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Metastatic Spinal Cord Compression in Prostate Cancer

Clinical and Morphological Studies

Sead Crnalic

Department of Surgical and Perioperative Sciences, Orthopaedics
Department of Medical Biosciences, Pathology
Department of Radiation Sciences, Oncology
Umeå University 2012

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To my parents

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Abstract:

Background: Bone metastases occur in most patients with advanced hormone-refractory prostate cancer causing pain, pathologic fractures, and spinal cord compression. Few studies specifically address surgical treatment of metastatic spinal cord compression (MSCC) in prostate cancer. Criteria for identifying patients who may benefit from surgery are poorly defined. Most of the current knowledge regarding tumor biology in prostate cancer is based on studies of primary tumors or soft tissue metastases. The mechanisms regulating growth of bone metastases are not fully established.

Aims: a) to evaluate outcome after surgery for MSCC in prostate cancer and to identify prognostic factors for survival and functional recovery; b) to evaluate current practice for referral of prostate cancer patients with MSCC; c) to analyze expression of androgen receptor (AR), cell proliferation, apoptosis, and prostate-specific antigen (PSA) in bone metastases with regard to survival after surgery for complications of bone metastases.

Patients and Methods: We retrospectively evaluated the hospital records of 68 consecutive patients operated for metastatic spinal cord compression. Tumor tissue from bone metastases was obtained on spinal surgery (54 patients), fracture surgery (4 patients) and biopsy (2 patients), and analyzed by immunohistochemistry.

Results:

Study I: Mortality and complication rate after surgery was high. Patients with hormone-naïve disease and those with hormone-refractory disease with good performance status and without visceral metastases had more favorable survival. The ability to walk after surgery was related to better survival.

Study II: A new score for prognosis of survival after surgery for spinal cord compression includes: hormone status of prostate cancer, Karnofsky performance status, evidence of visceral metastasis, and preoperative serum PSA. The score is simple, tumor specific, and easy to apply in clinical practice.

Study III: Our results suggest that delays in diagnosis and treatment may have negative impact on functional outcome. Pretreatment ability to walk, hormone status of prostate cancer, and time from loss of ambulation influenced neurological recovery after surgery for spinal cord compression.

Study IV: High nuclear AR immunostaining in bone metastases and high preoperative serum PSA were associated with a poor outcome after metastasis surgery in patients with hormone-refractory prostate cancer. Short-term effect of castration therapy disclosed that nuclear AR immunostaining was decreased and apoptosis was increased, but cell proliferation remained largely unaffected.

Conclusion: Prostate cancer patients with metastatic spinal cord compression represent a heterogeneous group. We identified prognostic factors for survival and functional outcome, which may help clinicians in making decisions about treatment. Our results also implicate the need for development of local and regional guidelines for treatment of patients with spinal cord compression, as well as the importance of information to patients at risk.

Svensk sammanfattning

Prostatacancer är den vanligaste maligna tumören hos svenska män med ca 10000 nya fall årligen. Ca 10 % av dem har skelettmetastaser redan vid diagnosen. De flesta utvecklar dock skelettmetastaser senare. Skelettmetastaser orsakar stort lidande med smärtor, patologiska frakturer och ryggmärgskompression. Det finns få studier som belyser ryggmärgskompression vid prostatacancer. Kriterierna för vilka patienter som kan ha nytta av operation är oklara. Bakomliggande mekanismer för utveckling av skelettmetastaser vid prostatacancer är fortfarande ej klarlagda.

Syftet med denna avhandling var att undersöka resultat av kirurgisk behandling för ryggmärgskompression hos patienter med prostatacancer samt att morfologiskt kartlägga karaktären av de vävnadsprover som togs från skelettmetastaser i samband med operation.

I *delstudie I* fann vi att dödlighet och komplikationsfrekvensen var höga efter operation för ryggmärgskompression. De patienter som vid operationstillfället hade obehandlad (hormon-naiv) prostatacancer visade jämförelsevis god överlevnad. God allmän kondition före operation, avsaknad av metastaser i inre organ och förmåga att gå efter operation var förenade med bättre överlevnad bland de patienter som hade tidigare varit behandlade för prostatacancer (hormon-okänslig).

I *delstudie II* identifierade vi preoperativa faktorer av betydelse för överlevnad efter operation för ryggmärgskompression (hormonstatus, patientens allmänna kondition, metastasering i inre organ och PSA nivå i blodet). Med de faktorer som bas konstruerade vi en poängskala som kan användas som beslutsstöd vid behandling av prostatacancerpatienter med ryggmärgskompression.

I *delstudie III* analyserades handläggningsprocessen vid tecken på ryggmärgskompression hos patienter med prostatacancer, samt vilka faktorer som har betydelse för neurologisk utgång efter operation. Vi fann att fördröjning i både diagnostik och behandling kan ha påverkat resultatet av kirurgi. Till exempel kunde vi konstatera att magnetröntgenundersökning ej utfördes under helger på alla sjukhus. Bättre gångförmåga efter operation noterades bland de patienter som kunde gå före operation och/eller de patienter som hade tidigare ej hormonbehandlad prostatacancer. Bland de patienter som hade tappat gångförmågan före

operation hade handläggningstiden stor betydelse för återhämtning av gångförmågan efter operation.

I *delstudie IV* analyserades mikroskopiskt de vävnadsprover som togs från skelettmetastaserna vid operation med särskild inriktning mot faktorer som man vet är viktiga för metastasaktiviteten: exempelvis androgenreceptor (mekanismer för cellerna att reagera på manligt könshormon), PSA (en blodmarkör för prostatacancer), celldelning (proliferation) och programmerad celldöd (apoptos). Högt uttryck av androgenreceptor i skelettmetastaser var förenad med sämre överlevnad hos patienter med hormon-okänslig prostatacancer. Hos de patienter som tidigare inte fått hormonbehandling för prostatacancer, vilka korttid före ryggoperation genomgick orchidectomi (borttagande av testiklarna), hade uttryck av androgenreceptor minskat och programmerad celldöd ökat medan celldelning var i stort sätt oförändrad. Anmärkningsvärt är att den mikroskopiska bilden skilde sig mellan primära tumörer och skelettmetastaser hos de patienter där vi hade tillgång på båda proverna.

Våra fynd talar för att androgenreceptor kan ha en viktig roll i utvecklingen och tillväxten av skelettmetastaser vid prostatacancer. Dessutom visar vår studie att det är viktigt att studera tumörbiologi i skelettmetastaser på de prover som tas vid operation istället för att enbart dra slutsatser om metastaser från studier av primärtumörer.

Vi fann att patienter med prostatacancer och samtidig ryggmärgskompression är en heterogen grupp. Vissa patienter är redan starkt påverkade av sin tumörsjukdom. Kirurgi hos dessa är förenad med hög risk för komplikationer samtidigt som utsikterna för förbättring är små. Det är då ett stort värde att kunna identifiera de patienter som kan dra nytta av en operation, med alla risker det innebär. Vi utvecklade därför ett nytt kliniskt klassningssystem, som kan vara värdefullt stöd vid bedömning av vilka patienter som bör erbjudas operation, och vilka som bör erbjudas någon annan form av behandling såsom strålbehandling eller enbart palliativ omvårdnad. Våra resultat antyder vikten av tidig diagnos och snabb behandling för att uppnå fördelaktigt resultat av behandling för ryggmärgskompression hos patienter med prostatacancer. Nödvändighet av förbättring av lokala och regionala riktlinjer för handläggning av denna patientgrupp har med denna avhandling tydliggjorts. Ökad information till behandlande läkare och till cancerpatienter är nödvändig för att medvetandegöra tidiga symptom och därmed öka möjligheten till tidig behandling av ryggmärgskompression.

Abbreviations

AR	androgen receptor
CI	confidence interval
CT	computerized tomography
HR	hazard ratio
KPS	Karnofsky performance status
LHRH	luteinizing hormone-releasing hormone
MRI	magnetic resonance imaging
MSCC	metastatic spinal cord compression
PSA	prostate-specific antigen

Original Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals:

I. **Outcome after surgery for metastatic spinal cord compression in 54 patients with prostate cancer.**
Crnalic S, Hildingsson C, Wikström P, Bergh A, Löfvenberg R, Widmark A.
Acta Orthop 2012; 83(1): 80-6.

II. **Predicting survival for surgery of metastatic spinal cord compression in prostate cancer: A new score.**
Crnalic S, Löfvenberg R, Bergh A, Widmark A, Hildingsson C.
Submitted.

III. **Early diagnosis and treatment is crucial for neurological recovery after surgery for metastatic spinal cord compression in prostate cancer.**
Crnalic S, Hildingsson C, Bergh A, Widmark A, Svensson O, Löfvenberg R.
Submitted.

IV. **Nuclear androgen receptor staining in bone metastases is related to a poor outcome in prostate cancer patients.**
Crnalic S, Hörnberg E, Wikström P, Lerner U, Tieva O, Svensson O, Widmark A, Bergh A.
Endocr Relat Cancer 2010; 17(4): 885-95.

