to be verified in larger studies.

8 CONCLUSIONS

Both MRI-based scales evaluated in this study demonstrated significant association with neurological function. These scales may provide a more precise definition of MSCC when selecting and comparing patients and treatment effects from different studies. Furthermore, our study identified a considerable number of patients with subclinical MSCC. This finding is important because identifying MSCC early prevents serious long-term disability and is a key aspect of current cancer care (Paper I).

RT provided an effective local control of spinal metastases. In the study population, the pain response following RT was not associated with any recorded MRI findings. Thus, all patients with painful spinal metastases may receive similar benefits from RT and MRI cannot be used to select patients at risk of not responding to the treatment (Paper II).

The primary tumor histology and the performance status were the major prognostic factors predicting survival in patients with painful spinal metastases and normal neurological function. Furthermore, the patient's pretreatment albumin level was identified as an important predictor for survival. The spinal MRI is a valuable method for the assessment of metastatic disease and treatment planning. However, the present study showed no prognostic value of MRI in predicting survival in these patients (Paper III).

9 REFERENCES

1. Abraham JL. Assessment and treatment of patients with malignant spinal cord compression. *J Support Oncol* 2004;2:377-88.
2. Algra PR, Heimans JJ, Valk J, et al. Do metastases in vertebrae begin in the body or the pedicles? Imaging study in 45 patients. *Am J Roentgenol* 1992;158:1275-9.
3. Arguello F, Baggs RB, Duerst RE, et al. Pathogenesis of vertebral metastasis and epidural spinal cord compression. *Cancer* 1990;65:98-106.
4. Asdourian PL, Mardjetko S, Rauschnig W, et al. An evaluation of spinal deformity in metastatic breast cancer. *J Spinal Disord* 1990;3:119-34.
5. Bach F, Larsen BH, Rohde K, et al. Metastatic spinal cord compression, occurrence, symptoms, clinical presentations and prognosis in 398 patients with spinal cord compression. *Acta Neurochir* 1990;107:37-43.
6. Batson OV. The function of the vertebral veins and their role in the spread of metastases. *Ann Surg* 1940;112:138-149.
7. Bauer HCF. Controversies in the surgical management of skeletal metastases. *J Bone Joint Surg* 2005;87-B:608-17.
8. Baur A, Huber A, Ertl-Wagner B, et al. Diagnostic value of increased diffusion weighting of steady-state free precession sequence for differentiating acute benign osteoporotic fractures from pathologic vertebral compression fractures. *Am J Neuroradiol* 2001;22:366-372.
9. Bauerle T, Semmler W. Imaging response to systemic therapy for bone metastases. *Eur Radiol* 2009;19:2495-507.
10. Bayley A, Milosevic M, Blend R, et al. A prospective study of factors predicting clinically occult spinal cord compression in patients with metastatic prostate carcinoma. *Cancer* 2001;92:303-10.
11. Becker A, Stadler P, Lavey RS, et al. Severe anemia is associated with poor tumor oxygenation in head and neck squamous cell carcinomas. *Int J Radiat Oncol Biol Phys* 2000;46:459-66.
12. Biffar A, Dietrich O, Sourbron S, et al. Diffusion and perfusion imaging of bone marrow. *Eur J Radiol* 2010;76:323-8.
13. Bilsky MH, Laufer I, Fourney DR, et al. Reliability analysis of the epidural spinal cord compression scale. *J Neurosurg Spine* 2010;13:324-28.
14. Bilsky MH, Boland PJ, Panageas KS, et al. Intralesional resection of primary and metastatic sarcoma involving the spine: outcome analysis of 59 patients. *Neurosurgery* 2001;49:1277-87.
15. Bollen L, van der Linden YM, Pondaag W, et al. Prognostic factors associated with survival in patients with symptomatic spinal bone metastases: a retrospective cohort study of 1043 patients. *Neuro Oncol* 2014;0:1-8.