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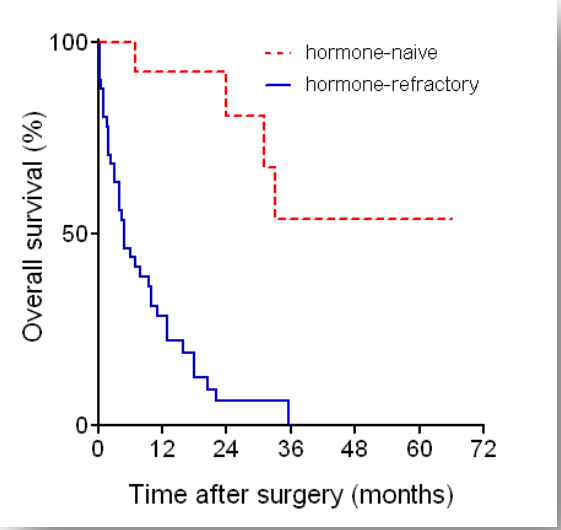
Thesis at a glance

Paper I. Surgery is not appropriate treatment for all patients with spinal cord compression.

Patients and methods: 54 consecutive patients, retrospective study

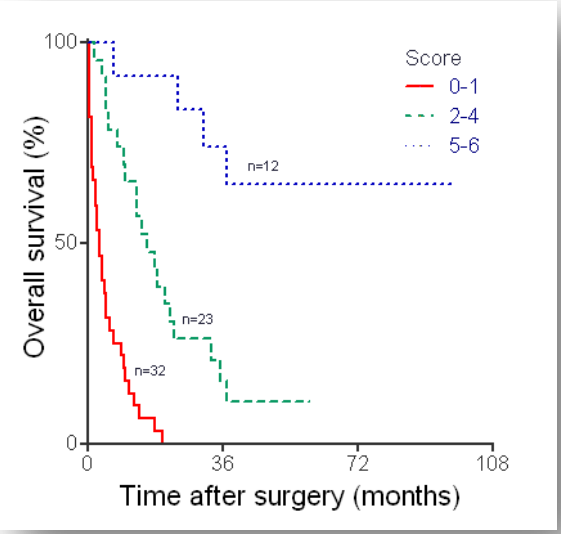
Conclusion: Mortality and complication rates after surgery were high. Hormone-refractory patients with low performance status and/or visceral metastases had less favorable survival. The ability to walk after surgery was related to better survival.



Paper II. A new score for predicting of survival after surgery.

Patients and methods: 68 consecutive patients, retrospective study

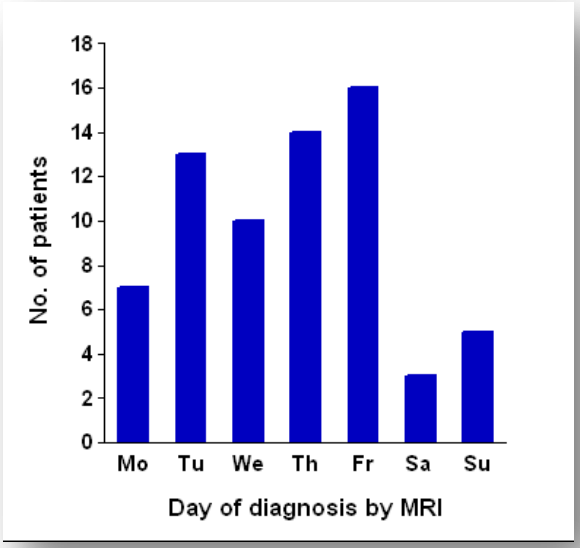
Conclusion: A new score for prognosis of survival includes: hormone status of prostate cancer, Karnofsky performance status, evidence of visceral metastasis, and preoperative serum PSA. The score is simple, tumor specific, and easy to apply in clinical practice.



Paper III. Early diagnosis and treatment is crucial for neurological recovery.

Patients and methods: 68 consecutive patients, retrospective study.

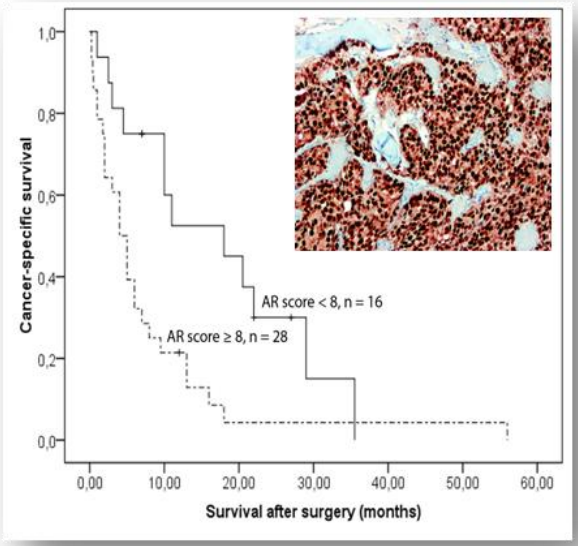
Conclusion: Delays in diagnosis and treatment may have negative impact on neurological recovery. Ability to walk before surgery, hormone naïve prostate cancer, or shorter time from loss of ambulation was associated with better functional outcome.



Paper IV. Androgen receptors have important role in prostate cancer bone metastasis.

Patients and methods: 60 patients, immunohistochemistry**.**

Conclusion: High nuclear androgen receptor (AR) immunostaining in bone metastases and high serum PSA were associated with a poor outcome after metastasis surgery in patients with hormone-refractory prostate cancer.



Introduction

Prostate cancer epidemiology

Prostate cancer is one of the leading causes of morbidity and mortality in men in Europe, accounting for about 190,000 new cases diagnosed and about 80,000 deaths per year (Damber and Aus 2008).

In Sweden, prostate cancer is the most common cancer in men with one of the highest incidences in Europe. In 2010, 9,697 new cases of prostate cancer were diagnosed (The National Board of Health and Welfare, Sweden). On average, the incidence has increased by 2.4% annually over the last 20 years following the advent of prostate-specific antigen (PSA) screening (Figure 1).

Consequently, interpretation of temporal trends in prostate cancer has become difficult. However, mortality has remained fairly constant (Figure 1).

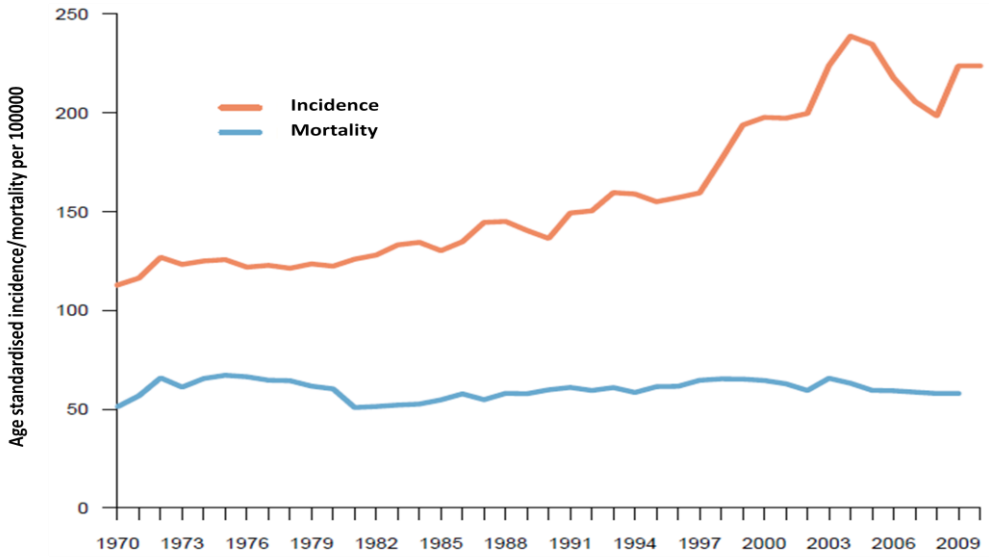


Figure 1. Age standardised incidence/mortality per 100000 men in Sweden between 1970 and 2010 (Adopted from the National Prostate Cancer Register in Sweden).

Prostate cancer is the leading cause of cancer-related deaths in Swedish men, contributing to about 2500 deaths each year. In 2010, the lifetime risk for a man to die of prostate cancer in Sweden was 5.5%. Most of men are diagnosed with prostate cancer between ages 65 and 69 years, while the majority of prostate cancer-related deaths occur in age over 79 years.

By the year 2009 there were 75,647 men living with a prostate cancer diagnosis in Sweden.

In 2010, 323 new cases were diagnosed in Västerbotten County and 1020 new cases in Umeå Medical Region (The National Board of Health and Welfare, Sweden).

Bone metastasis in prostate cancer

Metastatic mechanisms

Prostate cancer metastasizes predominantly to bone. Other common sites of metastases are lungs, liver, and lymph nodes. More than 80% of patients with advanced prostate cancer have bone metastases, mostly in the spine and pelvis (Bubendorf et al. 2000). There are two possible general explanations of metastatic process that may be involved in the development of bone and particularly spinal metastases in prostate cancer.

According to the hemodynamic hypothesis proposed by Ewing in 1928 the distribution of metastases is based on blood flow (Bubendorf et al. 2000). Consequently, the prostate cancer cells are selectively delivered to the bone. This could be explained by the existence of a paravertebral system of veins called Batson's plexus, which drains the prostatic venous blood to the lower lumbar spine (Batson 1940). This venous system is devoid of valves, and therefore any increased pressure in the vena cava system results in increased flow backwards into Batson's plexus. Results of one autopsy study on 1589 patients with prostate cancer lend support to this hypothesis as spine metastases were found in more than 80% of the patients with the highest frequency in the lumbar spine (Bubendorf et al. 2000). Alternatively, according to the hemodynamic hypothesis, dissemination of prostatic venous blood flow directly into the vena cava may account for lung and other visceral metastases.