16. Brufsky AM. Cancer treatment-induced bone loss: pathophysiology and clinical perspectives. *Oncologist* 2008;13:187-95.
17. Brown AL, Middleton G, MacVicar AD, et al. T1-weighted magnetic resonance imaging in breast cancer vertebral metastases: changes on treatment and correlation with response to therapy. *Clin Radiol* 1998;53:493-501.
18. Cleeland CS, Gonin R, Hatfield AK, et al. Pain and its treatment in outpatients with metastatic cancer. *N Engl J Med* 1994;330:592-6.
19. Clines GA. Overview of mechanisms in cancer metastases to bone. In: Rosen CJ, editor. *Primer on the Metabolic Diseases and Disorders of Mineral Metabolism*. Washington DC: ASBMR 2013.

20. Chow E, Khan LM, Bruland OS. Radiotherapy of skeletal metastases. In: Rosen CJ, editor. *Primer on the Metabolic Diseases and Disorders of Mineral Metabolism*. Washington DC: ASBMR 2013; p. 754-9.
21. Chow E, Hoskin P, Mitera G, et al. Update of the international consensus on palliative radiotherapy endpoints for future clinical trials in bone metastases. *Int J Radiat Oncol Biol Phys* 2012;82:1730-7.
22. Chow E, Wu JSY, Hoskin P, et al. International consensus on palliative radiotherapy endpoints for future clinical trials in bone metastases. *Radiother Oncol* 2002;64:275-80.
23. Chow E, Harris K, Fan G, et al. Palliative radiotherapy trials for bone metastases: A systematic review. *J Clin Oncol* 2007;25:1423-36.
24. Chow E, Harris K, Fung K. Successful validation of a survival prediction model in patients with metastases in the spinal column. *Int J Radiat Oncol Biol Phys* 2006;65:1522-7.
25. Chu S, Karimi S, Peck KK, et al. Measurement of blood perfusion in spinal metastases with dynamic contrast-enhanced MRI: evaluation of tumor response to radiation therapy. *Spine* 2013;38:E1418-24.
26. Cole JS, Patchell RA. Metastatic epidural spinal cord compression. *Lancet Neurol* 2008;7:459-66.
27. Cole DJ. A randomized trial of single treatment versus conventional fractionation in the palliative radiotherapy of painful bone metastases. *Clin Oncol (R Coll Radiol)* 1989;1:59-62.
28. Constans JP, DeDivitiis E, Donzelli R, et al. Spinal metastases with neurologic manifestations, review of 600 cases. *J Neurosurg* 1983; 59:111-18.
29. Cook AM, Lau TN, Tomlinson MJ, et al. Magnetic resonance imaging of the whole spine in suspected malignant spinal cord compression: Impact on management. *Clin Oncol (R Coll Radiol)* 1998;10:39-43.
30. Costelloe CM, Chuang HH, Madewell JE, et al. Cancer response criteria and bone metastases: RECIST 1.1, MDA and PERCIST. *J Cancer* 2010;1:80-92.
31. Dimar Jr JR, Voor MJ, Zhang YM, et al. A human cadaver model for determination of pathologic fracture threshold resulting from tumorous destruction of the vertebral body. *Spine* 1998;23:1209-14.
32. Douglas S, Schild SE, Rades D. A new score predicting the survival of patients with spinal cord compression from myeloma. *BMC Cancer* 2012;12:425.
33. Douglas S, Schild SE, Rades D. Metastatic spinal cord compression in patients with cancer of unknown primary. Estimating the survival prognosis with a validated score. *Strahlenther Onkol* 2012;188:1048-51.
34. Drake RL, Vogl AW, Mitchell AW, et al. *Gray's atlas of anatomy*. Philadelphia: Churchill Livingstone; 2007.
35. Ebihara H, Ito M, Abumi K, et al. A biomechanical analysis of metastatic vertebral collapse of the thoracic spine: a sheep model study. *Spine* 2004;29:994-9.
36. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45:228-47.
37. Fili S, Karalaki M, Schaller B. Mechanism of bone metastasis: the role of osteoprotegerin and of the host-tissue microenvironment-related survival factors. *Cancer Lett* 2009;283:10-9.
38. Findlay GF. Adverse effects of the management of spinal cord compression. *J Neuro Neurosurgery Psychiatry* 1984;47:761-8.
39. Frankel HL, Hancock DO, Hyslop G, et al. The value of postural reduction in the initial management of closed injuries of the spine with paraplegia and tetraplegia. I. Paraplegia 1969;7:179-92.
40. Gaze MN, Kelly CG, Kerr GR, et al. Pain relief and quality of life following radiotherapy for bone metastases: A randomized trial of two fractionation schedules. *Radiother Oncol* 1997;45:109-16.

41. Gerszten PC, Burton SA, Ozhasoglu C, et al. Radiosurgery for spinal metastases: clinical experience in 500 cases from a single institution. *Spine* 2007;32:193-9.
42. Gilbert RW, Kim JH, Posner JB. Epidural spinal cord compression from metastatic tumor: diagnosis and treatment. *Ann Neurol* 1978;3:40-51.
43. Godersky JC, Smoker WR, Knutzon R. Use of magnetic resonance imaging in the evaluation of metastatic spinal disease. *Neurosurgery* 1987;21:676-80.
44. Griffith JF, Adams JE, Genant HK. Diagnosis and classification of vertebral fracture. In: Rosen CJ, editor. *Primer on the Metabolic Diseases and Disorders of Mineral Metabolism*. Washington DC: ASBMR 2013.
45. Guillevin R, Vallee JN, Lafitte F, et al. Spine metastasis imaging: review of literature. *J Neuroradiol* 2007;34:311-21.
46. Gupta D, Lis CG. Pretreatment serum albumin as a predictor of cancer survival: a systemic review of the epidemiological literature. *Nutr J* 2010;9:69.
47. Hamamoto Y, Kataoka M, Senba T, et al. Vertebral metastases with high risk of symptomatic malignant spinal cord compression. *Jpn J Clin Oncol* 2009;39:431-34.
48. Hamaoka T, Costelloe CM, Madewell JE, et al. Tumor response interpretation with new tumor response criteria vs the World Health Organisation criteria in patients with bone-only metastatic breast cancer. *Br J cancer* 2010;102:651-7.
49. Hamaoka T, Madwell JE, Podoloff DA, et al. Bone imaging in metastatic breast cancer. *J Clin Oncol* 2004;22:2942-53.
50. Hanna SL, Fletcher BD, Fairclough DL, et al. Magnetic resonance imaging of disseminated bone marrow disease in patients treated for malignancy. *Skelet Radiol* 1991;20:79.
51. Hayward JL, Carbone PP, Heusen JC, et al. Assessment of response to therapy in advanced breast cancer. *Br J Cancer* 1977;35:292-8.
52. Harrington KD. Anterior decompression and stabilization of the spine as a treatment for vertebral collapse and spinal cord compression from metastatic malignancy. *Clin Orthop* 1988;233:177-97.
53. Hartsell WF, Scott CB, Bruner DW, et al. Randomized trial of short- versus long-course radiotherapy for palliation of painful bone metastases. *J Natl Cancer Inst* 2005;97:798-804.
54. Helweg-Larsen S, Sorensen PS, Kreiner S. Prognostic factors in metastatic spinal cord compression: a prospective study using multivariate analysis of variables influencing survival and gait function in 153 patients. *Int J Radiat Oncol Biol Phys* 2000;46:1163-69.
55. Helweg-Larsen S. Clinical outcome in metastatic spinal cord compression. A prospective study in 153 patients. *Acta Neurol Scand* 1996;94:269-75.