A 'seed and soil' hypothesis was proposed by Paget more than 100 years ago. According to this theory the predilection of certain tumors to spread to certain organs involves the existence of specific favorable interactions between tumor cells (seed) and the microenvironment at the metastatic site (soil). Fidler (2003) recently expanded this hypothesis to emphasize the high selectivity of the metastatic process which favors survival of only a small

subpopulation of cells from a heterogeneous primary tumor. Thus the specific affinity between tumor cells and bone may be an explanation of predominantly bone metastases in prostate cancer.

Interactions between prostate cancer cells and bone

Normal bone remodeling is a balance between resorption by osteoclasts and bone formation by osteoblasts. In prostate cancer bone metastasis this balance is disrupted. Consequently, disordered proliferation of osteoblasts results in bone deposition and incomplete bone calcification. The complex interactions between tumor cells, bone cells, and bone matrix are involved in a vicious cycle of osteoblastic bone metastasis (Figure 2).

Tumor cells affect osteoblasts

Prostate cancer cells can directly affect osteoblast function by secreting factors that regulate osteoblast proliferation and differentiation. These factors include bone morphogenic protein (BMP), transforming growth factor-ß (TGFß), insulin-like growth factor (IGF), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), endothelin-1 (ET-1), and the bone metastasis factor MDA-BF-1. Prostate cancer cells can also indirectly influence bone formation by producing factors that modify bone microenvironment, such as urokinase-type plasminogen activator (uPA) and prostate specific antigen (PSA) (Logothetis and Lin 2005, Pinski and Dorff 2005).

Osteoblasts affect tumor cells

Osteoblasts and fibroblasts from bone marrow secrete factors that may support growth of prostate cancer cells in bone. Bone matrix proteins (osteopontin, osteonectin, and bone sialoprotein) from newly formed bone may enhance capability of migration and invasion in prostate cancer cells (Rosol 2000).

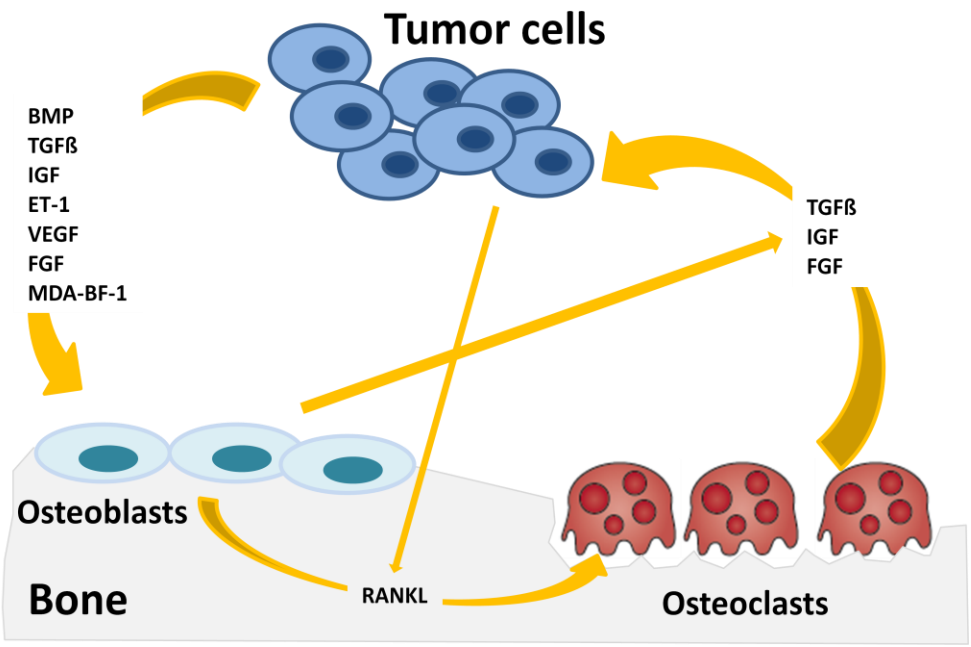


Figure 2. The vicious cycle of osteoblastic bone metastasis.
(Redrawn according to Logothetis and Lin 2005, Ibrahim et al. 2010)

Tumor cells and osteoblasts affect osteoclasts

Prostate cancer cells and osteoblasts can regulate osteoclast activity by trigging a receptor activator of nuclear factor-κB ligand (RANKL), a key activator of osteoclast differentiation. This activity is mediated by growth factors and cytokines such as interleukin, tumor necrosis factor-ά (TNF-ά), and parathyroid hormone-related protein (PTHrP) (Logothetis and Lin 2005, Morrissey and Vessella 2007). Level of RANKL is increased in prostate cancer bone metastases as compared with primary tumors and soft tissue metastases (Brown et al. 2001).

There is evidence suggesting that osteoblasts, due to their ability to influence the proliferation of both prostate cancer cells and osteoclasts, can function as major regulators of the progression of prostate cancer in bone (Logothetis and Lin 2005, Choueiri et al. 2006, Ibrahim et al. 2010).

Metastatic spinal cord compression

Frequency

In the U.S., patients dying of cancer have an estimated 3.4% incidence of metastatic spinal cord compression, with lung cancer (25%), prostate cancer (16%), and multiple myeloma (11%) as the most common underlying cancer diagnoses (Mak et al. 2011). In a population-based study from Canada the incidence of metastatic spinal cord compression in the last 5 years of life was 2.5% (Loblaw et al. 2003). Both studies rely on in-hospital data, thus probably underestimating the true incidence. Autopsy studies have indicated that 5% of patients dying of cancer have metastatic spinal cord compression (Cole and Patchell 2008). The incidence of metastatic spinal cord compression will probably increase in the future since the incidence of cancer is expected to rise due to an aging population.

Localization

The thoracic spine is mostly involved accounting for approximately 60% of cases, followed by the lumbosacral spine (30%) and the cervical spine (10%) (Helweg-Larsen et al. 1997, Schiff et al. 1998). Multiple sites of compression are seen in approximately 30% of patients (Schiff et al. 1998).

There are several explanations for predominant involvement of the thoracic spine. The number of vertebrae is highest in the thoracic spine, the size of spinal canal in proportion to the spinal cord is lowest, and the contour of the thoracic spine with the physiological kyphosis may aggravate the angulation caused by vertebral collapse (Helweg-Larsen et al. 1997).

Pathophysiology

The metastatic tumors usually compress the spinal cord indirectly from growth of the tumor in vertebral body, vertebral lamina, pedicle, or spinous process. The less common way is direct growth of paravertebral tumor through an interevertebral foramen, which is usually

seen in lymphomas or neuroblastomas (DeAngelis and Posner 2009). The pathophysiology of spinal cord compression and its consequences regarding neurologic symptoms and signs is not fully understood. Direct cord compression, edema, and secondary ischaemia play important roles. Edema results either from direct compression of the cord or from stenosis and occlusion of epidural venous plexus. Initially, edema can be partially reduced by corticosteroids, which temporarily improves clinical symptoms. At this stage decompression may improve neurologic recovery. If compression progresses, arterial blood flow to the spinal cord is impaired, which if untreated leads to infarction and irreversible neurologic damage (Figure 3).

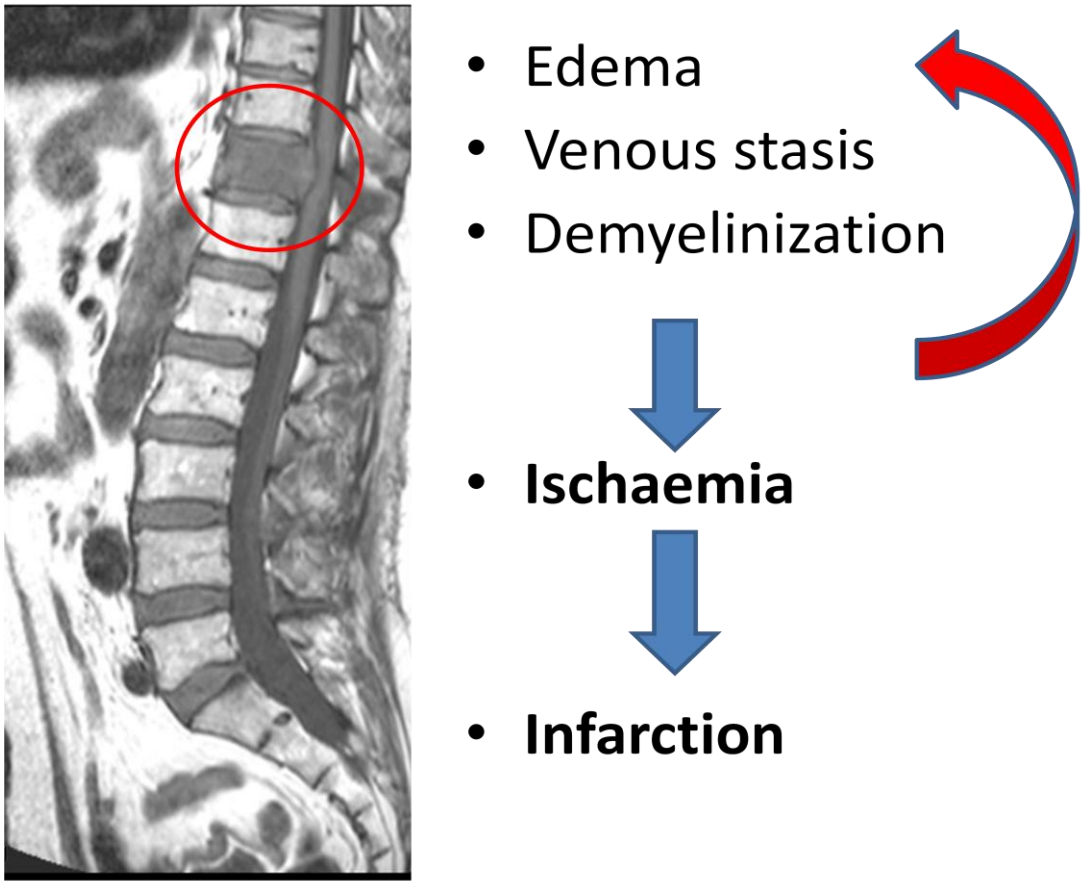


Figure 3. Pathophysiology of spinal cord compression.

Clinical symptoms

Back pain is the earliest symptom of spinal cord compression in 80 – 90% of patients, and is present in more than 95% of patients at diagnosis, with a median duration of 8 weeks (Prasad and Schiff 2005, DeAngelis and Posner 2009). Generally, there is discordance between the level of pain and the structural level of compression (Levack et al. 2002). Back pain caused by spinal metastasis may be local, radicular, mechanical, or referred.

Local pain is usually the first symptom, often at night, and is relieved by arising and walking (DeAngelis and Posner 2009). Radicular pain results from compression of nerve roots within the spinal canal or on exit through an intervertebral foramen. It presents either alone or in combination with local pain (Levack et al. 2002). Mechanical pain is associated with spinal instability. It is caused by collapse of the vertebral body and is aggravated by axial loading (i.e. sitting or standing).

Motor weakness is the second most common symptom at diagnosis and is present in 35 – 85% of patients (Prasad and Schiff 2005, DeAngelis and Posner 2009). It usually begins in the legs regardless of the compression site and the patient often complains of difficulty walking. In a study of Levack et al (2002) the median duration of weakness was 20 days before presentation. About 50 – 70% of patients are non-ambulatory at diagnosis (Husband 1998, Cole and Patchell 2005).

Sensibility loss is a late sign of spinal cord compression, usually concurrent with the development of motor deficits or shortly afterward. It seldom occurs before motor deficits or pain. Approximately 50 – 70% of patients have some type of sensory deficit at diagnosis of spinal cord compression (Levack et al. 2002). Loss of sensibility typically begins distally and ascends as the cord compression progresses. In one prospective study patients complained of sensory

abnormality in median 12 days before diagnosis (Levack et al. 2002). In the same study the clinical level of altered sensibility correlated poorly with the level of compression on MRI. In only 40% of the patients the sensory level was within 3 dermatomes (either above or below) of the MRI level, and in only 16% of patients the sensory level was helpful in identifying the level of compression.

Bladder and bowel dysfunction is present in more than 50% of patients at diagnosis (DeAngelis and Posner 2009). Usually these disturbances occur late in the progression of spinal cord compression, and rarely as the sole presenting complaint.

Diagnosis

MRI is the procedure of choice for the diagnosis of metastatic spinal cord compression, with an overall accuracy of 95% (sensitivity 93%, specificity 97%) (Cole and Patchell 2008). It is important to visualize the entire spine because up to a third of patients may have multiple sites of compression (Schiff et al. 1998).

Prognosis

Length of survival and the ability to walk are the most important outcomes when deciding about treatment of patients with metastatic spinal cord compression.

In general, survival in this group of patients depends on the primary tumor. Life expectancy of minimum 3 months is probably reasonable when considering patients eligible for surgery. For radiotherapy a minimum survival of at least a month is considered appropriate (Bartels et al. 2008).

The estimation of life expectancy is complex and needs a multidisciplinary approach. Therefore, scoring systems have been proposed for predicting survival in patients with spinal metastases. These are based on retrospective data from patients treated with surgery (Tokuhashi et al. 1990, Bauer and Wedin 1995, Sioutos et al. 1995, Tomita et al. 2001, Tokuhashi et al. 2005, North et al. 2005) or radiotherapy (Tokuhashi et al. 2005, van der Linden et al. 2005). The Tokuhashi score is mostly

used for prognosis of survival after surgery. Several studies reported good prognostic value of the score when evaluated on patient material consisting of different tumors (Enkaua et al. 1997, Ulmar et al. 2007, Yamashita et al. 2011) or on specific tumor types like renal cancer (Ulmar et al. 2007) or breast cancer (Ulmar et al. 2005). Other studies on various tumors (Leithner et al. 2008, Pointillart et al. 2011) or specifically lung cancer (Ogihara et al. 2006, Hessler et al. 2011) found the score less reliable. Van der Linden score was developed on the data from patients treated with radiotherapy and successfully externally validated (Chow et al. 2006). However, the score is not considered appropriate for patients who are candidates for surgery (Bartels et al. 2008). In general, these prognostic scores function better when applied on patient materials consisting of different primary tumors since the type of primary tumor is one prognostic parameter. However, the accuracy of the scores fades when it comes to the specific tumor type. Therefore there is a need for tumor specific prognostic tools or more universal models which could be applied with the same accuracy on all tumors. Recently, Bartels et al (2007) developed a model to predict the survival of patients with spinal metastasis based on retrospective data of patients having undergone radiotherapy. The model is promising due to its simplicity and universal prognostic parameters.

Treatment

Corticosteroids

Steroids reduce spinal cord edema and may have a tumoricidal effect on lymphomas and sometimes on breast cancer (DeAngelis and Posner 2009). A randomized study of high-dose steroids versus no steroids in patients who underwent radiotherapy for spinal cord compression indicated improved functional outcome in the steroid group at 3 and 6 months after treatment (Sørensen et al. 1994). There is no consensus on the optimal doses to be used in patients with

spinal cord compression. Without strong evidence for use of high doses of steroids any dose in the range of 16 – 100 mg dexamethasone daily is usually considered appropriate (Prasad and Schiff 2005, Cole and Patchell 2008). Interestingly, a phase II study reported that corticosteroids may not be necessary in combination with radiotherapy in patients without neurological dysfunction (Maranzano et al. 1996).

Radiotherapy

External beam radiotherapy has long been standard in the treatment of patients with metastatic spinal cord compression. Although the treatment is palliative, the radiotherapists are often faced with complex issues. A meaningful radiation dose must be balanced with avoiding adverse effects, and the fractionation scheme should be weighed against performance status and expected survival.

The most appropriate dose and fractionation schedule are still controversial (Rades et al. 2005, Prewet et al. 2010). Regarding functional outcome, there are no differences between short and long course treatments with exception of myeloma patients who benefit more from long course radiotherapy (Agarawal et al. 2006). In a randomized study Maranzano et al. (2005) compared short course (16 Gy in one week) with split course (30 Gy in 2 weeks) and found similar rates in back pain relief, maintaining ability to walk, and bladder function.

Recurrences after radiotherapy occur more often with short course radiation than with a long course schedule (Agarawal et al. 2006). In patients with longer expected survival such as breast cancer and prostate cancer, a long course schedule provided a better local control (Rades et al. 2006).

The prognostic factors associated with favorable functional outcome after radiotherapy are: favorable histology, longer interval between tumor diagnosis and spinal cord compression (>24 months), involvement of 1 to 2 vertebrae, slow development of motor deficits (>14 days),

ability to walk before radiotherapy, and good performance status (Helweg Larsen et al. 2000, Rades et al. 2002, Rades et al. 2006, Bartels et al. 2008).

Surgical treatment

Goals of surgery are relief of neurologic symptoms and pain by decompression and stabilization. Traditional indications for surgery include radioresistant tumors, neurologic deterioration during or after radiotherapy, spinal instability or bone fragment in the spinal canal, paraplegia not longer than 48 hours, life expectancy of at least 3 months (Klimo et al. 2005, Witham et al. 2006, Quraishi et al. 2010).

The results of one meta-analysis showed that the patients who underwent surgery (n=999) were 1.3 times more likely to be ambulatory after treatment and twice as likely to regain the ability to walk after treatment compared with the patients who received radiotherapy (n=543) (Klimo et al. 2005).

Surgery followed by radiotherapy was compared to radiotherapy alone in a randomized, multicenter, non-blinded study (Patchell et al. 2005). After surgery followed by radiotherapy significantly more patients were able to walk after treatment and maintained walking ability for a longer time than after radiotherapy alone. This study caused a major breakthrough in favor of the surgical treatment followed by radiotherapy. However, even in these highly selected patients median survival was only 4.2 months. In one later study, when the same data were stratified according to age, the authors found that at ≥65 years the beneficial effect of surgery fades to become equivalent to that of radiation alone (Chi et al. 2009).

Surgery is associated with significant morbidity. Mortality rates up to 13% and complication rates of up to 54% were reported in the literature (Loblaw et al. 2005). An overview of National Inpatients Sample, including 26,233 admissions of surgically managed spinal metastases in the U.S. between 1993 and 2002, showed

5.6% in-hospital mortality rate and 21.9% complication rate (Patil et al. 2007). Surgery is even more complicated in patients who had radiotherapy before surgery (Ghogawala et al. 2001).