56. Helweg-Larsen S, Sorenson PS. Symptoms and signs in metastatic spinal cord compression: a study of progression from first symptoms until diagnosis in 153 patients. *Eur J Cancer* 1994;30A:396-8.
57. Hosono N, Ueda T, Tamura D, et al. Prognostic relevance of clinical symptoms in patients with spinal metastases. *Clin Orthop Relat Res* 2005;436:196-201.
58. Hoskin P. Radiotherapy for bone metastasis. In: Coleman RE, Abrahamsson PA, Hadji P, editors. *Handbook of Cancer-Related Bone Disease*. Bristol: BioScientifica; 2012.
59. Husband DJ, Grant KA, Romaniuk CS. MRI in the diagnosis and treatment of suspected malignant spinal cord compression. *Br J Radiol* 2001;74:15-23.
60. Husband DJ. Malignant spinal cord compression: prospective study of delays in referral and treatment. *BMJ* 1998;317:18-21.
61. Jacobs WB, Perrin RG. Evaluation and treatment of spinal metastases: an overview. *Neurosurg Focus* 2001;11:e10.
62. Jindal G, Pukenas B. Normal spinal anatomy on magnetic resonance imaging. *Magn Reson Imaging Clin N Am* 2011;19:475-88.

63. Kanis JA, McCloskey EV, Powles T, et al. A high incidence of vertebral fracture in women with breast cancer. *Br J Cancer* 1999;79:1179-81.
64. Kaplan PA, Helms CA; Dussault R, et al. Basic principles of musculoskeletal MRI. In: Kaplan PA, editor. *Musculoskeletal MRI*. Saunders; 2001.
65. Katagiri H, Takahashi M, Inganaki J, et al. Clinical results of nonsurgical treatment for spinal metastases. *Int J Radiat Oncol Biol Phys* 1998;42:1127-32.
66. Kataoka M, Kunisada T, Tanaka M, et al. Statistical analysis of prognostic factors for survival in patients with spinal metastases. *Acta Med Okayama* 2012;66:213-9.
67. Kato A, Ushio Y, Hayakawa T, et al. Circulatory disturbance of the spinal cord with epidural neoplasm in rats. *J Neurosurg* 1985;63:260-5.
68. Kim RY, Spencer SA, Meredith RF, et al. Extradural spinal cord compression: Analysis of factors determining functional prognosis – prospective study. *Radiology* 1990;176:279-82.
69. Klepstad P, Loge JH, Borchgrevink PC, et al. The Norwegian brief pain inventory questionnaire: translation and validation in cancer patients. *J Pain Symptom Manage* 2002;24:517-25.
70. Klimo P, Thompson CJ, Kestle JRW, et al. A meta-analysis of surgery versus conventional radiotherapy for the treatment of metastatic spinal epidural disease. *Neuro Oncol* 2005;7:64-76.
71. Kozlow W, Guise TA. Breast cancer metastasis to bone: mechanisms of osteolysis and implications for therapy. *J Mammary Gland Biol Neoplasia* 2005;10:169-80.
72. Kricun ME. Red-yellow marrow conversion: its effect on the location of some solitary lesions. *Skeletal Radiol* 1985;14:10-19.
73. Kurth A. Orthopaedic treatment for skeletal metastases. In: Coleman RE, Abrahamsson PA, Hadji P, editors. *Handbook of Cancer-Related Bone Disease*. Bristol: BioScientifica; 2012.
74. Levack P, Graham J, Collie D, et al. Don't wait for a sensory level – listen to the symptoms: a prospective audit of the delays in diagnosis of malignant cord compression. *Clin Oncol (R Coll Radiol)* 2002;14:472-80.
75. Li KC, Poon PY. Sensitivity and specificity of MRI in detecting malignant spinal cord compression and in distinguishing malignant from benign compression fractures of vertebrae. *Magn Reson Imaging* 1988;6:547-56.