Spinal cord compression in prostate cancer

Frequency

In reports limited to material from single institutions, 3 – 7% of patients with prostate cancer have spinal cord compression (Kuban et al. 1986, Honens de Lichtenberg et al. 1992, Rosenthal et al. 1992).

One population-based study reported 7% cumulative incidence of spinal cord compression in the 5 years preceding death from prostate cancer (Loblaw et al. 2003). This incidence increased to 17% in men dying from prostate cancer in the age group 40 – 60 years. In the same study 0.2% of all prostate cancer patients had metastatic spinal cord compression at diagnosis (average for all cancers was 0.23%). Prostate cancer accounted for 16 % of approximately 15,000 cases of metastatic spinal cord compression in the U.S. Inpatient Sample between 1998 and 2006 (Mak et al. 2011). Remarkably, occult spinal cord compression was found on MRI in 27% (Venkitaraman et al. 2007) and 32% (Bayley et al. 2001) of patients with bone metastases in the absence of neurological symptoms. This frequency increased to 44% in patients with >20 metastases on bone scan (Bayley et al. 2001).

Treatment outcome

The results of surgery for spinal cord compression in prostate cancer are usually reported in series comprising different tumors, making it difficult to draw conclusions on this specific tumor type. In some studies limited to prostate cancer surgical treatment is analyzed together with the results of radiotherapy (Flynn and Shipley 1991, Huddart et al. 1997, Cereceda et al. 2003, Tazi et al. 2003). Only a few retrospective studies specifically address surgical treatment of metastatic spinal cord compression in prostate cancer (Iacovou et al. 1985,

Shoskes and Perrin 1989, Williams et al. 2009, Weiss et al. 2012). The median survival and ambulatory status in different series are shown in Table 1. Non-ambulatory patients regained their ability to walk in 48 – 67% cases after surgical treatment alone (Iacovou et al. 1985, Shoskes and Perrin 1989, Williams et al. 2009), whereas this proportion was 57 – 63% in mixed series (Huddart et al. 1998, Tazi et al 2003) and 33% in a study of radiotherapy alone (Rades et al. 2006). Generally, 75 – 100% of preoperatively ambulatory patients retained their functional status irrespective of the treatment modality (Iacovou et al. 1985, Shoskes and Perrin 1989, Huddart et al. 1998, Rades et al. 2006, Williams et al. 2009).

Patients with no previous hormone therapy are included in only a few reports. The survival and functional outcome for these patients were better if they were treated with surgery or surgery followed by radiotherapy (Iacovou et al 1985, Huddart et al. 1998, Tazi et al. 2003, Jansson and Bauer 2006) than after radiotherapy alone (Rades et al. 2006).

Table 1. Series reporting treatment of metastatic spinal cord compression in prostate cancer

Author	Year	No. of patients	Type of treatment			Ambulatory patients (%)		Median survival[a]
			S	RT	S+RT	Pre-treatment	Post-treatment	
Iacovou et al.	1985	37	37		NS	19	54	12
Shoskes & P.	1989	28	28			54	82	7[b]
Flynn & Shipley	1991	56	11	15	18	16	54	7
Rosenthal et al.	1992	29		21	6	NS	42	4.5
Smith et al.	1993	26		23	3	46	85	NS[c]
Huddart et al.	1997	69		53	14	42	67	7
Tazi et al.	2003	24		12	9	13	63	4
Rades et al.	2006	281		281		57	66	17
Williams et al.	2009	44	33		11	73	86	5.4
Weiss et al.	2012	193	193		NS[d]	25	62	6

S, surgery; RT, radiotherapy; NS, not stated
[a] Months; [b] Median survival of patients who had died; [c] Mean survival 18 months.
[d] Not stated, but institutional routine is radiotherapy after surgery.

Summary of diagnosis and management of metastatic spinal cord compression:

Key points

- Inform cancer patients at risk about early symptoms of metastatic spinal cord compression.
- Onset of neck or back pain in a patient with known cancer should be considered as a consequence of spinal metastasis until proved otherwise.
- Urgent referral is critical – early diagnosis and treatment improves functional outcome and quality of life.
- MRI of the whole spine should be performed:
  -within one week in the case of pain suggestive of spinal metastases
  -within 24 hours in the case of spinal pain and neurological symptoms suggestive of metastatic spinal cord compression
  -sooner if emergency treatment is needed.
- Initial treatment includes corticosteroids.
- Definitive treatment, either surgery or radiotherapy, should be started before any further neurological deterioration and ideally within 24 hours of the confirmed diagnosis.

Adopted according to NICE guidelines (National Institute for Health and Clinical Excellence 2008, White et al. 2008, Quraishi and Esler 2011).

Objectives

General aim

To study clinical and morphological aspects of metastatic spinal cord compression in patients with prostate cancer.

Specific aims

Study I

To evaluate results of surgery including complications, survival, and neurological outcome.

Study II

To identify parameters of importance for survival and to make a clinical score for prediction of survival after surgery.

Study III

To evaluate current practice for referral and diagnosis of spinal cord compression and to identify predictors for functional recovery.

Study IV

To analyze bone metastases in order to investigate possible associations between morphological markers of prostate cancer (androgen receptor, PSA, proliferation, apoptosis) and their relation to survival.

Patients and Methods

Papers I, II, and III

We analyzed 68 consecutive patients with prostate cancer operated for metastatic spinal cord compression at Umeå University Hospital, Sweden, between September 2003 and September 2010. Three patients with prostate cancer and metastatic spinal compression were excluded, two because of another coexisting malignancy, and one in whom spinal cord compression was caused by epidural hematoma due to previous epidural anesthesia during abdominal surgery.

The first 54 consecutive patients were included in Paper I, whereas all 68 patients were included in Papers II and III (Figure 4).

The indication for surgery was neurological deficit. At surgery 53 patients were already diagnosed with hormone-refractory (castration-resistant) prostate cancer, whereas 15 patients had previously untreated, hormone-naïve prostate cancer. The anatomic location of spinal lesions was assessed by preoperative MR imaging. Neurological function was graded according to the Frankel scale (Frankel et al. 1969; Table 2). The Karnofsky performance status scale (KPS) was used to assess functional status of the patients, as it was before presentation with neurological symptoms (Karnofsky et al.1948; Table 3).

The postoperative follow-up was defined as the interval between the date of operation and the latest follow-up examination or death. In Paper III, intervals to diagnosis and treatment were expressed in terms of whole days according to Husband (1998), where an interval of <24 hours = 0 days, ≥24<48 hours = 1 day, etc.

Table 2. Frankel scale

Frankel grade	Neurological function
A	Complete lesion (paraplegia)
B	Only sensory function
C	Motor function present but not of practical use (non-ambulatory)
D	Motor function present, sufficient to allow walking (ambulatory)
E	No neurological symptoms

Table 3. Karnofsky performance status scale.

Definition	%	Criteria
Able to carry on normal activity and to work. No special care is needed.	100	Normal; no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work. Able to live at home, care for most personal needs. A varying amount of assistance is needed.	70	Cares for self. Unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self. Requires equivalent of institutional or hospital care. Disease may be progressing rapidly.	40	Disabled, requires special care and assistance.
	30	Severely disabled; hospitalization is indicated although death not imminent.
	20	Very sick; hospitalization necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

Treatment before surgery for spinal cord compression

The surgical and medical therapies were not randomized. High-dose steroids were prescribed to 64 of 68 patients after the onset of neurological symptoms.

Hormone-refractory group

In this group 27 of 53 patients had bone metastases at primary diagnosis. Treatment of primary prostate cancer consisted of androgen deprivation therapy, either with luteinizing hormone-releasing hormone (LHRH) agonists (n=43) or orchiectomy (n=10). Two patients underwent previous radical prostatectomy, and 7 patients received curative radiation therapy (78 Gy). Additionally, 35 patients also received antiandrogens. After failure of hormone treatment 10 patients were given chemotherapy. Skeletal and non-skeletal metastases were treated with palliative radiotherapy in 23 patients. Six of them were in continuous pain and received radiotherapy to the same spinal level as the operation site at median interval of 7 (4 - 18) months before spinal surgery. Additionally 3 of these 23 patients had radiation treatment due to neurological symptoms 9 days, and 8 and 15 months, respectively, before spinal surgery. Four patients received bisphosphonates (zolendronic acid) and 5 were treated with radioisotopes. In addition, 11 patients were on continuous therapy with low-dose prednisone, mainly for pain relief, during 5.5 (1.5 – 12) months before surgery.

Hormone-naïve group

Patients were treated with androgen ablation (orhiectomy 14 patients, LHRH agonist 1 patient) either a short time before (2 – 7 days, 5 patients), or immediately after spinal surgery (10 patients). These patients were considered as clinically hormone-naïve and were thus included as a whole group in the three clinical studies. In paper IV, the short-term castrated patients were analyzed as a separate group.

Paper IV

Patients

This study comprised 60 patients with bone metastasis from prostate cancer. Tumor material for histological analysis was obtained from 54 patients operated for metastatic spinal cord compression, 4 patients operated for pathological fracture of the femur, and in 2 patients CT-guided vertebral needle biopsies were taken immediately before and 3 days after surgical castration. Biopsy material from primary tumors was available for 16 patients.