76. Lipton A. Clinical features of metastatic bone disease. In: Coleman RE, Abrahamsson PA, Hadji P, editors. *Handbook of Cancer-Related Bone Disease*. Bristol: BioScientifica; 2012.
77. Loblaw DA, Perry J, Chambers A, et al. Systematic review of the diagnosis and management of malignant extradural spinal cord compression: the Cancer Care Ontario Practice Guidelines Initiative's Neuro-Oncology Disease Site Group. *J Clin Oncol* 2005;23:2028-37.
78. Loblaw DA, Laperriere NJ. Emergency treatment of malignant extradural spinal cord compression: an evidence-based guideline. *J Clin Oncol* 1998;16:1613-24.
79. Loblaw DA, Mitera G, Ford M, et al. A 2011 updated systematic review and clinical practice guideline for the management of malignant extradural spinal cord compression. *Int J Radiat Oncol Biol Phys* 2012;84:312-7.
80. Loughrey GJ, Collins CD, Todd SM, et al. Magnetic resonance imaging in the management of suspected spinal canal disease in patients with known malignancy. *Clin Radiol* 2000;55:849-55.
81. Lurie JD, Tosteson AN, Tosteson TD, et al. Reliability of readings of magnetic resonance imaging features of lumbar spinal stenosis. *Spine* 2008;33:1605-10.
82. Maranzano E, Latini P. Effectiveness of radiation therapy without surgery in metastatic spinal cord compression: final results from a prospective trial. *Int J Radiat Oncol Biol Phys* 1995;32:959-67.
83. Maranzano E, Latini P, Beneventi S, et al. Radiotherapy without steroids in selected metastatic spinal cord compression patients: A phase II trial. *Am J Clin Oncol* 1996;19:179-83.

84. Maranzano E, Latini P, Checcaglini F, et al. Radiation therapy in metastatic spinal cord compression. A prospective analysis of 105 consecutive patients. *Cancer* 1991;67:1311-7.
85. McDonald R, Chow E, Lam H, et al. International patterns of practice in radiotherapy for bone metastases: A review of the literature. *J Bone Oncol* 2014;3:96-102.
86. McQuay H, Carroll D, Moore RA. Radiotherapy for painful bone metastases-a systematic review. *Clin Oncol* 1997;9:150-4.
87. McRobbie DW, Moore EA, Graves MJ, et al. Lose the fat! In: McRobbie DW, Moore EA, Graves MJ, Prince MR, editors. *MRI from picture to proton*. Cambridge University Press; 2010.
88. Messiou C, deSouza NM. Diffusion weighted magnetic resonance imaging of metastatic bone disease: a biomarker for treatment response monitoring. *Cancer Biomark* 2010;6:21-32.
89. Mitera G, Probyn L, Ford M, et al. Correlation of computed tomography imaging features with pain response in patients with spine metastases after radiation therapy. *Int J Radiat Oncol Biol Phys* 2010;81:827-30.
90. Mizumoto M, Harada H, Asakura H, et al. Prognostic factors and a scoring system for survival after radiotherapy for metastases to the spinal column: a review of 544 patients at Shizuoka Cancer Center Hospital. *Cancer* 2008;10:2816-22.
91. Mundy GR. Metastasis to bone: causes, consequences and therapeutic opportunities. *Nat Rev Cancer* 2002;2:584-93.
92. National Institute for Health and Clinical Excellence. Diagnosis and management of patients at risk of or with metastatic spinal cord compression. National Collaborating Centre for Cancer Cardiff; 2008. Available from: <http://www.nice.org.uk/nicemedia/live/12085/42668/42668.pdf>
93. National Institute for Health and Clinical Excellence. Metastatic spinal cord compression. Quality standard; 2014. Available from: <https://www.nice.org.uk/Guidance/QS56>.
94. Nielsen OS, Bentzen SM, Sandberg E, et al. Randomized trial of single dose versus fractionated palliative radiotherapy of bone metastases. *Radiother Oncol* 1998;47:233-40.
95. Oda I, Abumi K, Cunningham BW, et al. An in vitro cadaveric study investigating the biomechanical properties of the thoracic spine. *Spine* 2002;27:E64-70.
96. Ollivier L, Gerber S, Vanel D, et al. Improving the interpretation of bone marrow imaging in cancer patients. *Cancer Imaging* 2006;6:194-8.
97. Paget S. The distribution of secondary growths in cancer of the breast. *Cancer Metastasis Rev* 1989;8:98-101.
98. Padhani AR, Gogbashian A. Bony metastases: assessing response to therapy with whole-body diffusion MRI. *Cancer Imaging* 2011;11:S1-17.
99. Padhani AR, Liu G, Koh DM, et al. Diffusion-weighted magnetic resonance imaging as a cancer biomarker: consensus and recommendations. *Neoplasia* 2009;11:102-25.
100. Patchell RA, Tibbs PA, Regine WF, et al. Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomized trial. *Lancet* 2005;366:643-8.
101. Pointillart V, Vital JM, Salmi R, et al. Survival factors and clinical outcomes in patients with spinal metastases. *J Cancer Res Clin Oncol* 2011;137:849-56.
102. Rades D, Lang S, Schild SE, et al. Prognostic value of haemoglobin levels during concurrent radio-chemotherapy in the treatment of oesophageal cancer. *Clin Oncol* 2006;18:139-44.
103. Rades D, Stalpers LJ, Veninga T, et al. Evaluation of five radiation schedules and prognostic factors for metastatic spinal cord compression. *J Clin Oncol* 2005;23:3366-75.
104. Rades D, Fehlaue F, Schulte R, et al. Prognostic factors for local control and survival after radiotherapy of metastatic spinal cord compression. *J Clin Oncol* 2006;24:3388-93.
105. Rades D, Dunst J, Schild SE. The first score predicting survival in patients with metastatic spinal cord compression. *Cancer* 2008;112:157-61.

106. Rades D, Heidenreich F, Karstens JH. Final results of a prospective study of the prognostic value of the time to develop motor deficits before irradiation in metastatic spinal cord compression. *Int J Radiat Oncol Biol Phys* 2002;53:975-9.
107. Rades D, Douglas S, Veninga T, et al. A validated survival score for patients with metastatic spinal cord compression from non-small cell lung cancer. *BMC Cancer* 2012;12:302.
108. Rades D, Douglas S, Huttenlocher S, et al. Prognostic factors and a survival score for patients with metastatic spinal cord compression from colorectal cancer. *Strahlenther Onkol* 2012;188:1114-8.
109. Rades D, Douglas S, Veninga T, et al. A survival score for patients with metastatic spinal cord compression from prostate cancer. *Strahlenther Onkol* 2012;188:802-6.
110. Rades D, Douglas S, Schild SE. A validated survival score for breast cancer patients with metastatic spinal cord compression. *Strahlenther Onkol* 2013;189:41-6.
111. Rades D, Veninga T, Stalpers LJ, et al. Prognostic factors predicting functional outcomes, recurrence-free survival, and overall survival after radiotherapy for metastatic spinal cord compression in breast cancer patients. *Int J Radiat Oncol Biol Phys* 2006;64:182-8.
112. Rades D, Weber A, Karstens JH, et al. Prognostic role of the number of involved organs in patients with metastatic spinal cord compression. *Clin Neurol Neurosurg* 2014;118:12-5.
113. Rades D, Weber A, Bartscht T, et al. A new prognostic factor for the survival of patients with renal cell carcinoma developing metastatic spinal cord compression. *Strahlenther Onkol* 2014.
114. Rades D, Fehlaue F, Veninga T, et al. Functional outcome and survival after radiotherapy of metastatic spinal cord compression in patients with cancer of unknown primary. *Int J Radiat Oncol Biol Phys* 2007;67:532-7.