Immunohistochemistry

Paraffin sections (5µm) were stained with haematoxylin-eosin, and immunostained for ARs (PG-21, Upstate, Lake Placid, NY, USA), PSA (A0562, Dako, Stockholm, Sweden), activated caspase-3 (Cell Signalling, Danvers, MA, USA), Ki67 (MIB 1, DAKO), and chromogranin A (5H7, Novocastra, Leica Microsystems, Kista, Sweden). The cryostat sections were immunostained following the protocol as above, except that antigen retrieval was not used.

Quantification of immunohistochemical staining

The percentage of apoptotic (caspase-3-positive cells or cells showing the nuclear morphology of apoptosis in haematoxylin-eosin-stained sections) and proliferating (Ki67-positive) tumor epithelial cells was scored by evaluating 300 – 1000 cells per patient. The PSA staining and AR (Upstate antibody) staining were quantified by scoring the intensity (0, no staining; 1, weak; 2, moderate; and 3, intense staining) and the percentage of tumor cell stained (1, 1 – 25%; 2, 26 – 50%; 3, 51 – 75%; and 4, 76 – 100%). A combined staining score, ranging from 0 to 12, was then calculated by multiplying intensity with distribution. Occasional cases were excluded because of lack of staining in the positive control (Ki67), too few tumor cells to count (for caspase-3) and missing paraffin block (for Ki67, caspase-3 and ARs).

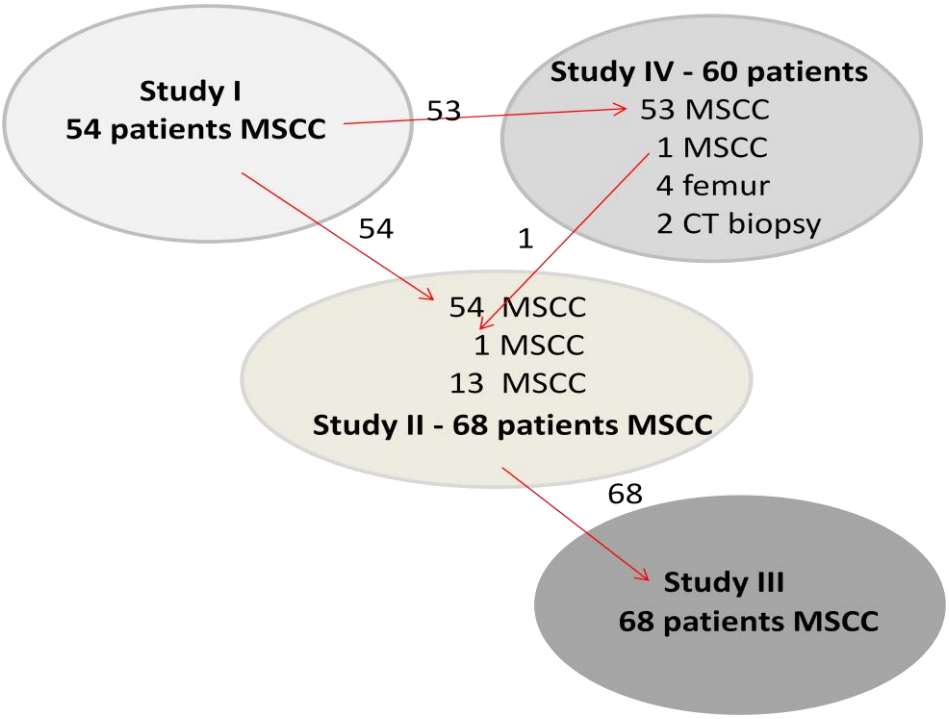


Figure 4. Distribution of patients through the studies (MSCC, metastatic spinal cord compression).

Statistical analysis

Two independent samples were compared with the Mann-Whitney *U* test and proportions with the Fisher's exact test. Correlations between variables were analyzed using Spearman rank test. Paired observations were compared using the Wilcoxon test.

Survival was estimated by Kaplan-Meier analysis with death from prostate cancer as event. Survival curves were compared with the log rank-test. The Cox proportional hazards model was used to assess the effects of prognostic variables. A p-value of ≤ 0.05 was considered statistically significant. Statistical analysis was performed using GraphPad Prism 5.0 (GraphPad Inc., San Diego, CA) and SPSS 17.0 and 18.0 (SPSS Inc., Chicago, IL) software.

Results

Papper I

Posterior decompression was performed in 29 patients, and posterior decompression with stabilization in 25. Within one month after surgery, complications occurred in 19 of the 54 patients and 6 of them died. Median survival was 5 months in the hormone-refractory group. Among these patients low performance status and/or presence of visceral metastasis were associated with less favorable survival. More than half of the patients in the hormone-naïve group were still alive at the latest follow-up (Figure 5). All 6 ambulatory patients retained their functional status and 27 of the 48 (56%) non-ambulatory patients regained their ability to walk one month after surgery. None of the patients, who were non-ambulatory 4 weeks postoperatively, improved neurologically on later follow-up. Ability to walk after surgery was related to improved survival (Figure 6).

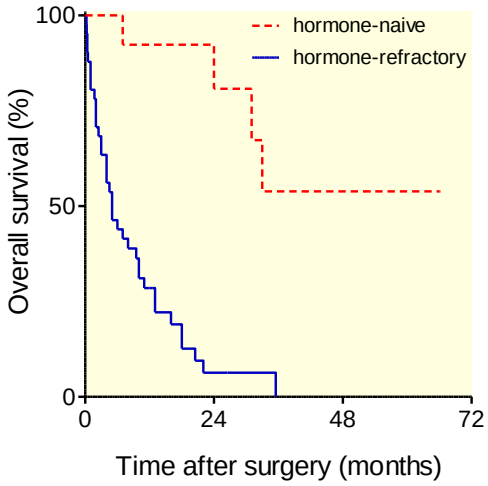


Figure 5. Survival according to hormone status.

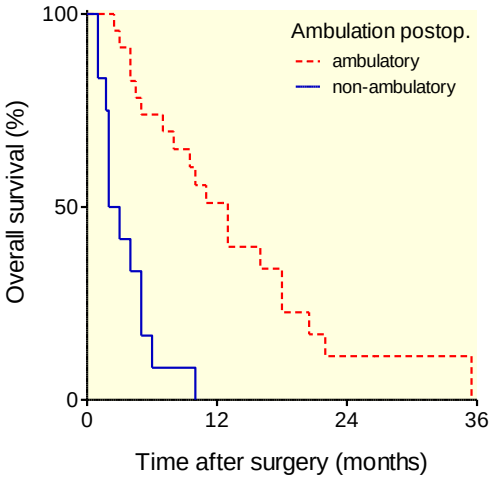


Figure 6. Survival according to the ambulatory status after surgery (hormone-refractory group).

Paper II

Hormone status, performance status (KPS), visceral metastasis, and serum PSA were related to survival in Kaplan-Meier analysis. Multiple Cox regression in the hormone-refractory group showed that KPS (≤70% vs. ≥80%; HR=4.0, 95% CI: 1.6-10) was the strongest predictor of survival compared with visceral metastasis and serum PSA. The prognostic score was constructed by adding the hormone status to these 3 parameters (Table 4). Consequently we gave more weight in the score to hormone status and KPS.

The total scores ranged from 0 to 6. Three prognostic groups were formulated: group A (n=32) with scores 0-1; group B (n=23) with scores 2-4, and group C (n=12) with scores 5-6 (Figure 7). The median overall survival was 3 (0.3 – 20) months in group A, 16 (1.8 – 59) months in group B, and in group C more than a half (7 of 12) of the patients were still alive.

Table 4. A new score

Prognostic factor	Points
Hormone status	
Hormone-naive	2
Hormone-refractory	0
KPS (%)	
80-100	2
≤70	0
Visceral metastasis	
Absent	1
Present	0
PSA (ng/ml)	
Hormone-naive	1
Hormone-refractory	
< 200	1
≥ 200	0

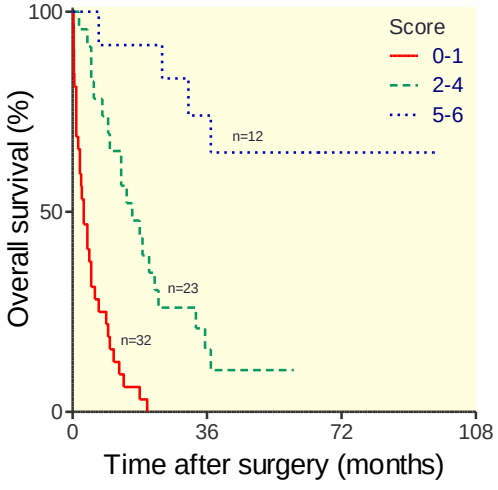


Figure 7. Survival curves for the score groups.

Paper III

Patients who initially presented to a local hospital had longer intervals to diagnosis and surgery than those who presented directly to the cancer centre (Table 5). The number of MRI investigations increased through the week being maximal on a Friday, with only few examinations during weekends. Median interval between admission to the cancer centre and surgery was 19 hours. Generally, ability to walk before surgery, hormone-naïve prostate cancer, and shorter interval from loss of ambulation were predictors of better neurological outcome (Table 6).