115. Rades D, Hueppe M, Schild SE. A score to identify patients with metastatic spinal cord compression who may be candidates for best supportive care. *Cancer* 2013;4:897-903.
116. Rades D, Dunst J, Schild SE. The first score predicting survival in patients with metastatic spinal cord compression. *Cancer* 2008;112:157-61.
117. Rades D, Douglas S, Veninga T, et al. Prognostic factors in a series of 504 breast cancer patients with metastatic spinal cord compression. *Strahlenther Onkol* 2012;188:340-5.
118. Roos DE, Turner SL, O'Brien PC, et al. Randomized trial of 8 Gy in 1 versus 20 Gy in 5 fractions of radiotherapy for neuropathic pain due to bone metastases (Trans-Tasman Radiation Oncology Group, TROG 96.05). *Radiother Oncol* 2005;75:54-63.
119. Rose PS, Laufer I, Boland PJ, et al. Risk of fracture after single fraction image-guided intensity-modulated radiation therapy to spinal metastases. *J Clin Oncol* 2009;27:5075-9.
120. Saarto T, Janes R, Tenhunen M, et al. Palliative radiotherapy in the treatment of skeletal metastases. *Eur J Pain* 2002;6:323-30.
121. Sande TA, Ruenes R, Lund JA, et al. Long term follow-up of cancer patients receiving radiotherapy for bone metastases: Results from a randomized multicenter trial. *Radiother Oncol* 2009;91:261-6.
122. Schiff D, O'Neill BP, Suman VJ. Spinal epidural metastases as the initial manifestation of malignancy: clinical features and diagnostic approach. *Neurology* 1997;49:452-6.
123. Schmidt GP, Baur-Melnyk A. MRI of bone metastases. In: Baur-Melnyk A, editor. *Magnetic resonance imaging of the bone marrow*. Springer-Verlag Berlin Heidelberg 2012.
124. Schmidt GP, Reiser MF, Baur-Melnyk A. Whole-body MRI for the staging and follow-up of patients with metastasis. *Eur J Radiol* 2009;70:393-400.
125. Sioutos PJ, Arbit E, Meshulam CF, et al. Spinal metastases from solid tumors, analysis of factors affecting survival. *Cancer* 1995;76:1453-9.
126. Sorensen S, Helweg-Larsen S, Mouridsen H, et al. Effect of high-dose dexamethasone in carcinomatous metastatic spinal cord compression treated with radiotherapy: A randomized trial. *Eur J Cancer* 1994;30A:22-7.

127. Sutcliffe P, Connock M, Shyangdan D, et al. A systemic review of evidence on malignant spinal metastases: natural history and technologies for identifying patients at high risk of vertebral fracture and spinal cord compression. *Health Technol Assess* 2013;17:1-274.
128. Steenland E, Leer JW, van Houwelingen H, et al. The effect of a single dose fraction compared to multiple fractions on painful bone metastases: a global analysis of the Dutch Bone Metastasis Study. *Radiother Oncol* 1999;52:101-9.
129. Sze WM, Shelley MD, Held I, et al. Palliation of metastatic bone pain: Single fraction versus multifraction radiotherapy-a systematic review of randomized trials. *Clin Oncol (R Coll Radiol)* 2003;15:345-52.
130. Talcott JA, Stomper PC, Drislane FW, et al. Assessing suspected spinal cord compression: A multidisciplinary outcomes analysis of 342 episodes. *Support Care Cancer* 1999;7:31-8.
131. Tombal B, Rezazadeh A, Therasse P, et al. Magnetic resonance imaging of the axial skeleton enables objective measurement of tumor response on prostate cancer bone metastases. *Prostate* 2005;65:178-87.
132. Tomita K, Kawahara N, Kobayashi T, et al. Surgical strategy for spinal metastases. *Spine* 2001;26:298-306.
133. Turnpenney J, Greenhalgh S, Richards L, et al. Developing an early alert system for metastatic spinal cord compression (MSCC): Red flag credit cards. *Prim Health Care Res Dev* 2013:1-7.