In patients with hormone-refractory cancer that were non-ambulatory before surgery factors associated with regaining of ambulation were: duration of paresis <48 hours, good preoperative performance status (KPS 80 – 100%), preoperative PSA serum levels <200 ng/ml, and surgery with posterior decompression and stabilization.

Table 5. Delay to surgery for spinal cord compression[a].

Delay to surgery (days)	Referred from local hospital	Directly admitted to cancer centre	P-value[b]
From first admission to hospital	2 (0 – 24)	1 (0 – 4)	0.004
From MRI diagnosis	1 (0 – 14)	0 (0 – 3)	0.017
From loss of ambulation	1 (0 – 7)	1 (0 – 3)	0.107

[a]Data are given as median (range); [b]Mann-Whitney test.

Table 6. Clinical features influencing functional status after surgery.

	4 weeks after surgery		P-value
Before surgery	Ambulatory	Non-ambulatory	
Functional status (no. of pat.)			
Ambulatory (n=8)	8	0	
Non-ambulatory (n=60)	32	28	0.017[a]
Non-ambulatory (no. of pat.)			
Hormone-naïve (n=14)	11	3	
Hormone-refractory (n=46)	21	25	0.037[b]
Non-ambulatory (days)			
Time from loss of ambulation	1 (0 – 3)	2 (0 – 7)	0.002[c]

[a] Before surgery ambulatory/non-ambulatory, Fisher's exact test.
[b] Hormone naïve/hormone refractory, Fisher's exact test.
[c] Data are presented as median (range), Mann-Whitney test.

Paper IV

The nuclear androgen receptor (AR) staining score in bone metastases was related to tumor cell proliferation but it was not associated with other downstream effects of AR activation such as apoptosis and PSA staining, and it was only marginally related to the presence of neuroendocrine cells. In patients with hormone-refractory prostate cancer, high nuclear AR immunostaining was associated with a poor outcome after surgery for complications of bone metastases (Figure 8).

In the hormone-refractory group, nuclear AR staining, apoptosis and PSA appeared to be lower whereas the Ki67 labeling index was higher in metastases than in primary tumors (Table 7).

After surgical castration median nuclear AR staining score was decreased, the PSA score and Ki67 labeling index were unaffected, and the apoptosis index was increased as compared to hormone-naïve metastases (Table 8).

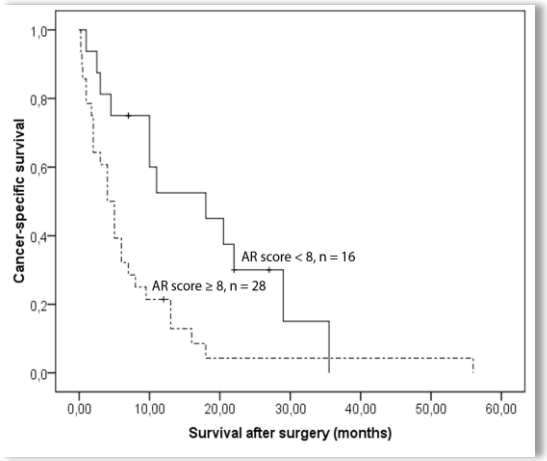


Figure 8. Survival according to AR score

Table 7. Comparison of primary tumors and corresponding metastases in 14 patients in the hormone-refractory group

Parameter	Primary tumor	Metastasis	P value
AR score	12	7	ns
Apoptosis index	1.5	1.2	ns
Ki67 index	6.2	16	<0.05
PSA score	12	8	<0.05

Table 8. Short-term effect (2 – 7 days) of surgical castration

Parameter	Hormone-naïve n=11	Short-t. castrated n=7	P value
AR score	8	3	<0.05
Apoptosis index	2.1	6.6	<0.05
Ki67 index	17	14	ns
PSA score	9	4	ns

Discussion

Do all benefit from surgery?

Prostate cancer patients with metastatic spinal cord compression represent a clinically heterogeneous group. Some of them are remarkably frail with limited physical and physiological reserve, not only due to underlying cancer disease but also to their age and different comorbidities. Particularly patients with long-time androgen deprivation therapy are at increased risk of osteoporosis, diabetes and cardiovascular ailments, including coronary heart disease, myocardial infarction, sudden cardiac death, or stroke (Eastham 2007, Saigal et al. 2007, Keating et al. 2010).

The patients with hormone-refractory prostate cancer in our study had a mortality rate of approximately 13% at one month and 40% at three months, a median survival of 5 months, and a complication rate of approximately 40%. These rates are high although rather similar to the results of one other study from Sweden (Jansson and Bauer 2006) with comparable patient material, or to a population-based study from Canada (Finkelstein et al. 2003), and an institutional report from U.S (Williams et al. 2009). Overall, up to 13% 30-day postoperative mortality rates and up to 54% complication rates were reported for patients with metastatic spinal cord compression (Loblaw et al. 2005). This is quite high compared with some other types of tumor surgery, as for example craniotomy for resection of brain metastases has an in-hospital death rate of 3.1% (Barker et al. 2004). This fact further reflects the fragility of the patients undergoing surgery for spinal metastases.

Strong effect of comorbidities and complications on mortality has been shown in a study by Patil et al. (2007), which comprised an in-patient sample with approximately 26,000 admissions due to metastatic spinal cord compression in the U.S. Generally, the patients with one single

complication were 4.6 times more likely to die compared with the patients with no complications, whereas a single comorbidity increased the risk of in-hospital death by 3.7-fold. Furthermore, with just 1 postoperative complication the mean length of stay in hospital increased by 7 days.

Traditionally, radiotherapy has been the standard treatment for the majority of patients with spinal metastases (Loblaw et al. 2005, Zaikova et al. 2011). Recently, a prospective, randomized study has showed that decompressive surgery plus radiation is superior for both preservation and regaining of walking ability compared to radiation alone (Patchell et al. 2005). This study caused a major breakthrough in favor of surgery and is frequently cited as a guide of current management of patients with spinal metastases. However, even in these highly selected patients median survival was only 4.2 months. Remarkably, it took 10 years to finish the study and to recruit 101 patients although 7 institutions from the U.S. were participating. This fact further emphasizes the importance of careful selection of patients who may benefit from surgery.

Whom not to operate?

Estimating survival

Life expectancy is one of the most important criteria in making a decision regarding surgical treatment in patients with metastatic spinal cord compression. Estimating survival is difficult and in many cases based on the physician's own clinical experience. Several studies reported that even oncologists may often be overly optimistic in predicting survival in terminally ill cancer patients (Christakis et al. 2000, Chow et al. 2001 and 2005). Why should then orthopedic surgeons, general surgeons, urologists, and general practitioners be expected to prognosticate more accurately? However, these physicians usually have an important impact on the process of diagnosis and decision about treatment of patients with spinal cord compression.

Consequently, different scoring systems have been proposed for predicting survival in patients with spinal metastasis. In general, these prognostic scores function when applied on patient materials consisting of various primary tumors since the type of primary tumor is always one important prognostic parameter. The accuracy of the scores fades when it comes to a specific tumor type. We found some of the scores either too complex (Tokuhashi) or less specific (Bauer, Tomita, van der Linden) to be applied on prostate cancer patients with spinal cord compression. Therefore, we tried to identify parameters of importance for survival and make a score that is specific for prostate cancer.

A new score

First, we identified predictors of survival in Kaplan-Meier analysis. These were hormone status (Paper I), and in hormone-refractory patients KPS and visceral metastasis (Paper I), and serum PSA (Paper IV). Then we extended the study and included 14 (25%) new consecutive patients. The four parameters mentioned above remained predictors of survival in Kaplan-Meier analysis. As patients in the hormone-naïve group had generally good survival we performed Cox-analysis only in the hormone-refractory group in order to give appropriate weight to the score items. Six clinically relevant parameters were included: age, interval from primary tumor diagnosis, KPS, visceral metastasis, preoperative neurological status, and serum PSA. The prognostic score was then developed by including hormone-status, KPS, visceral metastasis, and serum PSA. KPS showed the strongest association with survival in multiple Cox-analysis. Consequently, we gave KPS maximal weight in the score as compared with visceral metastasis and serum PSA.

Hormone status was also strongly related to survival in our patients. Therefore we gave it the same weight in the score as KPS. By including hormone-status in the score we wanted to increase awareness for the patients with hormone-naïve prostate

cancer as candidates for surgery of metastatic spinal cord compression. There is some evidence that they benefit more from surgery or surgery followed by radiotherapy (Huddart et al. 1998, Jansson and Bauer 2006) than from radiotherapy alone (Rades et al. 2006). We also found that these patients usually are in good general condition which makes them suitable for surgery.

We included visceral metastasis and serum PSA in the score although their significance was weakened in multiple Cox-analysis. Consequently, we gave them less weight in the score compared to hormone status and KPS. We believe that both parameters are clinically relevant for patients with advanced prostate cancer.

When analyzing preoperative neurological status, ambulatory patients had considerably longer median survival (13 months) than non-ambulatory patients (5 months), but statistical significance was not reached (p=0.3). This may be due to the low number (N=7) of patients in the ambulatory group. However, we did not find preoperative neurological status a reliable prognostic factor for survival for several reasons. First, neurological impairment is not only the main indication but also the main subject of treatment and in series reporting results of surgical therapy the proportion of patients who achieve neurological improvement is up to 70% (Witham et al. 2006). Second, the ultimate goal would be to treat all patients while they are still walking as the ability to walk before treatment is by far the most important predictor of functional outcome (DeAngelis and Posner 2009). Third, neurological status may deteriorate even after treatment decision is made, i.e. while waiting for surgery or radiotherapy, thus having impact on the total score. Fourth, patients with hormone-naïve prostate cancer had generally good survival irrespective of preoperative neurological status. More important, in our study (Paper I) like in other studies (Hill et al. 1993, Helweg-Larsen et al. 2000, Hirabayashi et

al. 2003) the ability to walk after surgery was clearly associated with favorable survival. Therefore, we believe that the ability to regain ambulatory status after treatment, rather than preoperative neurological function, may be important predictor of survival. This emphasizes the need to predict which patients have chance for neurological recovery.

Estimating neurological recovery

Patients who are able to walk at the start of therapy for spinal cord compression are more likely to retain this ability (Cole and Patchell 2008). This was also the case in our material where all preoperatively ambulant patients retained their ability to walk after surgery. This is in line with other studies on surgical treatment of spinal cord compression in prostate cancer (Shoskes and Perrin 1989, Williams et al. 2009, Weiss et al. 2012).

Our patients with hormone-naïve prostate cancer had better neurological outcome than the patients with hormone-refractory tumors, with two thirds of patients regaining ambulation. Possible explanations may be sensitivity of spinal metastases to androgen ablation (Paper IV), but also better general condition of these patients leading to better total outcome after surgery (Papers I and II).

In our study, one half of hormone-refractory patients regained the ability to walk after surgery, which is in agreement with other studies on prostate cancer (Iacovou et al. 1985, Shoskes and Perrin 1989, Williams et al. 2009). We found that duration of paresis in these patients of less than 48 hours was associated with regaining of ambulatory status. Other retrospective studies have reported that patients who presented with paresis for less than 48 hours (Chaichanna et al. 2008, Furstenberg et al. 2009) or less than 72 hours (Hessler et al. 2009) had increased likelihood of recovering ambulation. Thus, avoiding delays in diagnosis and timing of surgery seems to be important in achieving of favorable functional outcome.

Early diagnosis and treatment is essential

It would be reasonable to expect referral and treatment of patients with spinal cord compression in less than 24 hours, ideally before they lose the ability to walk (White et al. 2008). This goal was not achieved for the majority of the patients in the present study, which may have contributed to the less favorable functional outcome for some of the patients. Those referred from local hospitals had a significantly longer time interval to diagnosis and treatment than those who initially presented directly to the cancer centre. This may be caused by the unclear guidelines for referral and treatment of patients with spinal cord compression but also the consequence of the insufficient information given to the patients at risk. Patients with a previous history of cancer should have shorter interval to diagnosis and treatment than those in whom the spinal cord compression is the presenting sign of previously unknown cancer (Husband 1998, Levack et al. 2002), but this was not the case in our study. Indeed, almost a half of our patients with hormone-refractory disease had been hesitating for more than one week before they contacted their hospital in spite of neurological symptoms. These findings stress the need for improving awareness for the symptoms of spinal cord compression both among patients and in primary and secondary care providers (White et al. 2008). This is particularly important for patients with a previous history of prostate cancer and presence of bone metastases who have approximately 30 – 40% risk of occult spinal cord compression (Bayley et al. 2001, Venkitaraman et al. 2007).

Unfortunately, our results also highlight the low availability of MRI scans for this group of patients. This is in line with some other studies reporting delays in diagnosis and treatment of spinal cord compression (Poortmans et al. 2001, Levack et al. 2002, McLinton and Hutchison 2006). In our study half of the operations started out of

hours but a median time from admission at the cancer centre to surgery was still 19 hours. This fact further reflects the insufficiency of the resources at surgery department.

Deciding about surgery

Deciding about which patients are not appropriate candidates for surgery is both a medical and an ethical issue. In my opinion surgical treatment is always palliative with aim to improve the quality of the remaining period of life. Therefore, the surgical morbidity, life expectancy and anticipated neurological recovery must always be weighed against the possibility to provide a meaningful quality of life to the patients. Our study showed that some patients enjoyed benefit from surgery, which gave them prolonged survival as well as maintenance of walking ability. However, some of the patients had short survival, suffered from complications, and had prolonged hospitalization being separated from their families during the short remaining span of their lives. These patients probably should have been offered radiotherapy or dignified and compassionated palliative care instead of surgery.

Morphological results

The standard therapy for bone metastases is lowering of circulating androgens either by surgical or medical castration. The metastases initially respond to this therapy but eventually they relapse to castration-resistant growth. The mechanisms underlying castration resistance and growth of bone metastases in prostate cancer are still largely unexplained. Because of the lack of metastatic tumor samples from bone, most of current knowledge is based on studies on primary tumors or soft tissue metastases. Tissue from bone metastases is seldom obtained for analyses either from autopsies or during surgical treatment of clinical complications such as pathologic fractures or spinal cord compression. Autopsy conveys the opportunity to obtain sufficient amounts of tumor tissue for

analyses, however this tissue may be affected by the general pathophysiological and pathomorphological changes associated with death (Rubin et al. 2000, Shah et al. 2004). Only few investigators have reported on morphological studies on bone metastases obtained on surgery (Hobisch et al. 1995, Asmann et al. 2002, Cheville et al. 2002). The present study is part of a multidisciplinary project on prostate cancer bone metastases at the University of Umeå, which is based on tumor samples obtained during orthopedic surgery. When comparing untreated primary tumors with corresponding hormone-refractory metastases we found difference in AR staining, apoptosis, PSA staining, cell proliferation, and Gleason score. This further emphasizes the importance of studying bone metastases rather than drawing general conclusions from the studies of primary prostate carcinomas.

In our study, high nuclear AR expression in bone metastases was associated with less favorable outcome after surgery for complications of bone metastases, mostly spinal cord compression. This is in line with the findings in primary prostate tumors (Henshall et al. 2001, Li et al. 2004) and in lymph node metastases (Sweat et al.1999). Recently, it has been proposed that patients with high nuclear AR expression may benefit from novel drugs that block androgen synthesis (abiraterone) or ARs (MDV3100) in metastases (O'Donell et al. 2004, Tran et al. 2009, Reid et al. 2010, Scher et al. 2010, deBono et al. 2011). However, as patients with constitutively active ARs (AR-V) are detected by antibodies used in the present study, our results suggest that not all patients may be responders to that treatment. Consequently, a recent study on our material disclosed that expression of AR-V splice variants in bone metastases was associated with high nuclear AR staining scores, and with a poor outcome in some hormone-refractory patients (Hörnberg et al. 2011). This implicates the

need for therapy acting specifically on these AR-Vs rather than on inhibition of androgen synthesis. In addition, in cases with low AR staining it is likely that other factors are responsible for metastasis growth and that these patients may need other therapies than AR blockade. New results on radium-223 radioisotope (alpharadin) have recently been reported, which could be an option in these patients (Nilsson et al. 2007). Our study also indicates that castration may be more effective in reducing tumor cell PSA levels than to decrease tumor cell proliferation. This suggests that measurements of serum PSA levels may not always monitor other more important outcomes of therapy.

Limitations

The main limitation of these studies is the retrospective character. The patient records were retrospectively reviewed (Papers I, II, and III), although the material for morphological analyses was prospectively collected and analyzed (Paper IV). Consequently medical and surgical treatments were not randomized, but were determined according to the preference of clinicians, based on their individual experience as well as on institutional resources. Although it describes clinical and morphological aspects of bone metastases for a specific tumor type, the thesis is limited by a relatively small number of patients. Some of the patients who were referred and transported from a long distance may have been influenced by analgesia and sedation at the time of admission to the cancer centre, which potentially might mislead the clinicians to consider them as non-ambulatory. Another limitation is the fact that the data on pain assessment, as well as data on bladder or bowel continence, were missing or were not suitable for analysis. Finally, the data for patients who underwent only radiotherapy for spinal cord compression during the same period were not analyzed, which limits the conclusions from the present study regarding the accuracy of surgical treatment.

Conclusions

- Prostate cancer patients with metastatic spinal cord compression represent a heterogeneous group.
- Surgery is associated with high morbidity and mortality.
- Only carefully selected patients may benefit from surgery.
- The prognostic score including hormone status, performance status, visceral involvement, and serum PSA may be used as support in making decisions about treatment.
- Delays in diagnosis and treatment may negatively influence neurological recovery.
- Ability to walk before surgery and/or hormone-naïve prostate cancer is associated with favorable neurological outcome.
- High nuclear androgen receptor expression in bone metastasis is associated with a poor survival rate.

Clinical implications

Our results suggest that early diagnosis and prompt treatment should be imperative in order to achieve favorable functional outcome in prostate cancer patients with metastatic spinal cord compression. This emphasizes the need for improvement of local and regional guidelines. Information to patients at risk is also essential. As only carefully selected patients may benefit from surgery, the prognostic score may be a valuable support to clinicians in making decisions about treatment. Results of our morphological study implicate further investigations on androgen receptor (AR) as an important factor in the growth of bone metastases, suggesting potential possibility for development of new drugs acting on downstream of the constitutively active AR variants. Our data also stress the importance of studying the biology of bone metastases on the tumor tissue obtained at surgery as well as the importance of performing both clinical and morphological research in order to explain the complex issue of bone metastasis in prostate cancer.

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