134. Vakaet LA, Boterberg T. Pain control by ionizing radiation of bone metastasis. *Int J Dev Biol* 2004;48:599-606.
135. Van der Linden YM, Dijkstra SP, Vonk EJ, et al. Prediction of survival in patients with metastases in the spinal column: results based on a randomized trial of radiotherapy. *Cancer* 2005;103:320-8.
136. Van der Linden YM, Steenland E, van Houwelingen HC, et al. Patients with favorable prognosis are equally palliated with single and multiple fraction radiotherapy: Results on survival in the Dutch Bone Metastasis Study. *Radiotherapy and Oncology* 2006;78:245-53.
137. Van der Sande J, Boogerd W. Multiple spinal epidural metastases: an unexpectedly frequent finding. *J Neurol Neurosurg Psychiatr* 1990;53:1001-3.
138. Van Poznak C, Taxel P. Skeletal complications of breast and prostate cancer therapies. In: Rosen CJ, editor. *Primer on the Metabolic Diseases and Disorders of Mineral Metabolism*. Washington DC: ASBMR 2013.
139. Vanel D, Casadei R, Alberghini M, et al. MR imaging of bone metastases and choice of sequence: spin echo, in-phase gradient echo, diffusion and contrast medium. *Semin Musculoskelet Radiol* 2009;13:97-103.
140. Venkitaraman R, Barbachano Y, Dearnaley DP, et al. Outcome of early detection and radiotherapy for occult spinal cord compression. *Radiother Oncol* 2007;85:469-72
141. Venkitaraman R, Sohaib SA, Barbachano Y, et al. Detection of occult spinal cord compression with magnetic resonance imaging of the spine. *Clin Oncol* 2007;19:528-31
142. Venkitaraman R, Sohaib SA, Barbachano Y, et al. Frequency of screening magnetic resonance imaging to detect occult spinal cord compromise and to prevent neurological deficit in metastatic castration-resistant prostate cancer. *Clin Oncol* 2010;22:147-52
143. Weber A, Bartsch T, Karstens JH, et al. Survival in patients with metastatic spinal cord compression from prostate cancer is associated with the number of extra-spinal organs involved. *Anticancer Res* 2013;33:4505-7.
144. Weber A, Bartsch T, Karstens JH, et al. Breast cancer patients with metastatic spinal cord compression: Number of extraspinal organs involved by metastases influences survival. *Strahlenther Onkol* 2014;190:283-6.
145. Westbrook C, Roth CK, Talbot J. Pulse sequences. In: Westbrook C, Roth CK, Talbot J, editors. *MRI in practice*. Blackwell Publishing, 2005.

146. Willey JS, Lloyd SAJ, Bateman TA. Radiation therapy-induced osteoporosis. In: Rosen CJ, editor. *Primer on the Metabolic Diseases and Disorders of Mineral Metabolism*. Washington DC: ASBMR 2013.
147. World Health Organization (WHO). *WHO handbook for reporting results of cancer treatment*. World Health Organization Offset Publication: Geneva (Switzerland) 1979.
148. Wu JS, Wong R, Johnston M, et al. Meta-analysis of dose fractionation radiotherapy trials for the palliation of painful bone metastases. *Int J Radiat Oncol Biol Phys* 2003;55:594-605.
149. Yousem DM, Grossman RI. *Anatomy and degenerative diseases of the spine*. In: Yousem DM and Grossman RI, editors. *Neuroradiology: The Requisites*. Mosby: Elsevier; 2010.
150. Zaikova O, Fosså SD, Kongsgaard U, et al. Pain after palliative radiotherapy for spine metastases. *Clin Oncol (R Coll Radiol)* 2010;22:828-36.
151. Zaikova O, Fosså SD, Bruland OS, et al. Radiotherapy or surgery for spine metastases? *Acta Orthop* 2011;82:365-71.